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Cross-talk between biometal ions and immune cells for bone repair

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ABSTRACT

Biometal ions are crucial in the structure and function of living organisms and have extensively been employed to promote bone tissue regeneration. Nevertheless, the biological functions of biometal ions and the underlying mechanisms responsible for their pro-regenerative effects remain incompletely understood, since bone repair is an intricate physiological process involving multiple cell types and signals. Recent accomplishments in the osteoimmunological field have revealed the momentous involvement of the immune system in mediating the therapeutic effects of biometal ions. The inflammatory factors secreted by immune cells contribute to bone cell migration, activation, and proliferation. This review summarizes the immune system and its constituent cells, followed by the current perspective on immunomodulation during bone healing. Next, the physicochemical and physiological properties of various biometal ions, including lithium, sodium, potassium, magnesium, calcium, strontium, vanadium, iron, cobalt, copper, and zinc, are thoroughly reviewed. In addition, the interactions between biometal ions, immune cells, and bone tissue are discussed, aiming to provide insights into the prospective development of novel approaches to bone tissue regeneration by harnessing the therapeutic potential of these biometal ions.

1. Introduction

Bone injuries and defects have long been primary reasons for global mortality and disability [1]. There were 178 million new fractures worldwide in 2019, with an increase of 33.4% since 1990 [2]. In China, bone injuries are ranked as the fifth cause of mortality, surpassing the prevalence of various other diseases [3]. Between 1990 and 2019, the number for incidence of fracture in China increased from 12.54 million to 21.27 million, while the number for prevalence of fracture significantly raised from 28.35 million to 67.85 million [4]. Managing and reconstructing bone injuries, including sizable bone defects, delayed unions, and non-unions, pose persistent challenges in medicine [5,6]. Therefore, therapeutic strategies and mechanisms have been developed for the bone healing process. Natural and synthetic osteogenic materials have demonstrated their ability in cellular adhesion, migration, proliferation, and differentiation, thereby facilitating osteogenesis. These materials offer the necessary support for cellular processes, aiding bone regeneration and restoration [7–9]. Bioactive molecules, such as hormones [10], cytokines [11], and growth factors [12], function in the bone healing and regeneration process. These molecules activate intricate signaling cascades within cells, effectively regulating cellular behaviors and promoting osteogenic differentiation and proliferation. Biomechanical factors adjust the mechanical stimulation of bones and enhance local stability to accelerate bone growth [13]. However, the limitations of established therapeutic strategies are amplified following implementation. These include insufficient donor supply or poor bioactivity of the required materials, high cost, short bioactive half-life of bioactive factors, and the low operability of mechanical stimulations [14]. Considering this, researchers are still exploring new strategies to repair bone injuries.

In recent years, osteogenesis regulated by the immune system has been affirmed as a powerful therapeutic strategy because immune cells are crucial for cell function and, in turn, for homeostasis and recovery from injury [15,16]. Bone tissue functioning not only as a structural component of the musculoskeletal system but also as an integral part of the immune system [17]. Immune cells and local bone cells are synthesized into the traditional osteogenic environment to form an “osteoimmune system” [18]. The association between the immune system and os-

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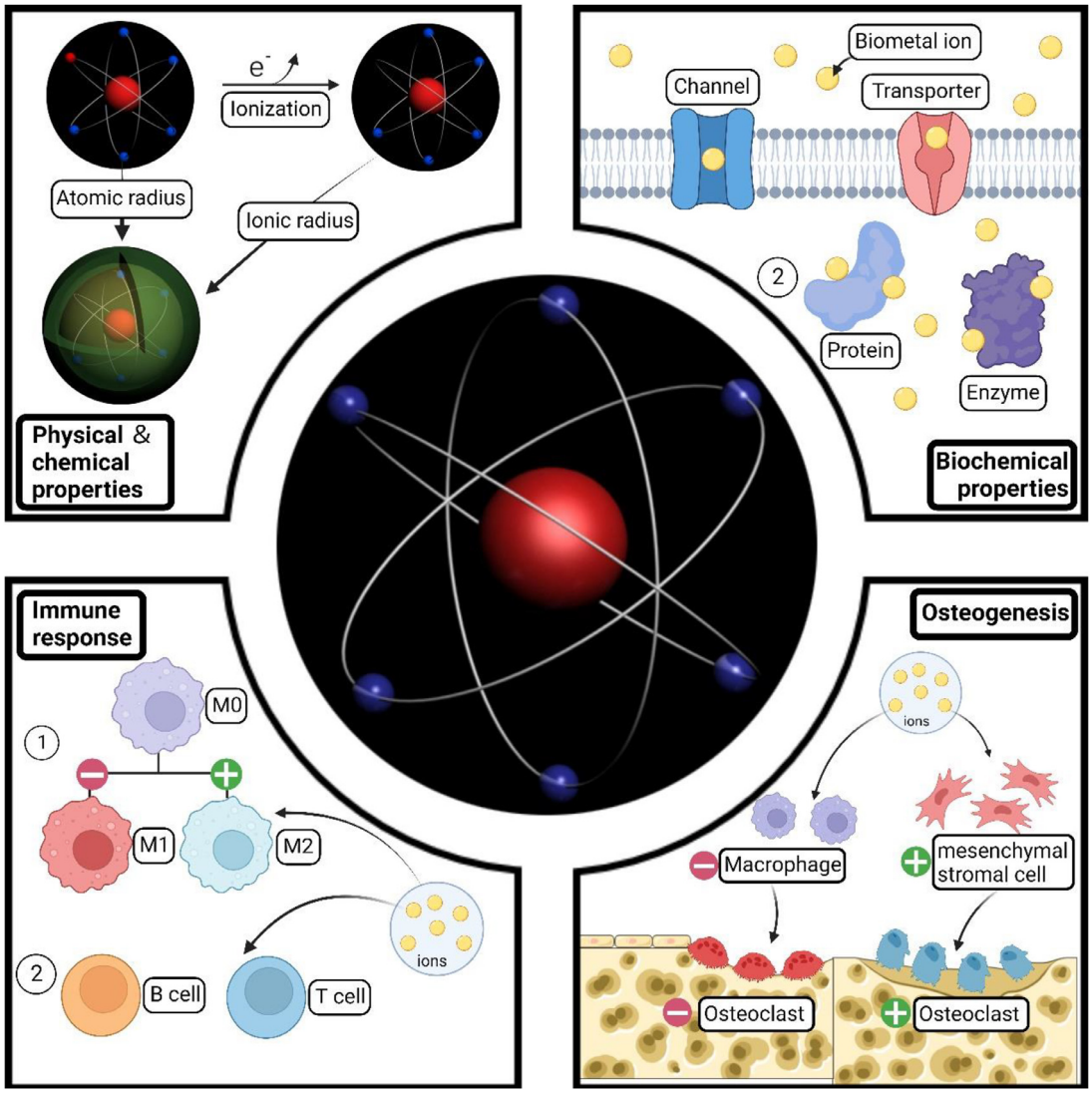

Fig. 1. Schematic illustration of properties and functions of biometal ions. Source: Created with BioRender.com.

seous homeostasis has garnered significant attention due to their strong regulatory relationship. Extensive research has confirmed the crucial role of crosstalk between immune cells and bone cells within bone regeneration. This interaction is essential for sustaining the balance between osteogenesis and osteolysis, ultimately contributing to the overall health and integrity of the skeletal system [19,20].

Metallic elements are vital for cellular structure, catalysis, and signaling [21]. These are indispensable cofactors of enzymes, either prosthetic groups or coenzymes, and are responsible for the direct or analogous activation of ion channels and secondary signaling pathways [22,23]. In recent decades, metal ions have gained considerable research attention as regenerative improvers for bone tissue repair, and the release of metal ions has been found to promote implant–bone integration and regeneration [24]. The distinctive characteristics of metal ions have given rise to novel strategies to augment immunomodulation and tissue healing. Immune cells can interact with biometal ions at biologically safe concentrations locally within tissue microenvironments systemically [25]. Immune cells exhibit sensitivity to ions, and their mechanisms and behaviors can be modulated, to some degree, by these inorganic species. The interactions among bone cells, inflammatory mediators, and components of the immune system involved in bone regeneration remain a topic of significant scientific interest for clinicians and researchers [26,27]. However, the intricate mechanisms underlying the interactions between multiple systems necessitate further exploration. The elucidation of the complex interrelationship of the immune system and the skeletal system in the context of biomaterial implantation is an evolving frontier of scientific inquiry, still in its incipient stages. Consequently, an urgent need is to explore further and understand the interactions between biometal ions and multiple systems (Fig. 1).

2. Immune system and immune cells

2.1. Immune system

The immune system in humans is composed of innate and adaptive immunity, each with unique characteristics. These systems vary regarding the rapidity and specificity of the immunological response, immune cells, cytokines, and biological macromolecules involved, and the duration and intensity of the inflammatory response [28,29]. Despite these differences, these two immune responses interact throughout the immune regulatory process to maintain our body's homeostasis. Innate immunity serves as the foundation of adaptive immunity through the presentation of antigens, while the immune substances produced by adaptive immunity also shape the actions of innate immunity. For instance, macrophages can present antigens to lymphocytes, activating them to

eliminate target cells. Concurrently, antibodies and cytokines also modulate macrophage chemotaxis, activation, and phagocytosis [30].

Innate immunity serves as a tissue barrier mechanism involving immune cells (monocytes, macrophages, neutrophils) and biomacromolecules (complement, cytokines, inflammation-associated proteins). These constituents are pivotal in orchestrating innate immunity, thereby turning into the cornerstone of the acute immune response. Innate immunity is distinguished by its broad-spectrum efficacy, rapidity of action, and inherent stability, rendering it the organisms' fundamental and indispensable immune defense system [31]. Adaptive immunity, also called specific immunity, is triggered by specific antigenic substances during infection or active vaccination, resulting in a robust, targeted immune response and potent killing effect against the respective pathogen. It is thus more accurate than innate immunity but takes a longer time to develop. Adaptive immunity can be further divided into cellular and humoral immunity, involving T and B lymphocytes, respectively. Cellular immunity is facilitated primarily by cytotoxic T lymphocytes, which account for eliminating infected cells and intracellular pathogens. In contrast, humoral immunity is primarily driven by plasma cells that synthesize and secrete immunoglobulins (Ig) upon antigen stimulation, binding to target antigens and participating in immune responses [32].

2.2. Immune cells

2.2.1. Monocytes/macrophages

Monocytes and macrophages possess a diameter of 15 to 22 μm and a pin-like nucleus originating from the mononuclear phagocytic system [33]. Monocytes can be distinguished by identifiable surface markers, which shape a uniform size and distinctive nucleus. Typically, they are usually classified into three subtypes based on the intensity of fluorescence of cluster of differentiation (CD) 14 and CD16 on their surfaces: the classical monocyte with $CD14^{++}/CD16^{-}$(CD14 overexpressed and CD16 not expressed), the non-classical monocyte with $CD14^{dim}/CD16^{++}$(CD14 weak expressed and CD16 overexpressed), and the intermediate monocyte with $CD14^{++}/CD16^{+}$(CD14 overexpressed and CD16 moderate expressed) [34].

Monocytes are the common precursors of macrophages. Upon receiving signals from infected sites, monocytes are among the first to arrive at the inflammatory tissues from the bloodstream, where they proliferate and differentiate into macrophages to bolster the innate response [35]. Monocytes themselves also perform phagocytosis, either with the assistance of antibodies or immune complexes or by recognizing pathogens through pattern-recognition receptors (PRRs) [36]. PRRs can recognize pathogen-associated molecular patterns (PAMPs), which are related to infected pathogens, or damage-associated molecular patterns (DAMPs), which are related to fragments of dead cells and non-infectious debris [37].

Macrophages, derived from monocytes or residing in tissues, represent a specialized subset of white blood cells that serve a pivotal role in defending against foreign invasions. They are ubiquitously present throughout the body but classified into distinctive forms with different names based on their residing sites and surface markers. For instance, macrophages residing in the liver are specifically referred to as Kupffer cells, those present in the nervous system are known as microglia, and in bone tissue, they are commonly referred to as osteal macrophages (OsteoMacs) [38]. Macrophages are so named because of their large size and remarkable phagocytic capacity. In the initial phase of innate immunity, macrophages recognize foreign molecules and exert profound effects–presenting antigens, performing phagocytosis for self-digestion, and releasing a series of pro-inflammatory or anti-inflammatory cytokines. These activities upregulate the inflammatory responses and intricately result in the harmonious coordination of the entire immune system [39]. Macrophages exhibit crucial functions encompassing the recognition, phagocytosis, and elimination of bacteria and other detrimental pathogens. The detection of microbes is accomplished by PRRs expressed on the macrophage surface [40]. For phagocytosis, a central function of the macrophages, pathogens are engulfed into a phagosome, which then fuses with a lysosome and digests pathogens by enzymes and toxic peroxides [41–43]. Additionally, macrophages orchestrate the release of a spectrum of chemokines and cytokines, which serve as mediators in eliciting inflammatory and antibacterial actions. Notably, immunological inducers including nitric oxide synthase (NOS) and interleukin-1 (IL-1) facilitate the activation and selective homing of supplementary immune cells to the inflammatory site [28].

Typically, the subtypes of macrophages can be classified into M1 (pro-inflammatory) and M2 (anti-inflammatory) types based on their cytokine productions. M1 macrophages primarily contribute to inflammation by promoting phagocytic responses and releasing cytokines [44]. M1 macrophages induce NO production by iNOS, which may exacerbate the inflammatory response under specific conditions. This inflammatory response can provide a suitable environment for macrophages to phagocytose pathogens. However, it may also have a killing effect on normal tissues [45]. By contrast, M2 macrophages predominantly release anti-inflammatory cytokines: IL-4, IL-10, IL-13, and transforming growth factor (TGF), to facilitate tissue regeneration at the injury site. In the present study, M2 macrophages can be further divided into four subtypes: M2a, M2b, M2c, and M2d, each of which exhibits nuanced variations in their functional attributes [46,47]. IL-4 and IL-13 induce M2a macrophage differentiation, which is well-known as classically activated alternatively activated macrophages. These M2a macrophages function in the tissue regeneration process by producing various components of the extracellular matrix [37]; M2b macrophages are commonly recognized as regulatory macrophages (Mregs), characterized by their secretion of high levels of IL-10 and lower doses of IL-12 than other M2 cell subtypes [48]; M2c macrophages can be selectively induced in response to glucocorticoids and TGF-β, leading to the acquisition of a distinct phenotype. M2c macrophages exhibit an enhanced capacity for secreting elevated levels of TGF-β and IL-10, contributing to their immunoregulatory and tissue-reparative functions [49]; M2d macrophages display a pro-angiogenic role by releasing vascular endothelial growth factor (VEGF), TGF-β, and IL-10 [50]. Nevertheless, it is crucial to acknowledge that recent studies have revealed a more complex spectrum of macrophage phenotypes that extends beyond the traditional M1 and M2 classifications. Moreover, macrophages have been found to possess the ability to transition between phenotypes [44].

There are two main sources of macrophages: residential cells and blood infiltration [51]. Both sources are essential for regulating and stabilizing the injured site. Before infection or inflammation, resident macrophages are defensive patrols that proliferate regularly in the tissue and are more likely to transform into M2 phenotypes. Upon sensing a local infection or foreign substance, resident macrophages undergo activation and secrete a variety of inflammatory cytokines and chemokines: IL-1, IL-6, IL-8, IL-12, and tumor necrosis factor-α (TNF-α). These molecules serve to attract other immune cells to the affected site against the aberrant stimulus [52]. IL-8 which is secreted by local macrophages recruits neutrophils from blood vessels [53]. With the help of IL-12, NK cells are drawn into the signal site and release cytokines to maintain macrophage activity [54]. At the early stage of inflammation, macrophages present at strategic locations remove dying cells and engulf foreign particles. If needed, resident macrophages can recruit circulating monocytes to diseased sites, where they differentiate into activated macrophages later [55]. Monocytes, recruited by cytokine chemotaxis and differentiated by the local inflammatory cues, provide a larger proportion of activated macrophages responsible for the regulation of the immunological microenvironment.

2.2.2. Dendritic cells

Dendritic cells (DCs) are widely acknowledged as the most proficient antigen-presenting cells (APCs) within the adaptive immune system [35,56]. They perform the tasks of engulfing, digesting, and presenting antigens to immature T cells as a transporter and activator. Be-

fore penetrating tissue barriers and entering the bloodstream, pathogens like bacteria and viruses are recognized by numerous toll-like receptors (TLRs) expressed on the local DCs. They are internalized by DCs and subsequently processed into smaller particles that are compatible with major histocompatibility complex (MHC) class I and II molecules. The presence of adhesion and co-stimulatory molecules empowers DCs to carry out antigen presentation [57]. Accompanied by alterations in cell surface morphology, structure, and molecular signaling, dendritic cells undergo migration from the site of infection to the secondary lymphoid organs. Among these, DCs present antigens to primary lymphoid cells, thereby triggering their activation and initiating the process of adaptive immunity [57]. Subsequently, DCs become activated, limiting their ability to process new antigens and instead concentrating on presenting antigens to naive T lymphocytes [57]. They congregate in the lymph node, but only a select few are carefully chosen by MHC-peptide complexes to evolve into effector T cells, given their potency when targeting cells [58].

2.2.3. Granulocytes and mast cells

Granulocytes are categorized as neutrophils, eosinophils, basophils, or mast cells based on their chemical properties. Their cytoplasm houses granules that are released and act on infected sites [59]. Neutrophils carry out functions identical to macrophages in engulfing microorganisms; however, they have a shorter lifespan and circulate independently until they are summoned to an inflammatory response [60]. Neutrophils are ubiquitous in the blood and bone marrow cavity in response to the initial infection. During the early stages of an infection, neutrophils exhibit important functions by undergoing degranulation and engaging in phagocytosis at the sites of infection. These processes are crucial for eliminating pathogens and foreign substances. However, it is worth noting that these activities can also exacerbate inflammation and contribute to the formation of pus, which is also a consequence of the immune response [61].

In the connective tissue, mast cells, basophils, and eosinophils function as inductors of acute hypersensitivity [62]. High-affinity immunoglobulin E receptor I (FcεRI), which is produced on their surfaces, may bind IgE released by plasma cells and generate an irreversible binding force [63]. These cells are, therefore, primed to identify pathogens and bind to their antigen isotypes. Upon binding with IgE antibodies through interactions with two or more FcεRI molecules on their surface, pathogens trigger rapid activation of mast cells or basophils. Eosinophils employ their FcεRII receptors and pre-packaged granules to inflict damage upon parasites [64]. Basophils, distinguished by their two-lobed nucleus and numerous cytoplasmic granules, represent one of the least abundant cell types found in both the bone marrow cavity and the bloodstream. Upon infection, mature basophils are released from the bone marrow with a secretion of histamine and prostaglandins, which induce capillary dilation and increased permeability. Consequently, blood flow is enhanced, creating an inflammatory milieu at the injury site. This process facilitates the migration of phagocytes, contributing to the immune response against pathogens [65].

2.2.4. Nature killer (NK) cells

Natural killer cells (NK cells) constitute 5 to 25 percent of total lymphocytes in a healthy individual [66]. The major assignment of NK cells is to eradicate infected or harmful cells. NK cells can be activated and recruited through the action of cytokines released by infected cells. These secreted factors further stimulate phagocytosis and macrophage lysis to promote direct cell killing [67]. During the antibody-dependent cell-mediated cytotoxicity (ADCC) process, antigens are recognized by FcγRIII (CD16) receptors binding to antibodies and then leading to NK cell activation. This activation triggers the production of cytolytic granules, ultimately resulting in the apoptosis of the targeted cells [68]. The fluorescence intensity of specific markers, such as CD56, can be utilized to differentiate between different subtypes of NK cells. Classification of NK cells refers to $CD56^{bright}$ or $CD56^{dim}$ based on the intensity of CD56 fluorescence [69]. $CD56^{bright}$ NK cells comprise the majority of NK cells with several cytokine productions (IL-2, IL-12, type I interferon), while $CD56^{dim}$ NK cells are identified by their Characteristics of killing [70].

2.2.5. T lymphocytes

T lymphocytes assume a fundamental and indispensable function in orchestrating the adaptive immune response. Due to the presence of the T-cell receptor (TCR) on the cell membrane, they possess a unique characteristic that sets them apart from other lymphocytes. T cells experience a complex process of maturation within the thymus gland. Serving as formidable assassins against infected and tumor cells, these remarkable cells exhibit surface markers, primarily CD4 and CD8, which are indicative of their distinct identities. To attain full maturity and functionality within the adaptive immune response, early thymic progenitor (ETP) cells, initially lacking both CD4 and CD8 markers, undergo a series of intricate developmental stages, including TCR development, positive selection, and negative selection [71]. T cell maturation requires the combination of functional TCR. Once a functional TCR has been developed, the T cell will go through the positive selection with rearrangement of the TCRα locus. Then, positive selection enables progenitor cells to develop into adult cells [72]. T lymphocytes expressing TCRs that bind strongly to MHC class I molecules may be prompted to undergo further maturation and differentiation [73]. These double-positive ($CD4^+/CD8^+$) cells are then evaluated by MHC class I and II to determine which chemical they bind. CD4 interacts specifically with MHC class II, while CD8 binds to MHC class I. The contact between a particular receptor and a self-MHC complex, therefore, affects whether a T cell matures into a T cell possessed either $CD4^+$ or $CD8^+$. In contrast, negative selection identifies antigen receptors that bind too strongly with self-peptides and eliminates their numbers [74,75]. Consequently, these highly responsive lymphocytes receive apoptotic signals that prompt cell death. After the whole process, only 2% of lymphocytes become mature immunocompetent T cells with $CD4^+$ or $CD8^+$ and circulate in the bloodstream.

Subsequent to antigen recognition, a select population of naive T lymphocytes undergoes a process of intricate differentiation, culminating in the formation of memory T lymphocytes. These cells possess a remarkable capacity to rapidly expand into a formidable cohort of effector T cells upon subsequent encounters with their cognate antigen. After that, Memory T cells will further differentiate into effect Memory T cells (T_{EM}) or central memory T cells (T_{CM}) according to the intensity of antigen stimulation. In the peripheral blood, T_{CM} cells predominantly exhibit the CD4 phenotype, while T_{EM} cells primarily bear the CD8 marker [76]. Depending on the types of pathogens and the environment of infection, T cells have multiple differentiated states [77]. Furthermore, mature T lymphocytes can be subdivided into $CD4^+$ helper cells and $CD8^+$ killer cells. $CD4^+$ helper T cells support other immune cells in coordinating and enhancing immune activities, such as cytotoxic T cells and B cells. $CD8^+$ killer T cells possess a dual ability to directly eliminate virus-infected cells or tumor cells, while also releasing cytokines that augment the recruitment of other immune cells and enhance their cytotoxic capacity. Additionally, regulatory T cells (Treg) serve to suppress inappropriate immune responses, specifically from other T cells. They secrete cytokines that regulate abnormal immune functions, maintaining immune balance.

Helper T cells (Th) are subtypes of $CD4^+T$ cells with supplemental and auxiliary instructions that are divided into Th1, Th2, Tfh, Th17, and Treg [73,78]. Effector Th1 cells take part in the immune response by regulating macrophages to enhance the efficiency of pathogen elimination during infections. The interaction between Th1 cells and macrophages yields several beneficial effects. It promotes the enhancement of phagocytic activity, enabling macrophages to digest engulfed pathogens more effectively. Moreover, Th1 cells stimulate macrophages to produce and release microbicidal agents, including oxygen radicals, nitric oxide (NO), and proteases. These potent substances exert antimicrobial effects, contributing to the extermination of invading pathogens

and bolstering the immune defense against infections [79]. Th1 cells express TLRs to identify antigens presented by MHC II molecules on macrophages and activate them preferentially [80]. Once they establish a strong connection with each other, signals are exchanged throughout the whole process. IFN-γ and CD40L released by the Th1 cells stimulate the activation of macrophages [79]. Within infected tissues, the release of molecules such as TNF-α and IL-2, influences the differentiation of macrophages into distinct functional subsets. Th2 cells exert inhibitory functions via secreting cytokines (TGF-β, IL-4, IL-10, IL-13) on macrophages [81]. They may also damage healthy cells by magnifying the signals of parasite infections, which will activate basophils and mast cells to generate an allergic reaction [82,83]. The maturation of Tfh cells leads to an enhanced antibody production of B cells [84]. By recognizing the antigen: MHC complex, Tfh cells bind to the particular antigen and subsequently release CD40L to combine with CD40 on the B cell's surface. Th17 cells stimulate neutrophils to respond to fungal and bacterial infections. However, the overactivation of Th17 cells may cause type IV hypersensitivity and several related diseases, including asthma and rheumatoid arthritis (RA) [85,86]. Treg cells can reduce the self-reaction of relatively high-functional $CD4^+T$ cells by negative feedback [87]. Effector T cells become activated and exhibit their cytotoxic function upon encountering antigen-presenting cells. They effectively eliminate target cells that are infected or cancerous. By contrast, Treg cells employ immunomodulatory mechanisms to maintain immune balance. The inhibitory effect of Treg cells upon effector T cells prevents excessive damage to normal tissues in vivo, minimizing the potential for immune-mediated destruction. Treg cells are essential in maintaining immune tolerance and preventing autoimmune reactions [87]. Based on the study of T cell subtypes above, other subtypes of Th cells have been discovered, such as Th9 and Th22 cells. Th9 cells produce IL-9 to defend against helminths and cell-dependent allergic inflammation [88], while Th22 cells release IL-22 and participate in self-immune diseases like Crohn's Disease and RA [89].

$CD8^+T$ cells are called cytotoxic T cells due to their cell-killing capability [90]. Upon recognition of MHC1 molecules by $CD8^+T$ cells, cytotoxic mediators including perforin, serine esters, interferon, and tumor necrosis factor, are secreted to destroy target cells. After identifying particular antigen-presenting cells, $CD8^+T$ cells attach to target cells and release lytic granules at the fusion site [91]. This process, also known as programmed cell death, prevents the production of inflammatory factors and transforms potential pathogens into a static form that can be engulfed. $CD8^+$ T cells secrete cytokines: Interferon gamma (IFN-γ), and IL-2, for upregulating macrophages' ability to clear apoptotic cells. This cooperation between $CD8^+$ T cells and macrophages maintains tissue homeostasis and alleviates inflammation by promoting the efficient removal of cellular debris [91].

2.2.6. B lymphocytes

B lymphocytes are a unique subtype of lymphocytes from the bone marrow. They are characterized by B-cell receptors (BCRs), which bind to antigens and initiate an antibody response. The dominating function of B cells is to produce a wide variety of antibodies, resulting in a targeted immune response [92]. This process requires antigen activation. In draining lymph nodes, B cells detect antigen-MHC II complexes provided by follicular dendritic cells or macrophages and activate CD40 ligand expression [93]. Then, antigen-activated B cells migrate from the B region to the juncture between B cells and T cells, where they form a cognate pair to exchange cytokines. This process enhances naive B cells to differentiate into plasma cells for generating antibodies or transforming into memory B cells for possible secondary infections in the future.

Plasma cells produce antibodies to neutralize infections and activate effector cells to eradicate pathogens [94,95]. The antibodies they secreted can be classified as IgM, IgA, IgE, IgG, and IgD. IgM is the first antibody isotype that plasma cells produce in the blood and tissues when encountering infections [96]. The pentameric form of IgM binds to pathogens, traces complement receptors on phagocytes, and then activates the immune system through the classic pathway. However, IgM has the disadvantage of being too large to permeate tissues and having a limited affinity for combining with infections [97]. After the adaptive immune response, mature IgG with high affinity is created to cover pathogens, while monomeric IgA is transported to the particular receptors on phagocytes [98]. In addition, dimeric IgA is secreted in the mucosal tissues of the digestive, respiratory, and urogenital systems to serve as the initial line of immunological defense [99]. IgE acts as the primary source of acute allergy responses identified by mast cell Fc receptors [100]. Mast cells carry substantial amounts of IgE on their surface because of their high affinity after combination [101]. Cytokines regulate B cells in significant ways. IFN-γ, for instance, causes the B cell to create a powerful opsonizing IgG antibody; IL-4 causes it to make IgE; IL-5 increases the synthesis of IgA, and TGF-β triggers the release of IgG2b and IgA [102].

3. Immunoregulation during bone healing

Bone fractures are a pervasive medical issue within human populations, with an escalating incidence reported in recent years [103,104]. Typically, fracture healing can be categorized into two subtypes: direct (primary) and indirect (secondary) repair. Direct bone healing necessitates a minimal fracture end gap, typically less than 0.1 mm, facilitating direct ossification and subsequent Haversian remodeling without the need for callus formation [11]. Conversely, indirect or secondary fracture repair is a more prevalent mode of bone healing, typically associated with fractures that maintain some degree of mobility. This process involves the recruitment of mesenchymal stem cells (MSCs) and their differentiated progeny, including osteoblasts and osteoclasts, to the fracture site, where they contribute to matrix deposition [16]. Secondary fracture healing is traditionally delineated into four stages: the inflammatory phase, the cartilaginous callus phase, the bony callus phase, and the remodeling phase [105]. The healing process involves the restoration of bone continuity, regeneration of surrounding soft tissues, and, crucially, angiogenesis and neurogenesis [11]. Fig. 2 provides a comprehensive depiction of the origins and differentiation pathways of osteogenic and immune cells in the bone marrow cavity.

3.1. Inflammation stage

The inflammatory phase of bone healing is triggered when damage to surrounding vasculature initiates clotting and hematoma formation to arrest bleeding [106–108]. A group of inflammatory immune cells are subsequently recruited to commence the inflammatory response. Polymorphonuclear neutrophils (PMN), including neutrophils, infiltrate the hematoma in substantial numbers early on, secreting chemokines such as Chemokine ligand 2 (CCL-2) and IL-6 to draw long-lived macrophages into the fray during the ensuing phase [109]. Granulation tissue supplants the hematoma with the ingress of immune cells, predominantly neutrophils, and macrophages [110]. This inflammation phase serves to purge potentially cytotoxic debris and necrotic cells from the lesion site, transitioning the microenvironment towards an anti-inflammatory state [111,112]. Fig. 3 delineates the four stages of bone healing, highlighting the immune cells associated with each phase as well as the morphological changes occurring during bone healing.

Inflammatory cells actively participate in the resorption of injured tissues and contribute to the formation of new bone matrix [113–115]. Monocytes differentiate into macrophages, while resting macrophages transition into an activated state, inciting intense inflammation and presenting MHC-peptide complexes to dendritic cells, thus sparking the adaptive immune response [116,117]. Generally associated with allergic reactions, mast cell mediators, including histamine and VEGF, can expedite vascularization and augment the proliferation of MSCs and osteoblasts [118–121]. NK cells may also function in the early phase of inflammation, although the precise mechanisms remain elusive [122]. T

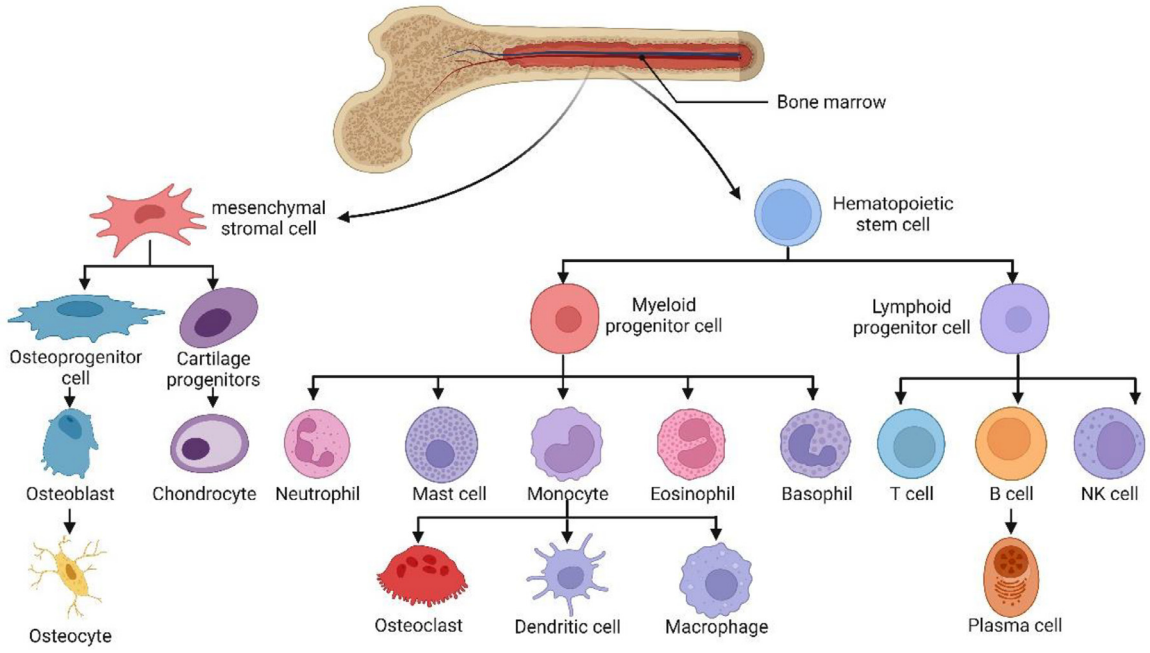

Fig. 2. The development of immune cells and bone cells. Source: Created with BioRender.com.

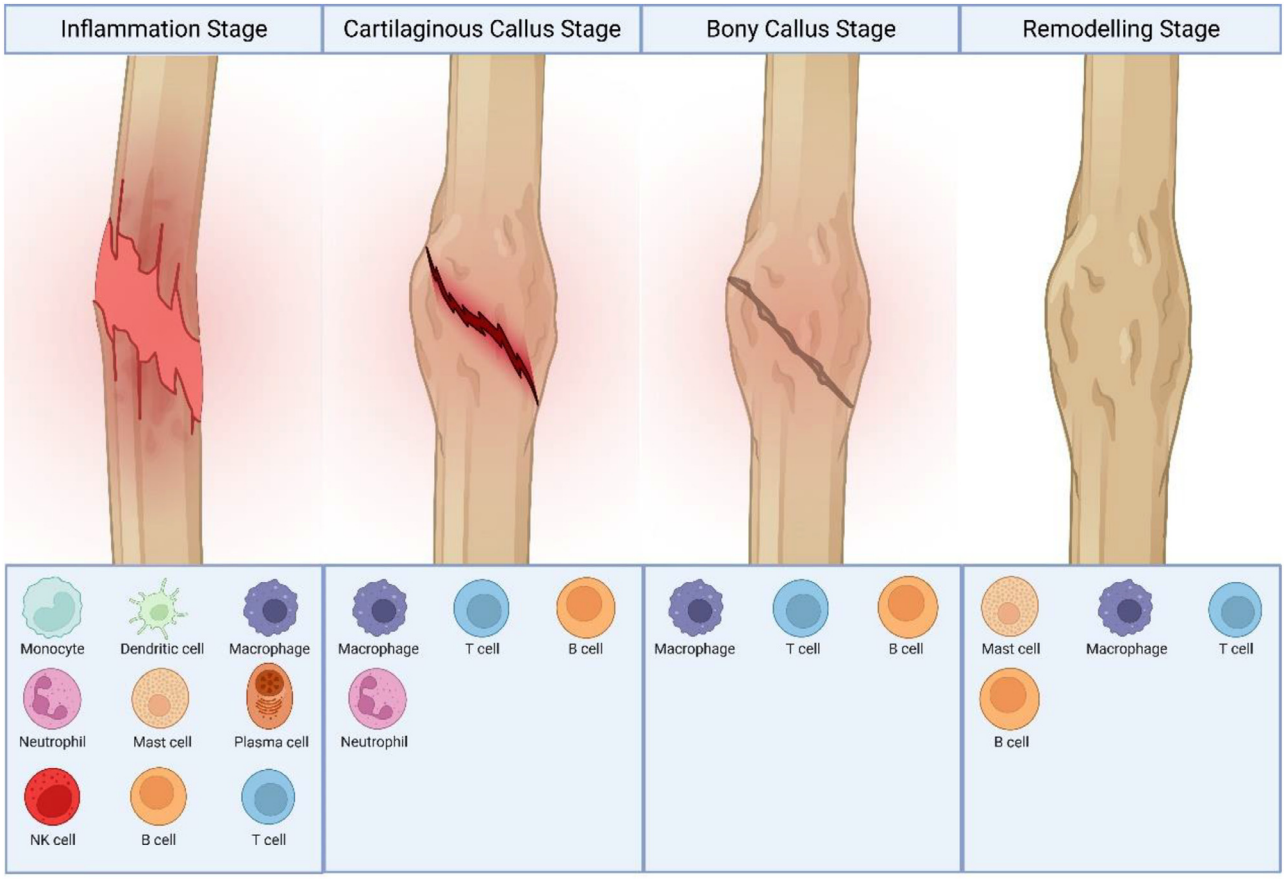

Fig. 3. Immune cells in different bone healing stages. Source: Created with BioRender.com.

and B cells launch adaptive immune responses once antigen-presenting cells have been activated. Generation of the T cell takes 3 to 28 days, whereas the generation of the B cell takes 3 to 5 days [123,124]. Unlike resident macrophages, which can potentially promote osteogenesis, circulating macrophages, typically classified as M1 type, are prone to stimulating inflammation and releasing inflammatory cytokines: IL-1, IL-6, macrophage colony-stimulating factor (M-CSF), TNF-α, to initiate the subsequent adaptive immune response [125,126]. Neutrophils attracted by IL-1 and TNF-α, contribute to the clearance of cellular and tissue debris. Under inflammatory conditions, neutrophils secrete a range

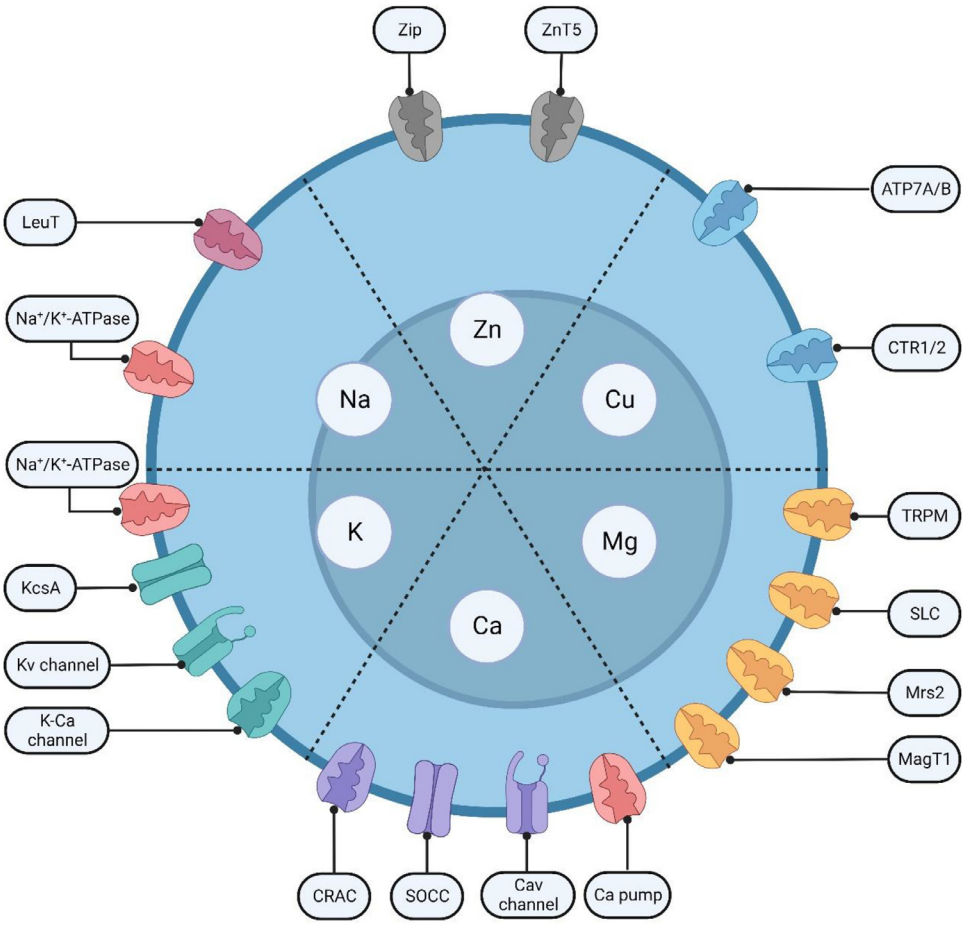

Fig. 4. Important ion channels and transporters on immune cells. Source: Created with BioRender.com.

of cytokines: IL-1, IL-6, IL-10, TNF-α, CCL2, CXC chemokine ligand 1α (CXCL-1α), and CCL4, to recruit monocytes and foster their differentiation into activated macrophages [85]. Upon the clearance of debris and pathogens, inflammation-induced cells and osteogenic cells collaborate to compose a cartilaginous callus. These cells secrete cytokines, including fibroblast growth factor (FGF), platelet derived growth factor (PDGF), and TGF-β, which foster the growth of granulation tissue and its transformation into a primary callus [18].

3.2. Cartilaginous callus formation

The cartilaginous callus formation stage serves as the initial phase in reestablishing bone continuity. Here, endothelial cells and fibroblasts create a sufficient blood supply within the granulation tissue, supporting nutrient metabolism. Concurrently, chondrocytes are drawn to the callus, stimulating chondrogenesis and endochondral ossification. This period sees an increased type II collagen expression and deposition of the cartilage matrix [127]. Meanwhile, the angiogenesis process is initiated with the production of a cluster of pro-angiogenic factors: VEGF, bone morphogenetic protein (BMPs), FGF-1, and TGF-β3 [128].

During this phase, macrophages continue to be present in the bone repair microenvironment. They play an immunomodulatory role and help remodel the cartilage callus. Working alongside neutrophils, they remove dead cells and debris left over from the inflammation stage [115]. While phagocytosis is a key function of macrophages, the cytokines they produce are also essential. These substances help regulate the metabolism of the fracture site's microenvironment and maintain bone homeostasis [129–131]. Inflammatory molecules: bacterial lipopolysaccharide (LPS), granulocyte-macrophage colony-stimulating factor (GM-CSF), IFN-γ, stimulate the formation of M1-type macrophages. By contrast, anti-inflammatory cytokines (IL-4, IL-13) promote the generation of M2-type macrophages. There's further polarization of regulatory and wound-healing M2 subtype macrophages to aid bone regeneration [111,132-135]. Lymphocytes also help to balance osteogenesis during the creation of the soft callus. T cells activate osteoclasts by producing receptor activator of nuclear factor-κB ligand (RANKL) for fibrin thrombus removal, while B cells secrete OPG, impacting the RANK/RANKL pathway by binding RANK receptors [123,136]. Despite B cells outnumbering T cells [136], various T cell phenotypes have significant roles during this phase. Helper T cells, in particular, crucially influence B cell development. IL-17, released by Th17 cells, has been demonstrated to induce osteoblast differentiation, simultaneously assisting in osteoblast maturation [137,138].

3.3. Bony callus formation

The process of bony callus formation, which follows the cartilaginous callus phase, begins with the infiltration of osteogenic cells. These cells prompt the cartilaginous callus to start endochondral ossification, leading to a more robust and rigid bony callus [105]. During this phase, chondrocytes transition into a hypertrophic state, expanding their size significantly by filling with collagen X. After another round of vascularization, hypertrophic chondrocytes release bone formation markers: alkaline phosphatase (ALP), osteopontin (OPN), osteocalcin (OCN), thereby stimulating the growth of the bony callus [139].

The fragile and pliable cartilaginous callus is resorbed by osteoclasts and immune cells [85]. As the inflammatory response subsides, the population of T and B lymphocytes declines. However, during the initial stage of callus formation, they reappear in the vicinity of the woven bone. The differentiation patterns of their subtypes undergo changes

compared to the inflammatory phase. The numbers of $CD4^+$ and $CD8^+$ *T* lymphocytes decrease while the proportion of Treg cells increases. Among B cells, the predominant population detected is naive B cells ($B220^+IgM^+IgD^+$). These lymphocytes reemerge in the callus and correlate with the inhibition of osteoclast formation in a time-dependent manner. This suggests that they may act on suppressing osteoclast activity and promoting osteogenic repair during the process of callus formation [123]. During callus formation, the differentiation of lymphocyte subtypes changes. Similar to the cartilaginous callus phase, M2 macrophages are the primary macrophage population observed during this stage, contributing significantly to tissue repair and regeneration [140]. In the subsequent phase, there is a transition from hyaline cartilage and woven bone to lamellar bone, which can be observed both histologically and mechanically. Similar to the cartilage callus formation phase, B lymphocytes infiltrate the luminal side of the callus. These B cells release RANKL and OPG to regulate the RANK/RANKL pathway [105].

3.4. Remodeling phase

During the remodeling phase, the initially formed woven bone hard callus transforms into a configuration of cortical and/or trabecular bone with a highly organized structure [105]. Osteoclasts originate from the monocyte-macrophage cell line with a function of decomposing bone tissue [141–143]. Simultaneously, osteogenic cells, particularly chondrocytes and osteoblasts, secrete matrix metalloproteinases (MMPs) to repair collagens and proteoglycans. The MMP superfamily, which includes matrix metalloproteinases 9 (MMP9) and MMP13, targets specific protein synthesis processes [144].

Immune cells that infiltrate during the remodeling phase also function within the osteogenic microenvironment. T and B lymphocytes primarily produce osteoclastogenesis inhibitory factor (OPG) and regulate the RANK/RANKL pathway leading to osteogenesis. Studies have illustrated that Th17 cells secrete IL-17, which can regulate the expression of RANKL, promote the generation and activation of osteoclasts, and aid in the reconstruction of new bone [52,145]. Meanwhile, macrophages that interact with osteoclasts promote remodeling and mineralization [140]. Mast cells reappear and enhance the resorption of the convex side of the callus [146,147].

4. Biometallic ions and immune cells

4.1. Alkali metals

The alkali metals constitute a group of elements that share striking similarities owing to the presence of a single outermost electron occupying an *s*-orbital, which readily undergoes ionization. This characteristic endows them with the lowest first ionization energies within their respective periods in the periodic table, primarily attributed to their low effective nuclear charges. The facile attainment of noble gas electronic configurations by relinquishing the outer electron further reinforces their unique behavior. However, the second outermost electron is situated within a filled electron shell, resulting in a significantly higher second ionization energy. Consequently, under typical conditions, alkali metals tend to form monovalent ions. Furthermore, as one progresses along the alkali metal series, an increasing trend is observed in both atomic radius and ionic radius, reflecting the larger spatial extent of the valence electron cloud.

In biological systems, alkali metal ions, notably sodium and potassium, are crucial for maintaining osmotic pressure and pH value. These ions interact with multiple ion channels and transporters on the cell membrane, thus necessitating meticulous regulation for basic homeostasis [148]. The atomic number of alkali metals influences their binding characteristics with biomacromolecules and their hydration preferences. Ion channels generally select one ion type based on its specific atomic radius. For instance, the leucine transporter (LeuT) transports leucine and Na^+ across the cell membrane in the same direction. Within the atomic structure of LeuT, Na^+ is surrounded by six oxygen atoms originating from the main-chain carbonyl or side-chain hydroxyl atoms. These oxygen atoms carry only a partial negative charge, sufficient to neutralize Na^+ with an average Na^+-O distance of 2.28 Å for each oxygen atom [149]. Similarly, K^+ channels, like KcsA K^+ channel, form a selective structure based on the atomic radius of K^+. The KcsA K^+ channel comprises four *K*+ binding sites in a row, forming a selectivity filter. Due to its larger atomic radius, K^+ can attract eight oxygen atoms surrounding the ion with an average K^+-O distance of 2.84 Å [149]. However, Li^+ has not been comprehensively studied via specific proteins transporting into the cell.

4.1.1. Lithium

4.1.1.1. physicochemical and physiological properties of lithium. Lithium, a metallic element, is the lightest and possesses the smallest ionic radius among alkali metals, exhibiting the lowest reactivity [150]. Like other alkali metals, it readily forms a cation (Li^+) by losing a single valence electron. However, due to the proximity of the electron to the nucleus, the reactivity of lithium is lower. Lithium's small atomic diameter results in relatively high solubility in solution. The basic physical and chemical properties of lithium ion, including its ionic radius and oxidation state, are presented in Table 1, along with the other ions discussed later. As a monovalent ion, lithium can compete with other metal ions [151]. For example, the interaction between magnesium and lithium can be explained by the "diagonal principle," suggesting that lithium ions may compete with magnesium ions in biomacromolecule synthesis or simply reduce the intracellular concentration of magnesium ions [152]. Furthermore, Li^+ can traverse cell membranes via Na^+ or K^+ ion channels due to their similar chemical properties, resulting in a vital role in ion homeostasis. Despite the exact lithium transport mechanism remaining elusive, eight major transmembrane transportation mechanisms have been identified: (1) Voltage-gated Na^+ channels and Epithelial Na^+ Channels, (2) kidney sodium-phosphate cotransporter, (3) sodium-lithium countertransport, (4) sodium-proton pump, (5) ENA transporters, (6) NHA1 antiporter, (7) sodium-calcium/lithium exchange on the mitochondrial membrane, (8) pentameric ligand-gated ion channels (Fig. 5a) [153].

4.1.1.2. Immunoregulation of lithium. Beyond its anti-infection effects, studies have explored lithium's impact on immune cells (Fig. 5b). Lithium has been studied extensively in the field of immunology for its potential therapeutic applications in mood regulation, cancer treatment, infections, and autoimmunity. Li^+ ions, either by directly competing with magnesium or by inducing serine phosphorylation, can effectively inhibit the activity of glycogen synthase kinase-3 beta (GSK3β). It conducts as a negative indicator of the Wnt signaling pathway [154]. Depending on the inhibition of GSK3β by Li^+, the NF-κB pathway activates by Li^+ ions via a reduction of inflammatory cytokines: IL-1β, IFN-γ, IL-6, and monocyte chemoattractant protein (MCP1), and simultaneously an increase of anti-inflammatory cytokines: arginase 1 (Arg-1), IL-10, leading to M2 type macrophage polarization [155]. Although most research suggests lithium's anti-inflammatory actions alleviate inflammation-induced disorders, some studies have indicated the pro-inflammatory effects of lithium. Petersein et al. noted that lithium ions increased inflammatory cytokines production either alone or in combination with antidepressants [156]. LiCl treatment decreased the proportion of NK cells by over 43% after the sixth day but increased them by 2.5-fold in comparison with the control group with a prolonged 21-day treatment [157]. This result showed that the immunomodulatory impact of lithium ions was dependent on time and dosage. Liu et al. reported an elevation of inflammatory cytokines in immature DCs when exposed to LiCl, resulting in an increased activation of monocyte-derived dendritic cells [154]. T and B lymphocytes can be affected by lithium ions as well [155]. Lithium compounds have been demonstrated to enhance the synthesis of IgG and IgM in B cells, along with the enhance-

Table 1
Atomic properties of biometal ions.

Ion	Atomic number	Electron configuration	Electronegativity (Pauling scale)	Oxidation states*	Atomic radius (Calculated)	Ionic radius**	Ionization energy (kJ/mol)		
Lithium	3	[He] $2s^1$	0.98	+1	167 pm	+1: 90 pm	1st: 520.2	2nd: 7298.1	3rd: 11,815
Sodium	11	[Ne] $3s^1$	0.93	−1, **±1**	190 pm	+1: 116 pm	1st: 495.8	2nd: 4562	3rd: 6910.3
Potassium	19	[Ar] $4s^1$	0.82	−1, **±1**	243 pm	+1: 152 pm	1st: 418.8	2nd: 3052	3rd: 4420
Magnesium	12	[Ne] $3s^2$	1.31	0, +1, **±2**	145 pm	+2: 86 pm	1st: 737.7	2nd: 1450.7	3rd: 7732.7
Calcium	20	[Ar] $4s^2$	1.00	+1, **±2**	194 pm	+2: 114 pm	1st: 589.8	2nd: 1145.4	3rd: 4912.4
Strontium	38	[Kr] $5s^2$	0.95	+1, **±2**	219 pm	+2: 132 pm	1st: 549.5	2nd: 1064.2	3rd: 4138
Vanadium	23	[Ar] $3d^3$ $4s^2$	1.63	−3, −1, 0, +1, **±2, ±3, ±4, ±5**	171 pm	+2: 93 pm +3: 78 pm +4: 72 pm +5: 68 pm	1st: 650.9	2nd: 1414	3rd: 2830
Iron	26	[Ar] $3d^6$ $4s^2$	1.83	−4, −2, −1, 0, +1, **±2, ±3**, +4, +5, +6, +7	156 pm	+2: 75 pm (ls) +2: 92 pm (hs) +3: 69 pm (ls) +3: 78.5 pm (hs)	1st: 762.5	2nd: 1561.9	3rd: 2957
Cobalt	27	[Ar] $3d^7$ $4s^2$	1.88	−3, −1, 0, +1, **±2, ±3**, +4, +5	152 pm	+2: 79 pm (ls) +2: 88.5 pm (hs) +3: 68.5 pm (ls) +3: 75 pm (hs)	1st: 760.4	2nd: 1648	3rd: 3232
Copper	29	[Ar] $3d^{10}$ $4s^1$	1.90	−2, 0, **±1, ±2**, +3, +4	145 pm	+1: 91 pm +2: 87 pm	1st: 745.5	2nd: 1957.9	3rd: 3555
Zinc	30	[Ar] $3d^{10}$ $4s^2$	1.65	−2, 0, +1, **±2**	142 pm	+2: 88 pm	1st: 906.4	2nd: 1733.3	3rd: 3833

* Underlined bold numbers: the usual number of valence electrons gained or lost by an atom under natural conditions.
** ls: low spin; hs: high spin.

Table 2
Interactions between biometal ions and immune cells.

Element classification	Ion	Innate immune cell			Adaptive immune cell	
		Neutrophil	Macrophage	NK cell	T lymphocyte	B lymphocyte
Alkali metal	Lithium		M2 polarization [155]	Proliferation [157]	Proliferation [158]	Cell activity [155]
	Sodium		Signal transduction, cytokine production [169]		Phonotype differentiation [169]	
	Potassium			Function [187]	Activation [185]	Proliferation [188]
Alkaline earth metal	Magnesium		M2 polarization [224]		Cell metabolism, signal transduction [228,229]	
	Calcium				Cytokine production, phonotype differentiation [251,252]	
	Strontium	N2 polarization [267]	M2 polarization [268,269]	Function [265]		
Transition metal	Vanadium	ROS production [277]			Function [279]	
	Iron		Phonotype polarization [305]		Differentiation, cell activity [305]	
	Cobalt	Signal transduction [314]	Phonotype polarization [316,318]			
	Copper	Proliferation, function [352]	M1 differentiation [316,352]		Proliferation, cytokine production [332]	
	Zinc	Chemotaxis, phagocytosis, and cytokine production [364]	Signal transduction [358]	Differentiation, proliferation [359]	Differentiation, proliferation [368]	Proliferation, signal transduction [370]

ment of B cell activity [155]. Li^+ inhibits GSK3 production and increases the production of β-catenin involved in the Wnt pathway to drive T cell proliferation [158]. Lithium ions exhibit distinct immunomodulatory effects on immune cells within both immune systems. An overview of the immunological regulatory properties of lithium ions, as well as other subsequent ions, can be found in Table 2.

4.1.1.3. Osteogenic effects of lithium. Studies validated the bone-protective function of the lithium ions [159]. Fig. 5c illustrates the regulatory role of lithium ions in osteoblastic-specific gene expression through signal pathways, which include the canonical Wnt/β-catenin pathway, BMP-2 signal pathway, and the PI3K/Akt pathway. Fig. 5d shows signal pathways of M-CSF, mitogen-activated protein kinase (MAPK), RANK/RANKL/OPG, NF-κB, and calcium signaling, which regulate osteoclast-specific gene expressions by lithium ions [159]. After being cultivated with Li^+, osteoblast precursor cells, and osteoblasts progressively released osteoblast development markers, including ALP, Runt-related transcription factor 2 (Runx-2), OCN, and collagen-1 [160]. Zhang J. et al. examined the ossification by bone marrow stromal cells (BMSCs) cocultured with lithium-doped nanosphere-containing materials [161]. Their results indicated that several genes, such as ALP, Runx-2, ALP, OCN, and OPN increased, suggesting that a Li^+ enriched environment had a beneficial influence on the development of osteoblastic cells. Loiselle et al. created a femur fracture model using connexin43 (Cx43) conditional gene knockout mice [162]. The Cx43 is extensively expressed in the bone-to-link bone matrix, hence Cx43-deficient animals with fractures had delayed union. Arioka et al. applied GSK-3 inhibitors LiCl and Li_2CO_3 in vitro and in vivo, respectively. The results illustrated that LiCl promoted osteoblast differentiation, and the application of Li_2CO_3 accelerated bone regeneration within local tibial bone defects of rats [163]. Pepersack et al. demonstrated that lithium ions reduced the resorption of fatal long bones via modulating parathyroid hormone (PTH) and prostaglandin E2 (PGE2). It has a full-blocking effect on vitamin D3-induced osteogenesis [164]. Lithium ion may be a potential factor for bone regeneration; however, inflammatory effects must be closely controlled. Table 3 lists the names

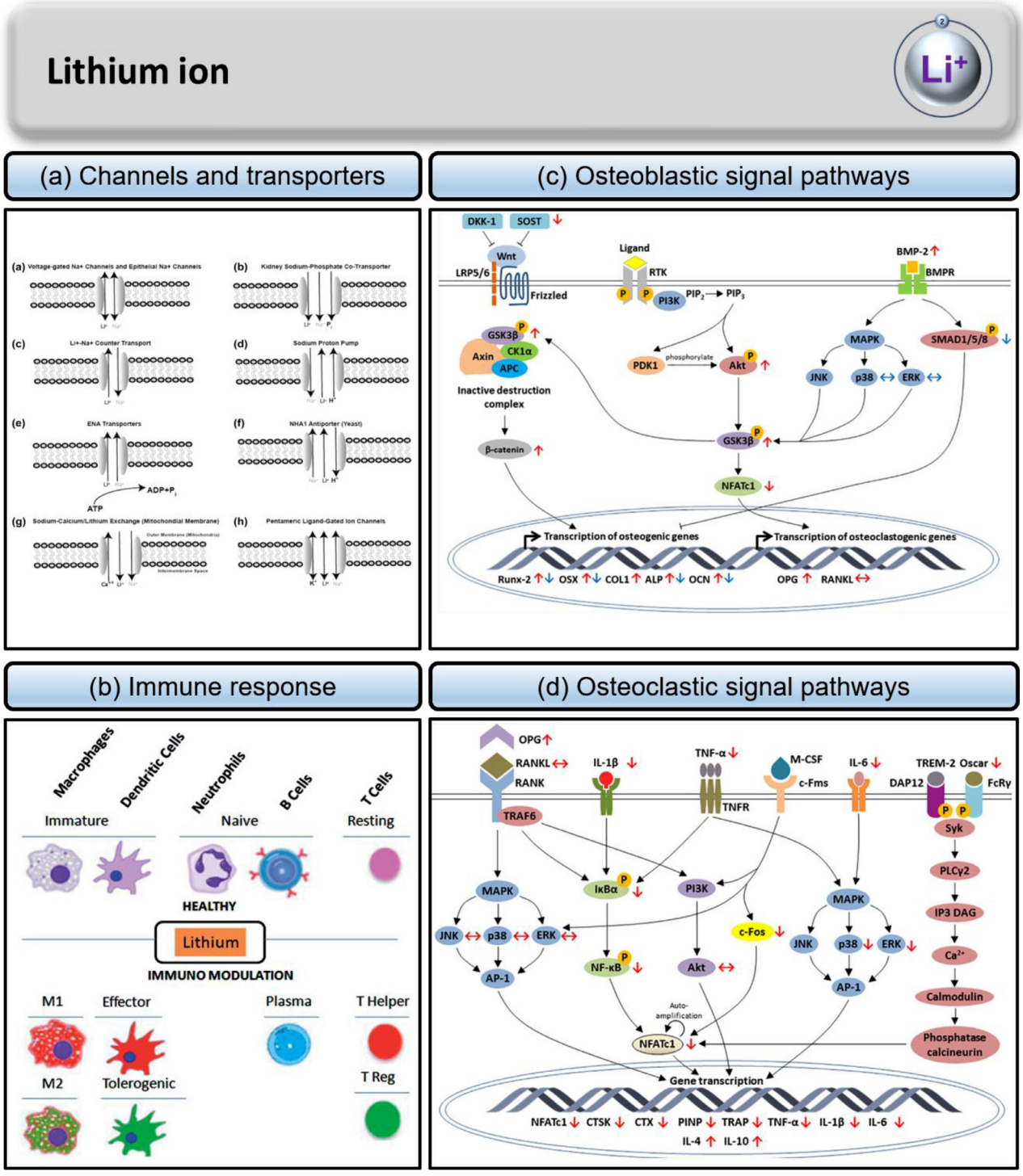

Fig. 5. Properties of lithium ion. (a) Ion channels and transporters of lithium ions on different cell membranes. Adopted from ref. [153], copyright 2023, Springer Nature. (b) Schematic diagram of the differentiation and response of immune cells in a healthy state or immunomodulation by lithium salts. Adopted from ref. [158], copyright 2023, Elsevier. (c) Schematic diagram showing the regulatory response of lithium ions in the osteoblastic-specific gene expression through three major signaling pathways. Adopted from ref. [159], copyright 2020, Frontiers Media S.A. (d) Schematic diagram showing the regulatory response of lithium ions in the osteoclastic-specific gene expression. Adopted from ref. [159], copyright 2020, Frontiers Media S.A.

and applications of lithium ion and other bioactive metal ions-related biomaterials.

4.1.2. Sodium

4.1.2.1. physicochemical and physiological properties of sodium. Sodium, also referred to as natrium (Na), has an atomic number of 11. It is characterized by an atomic radius of 186 pm, an ionic radius of 116 pm, and a covalent radius of 166 ± 9 pm. Like lithium, sodium readily ionizes, shedding one ion. Sodium homeostasis is of critical importance to organisms, as sodium and potassium ions maintain the osmotic pressure of the intracellular and extracellular fluid, regulating the membrane potential to ensure normal cell functions. It is the dominant cation in the

Table 3
Biometallic ion-related materials and their functions.

Element classification	Ion	Biometallic ion-related materials	Functions
Alkali metal	Lithium	Li^+ doped mesoporous silica nanospheres (LMSNs) [161]	Osteogenesis [161]
	Potassium	Kappa-carrageenan/chitosan/gelatin +KCl (KCG-KCl) [192]	Osteogenesis [192]
Alkaline earth metal	Magnesium	1. Magnesium-calcium phosphate cement (MCPC) [235] 2. Porous PLGA/TCP/Mg (PTM) scaffold [237] 3. PLGA/Mg-GA MOF scaffold [230] 4. Ultrapure magnesium pin [239]	1. Osteoimmunomodulation, osteogenesis, angiogenesis [235] 2. Osteogenesis, angiogenesis [237] 3. Osteogenesis, angiogenesis, anti-inflammation [230] 4. Neural regulation of osteogenesis [239]
	Calcium	1. β-Tricalcium phosphate (TCP) [261] 2. Hydroxyapatite (HA) [256] 3. HA nanoparticles (n-HA) [260]	1. Osteogenesis [261] 2. Immunomodulation, angiogenesis, osteoclastogenesis, osteogenesis [256] 3. Antitumor effect, osteogenesis [260]
	Strontium	1. Sr-crosslinked RGD with alginate hydrogel [268] 2. Sr-incorporated micro/nano titanium (SLA-Sr) [271]	1. Osteogenesis, anti-osteoclastogenesis, immunomodulation [268] 2. Immunomodulation, angiogenesis, osteogenesis [271]
Transition metal	Vanadium	Mesoporous bioactive glass doped Vanadium (V-MBG) [281]	Osteogenesis [281]
	Iron	Iron-matrix composites with silicate-based bioceramic particles [308]	Osteogenesis [308]
	Cobalt	1. Cobalt-doped bioactive borosilicate glass scaffolds [320] 2. Tricalcium phosphate scaffolds with cobalt (Co-TCP) [321]	1. Osteogenesis, angiogenesis [320] 2. Osteogenesis, angiogenesis [321]
	Copper	1. Cu-incorporated TCP [348] 2. Cu-containing bioactive glass ceramics (Cu-BGC) [340] 3. Implant surface self-assembled copper nanoparticles (CuS NP) and reduced graphene oxide (rGO) [347] 4. Copper containing bioactive glass [350]	1. Immunomodulation, Osteogenesis, angiogenesis, anti-osteoclastogenesis [348] 2. Osteochondral regeneration, anti-inflammation, immunomodulation [340] 3. Antibacterial, osteogenesis [347] 4. Antibacterial, osteogenesis, angiogenesis [350]
	Zinc	1. Zn-MEM [376] 2. Zinc silicate/nanohydroxyapatite/collagen (ZS/HA/Col) [377]	1. Osteogenesis [376] 2. Osteogenesis, angiogenesis, immunomodulation [377]

extracellular fluid regulated by a group of ion channels, transporters, and proteins on the cell membrane or within the cell. For instance, the Na^+/H^+ exchanger-3 (NHE-3) functions as an indirect Na^+ and HCO^{3-} reabsorption channel [165]. The Na^+/K^+-ATPase specifically selects K^+ and Na^+ while allowing other ions to flow through the pump. The pump consumes adenosine triphosphatase (ATP) to export 3 Na^+ and import 2 K^+ to generate an electrochemical gradient [166]. The Na^+/K^+-ATPase maintains a sodium concentration ratio of 1:10 between the intracellular and extracellular environments of the cell so that its activity remains stable [166]. Fig. 4 represents the transporters and channels on immune cells.

Additionally, a protein named glycosaminoglycans (GAGs) permits Na^+ to bind due to its negative charge, leading to non-osmotic behavior in the microenvironment and assisting in the redistribution of Na^+ in the local area. Disruption of sodium balance in humans can lead to hypernatremia (water loss) or hyponatremia (water absorption), which disrupts osmoregulation and causes severe dysfunction of multiple systems [167]. Overconsumption of sodium can damage the immune barriers and the defense functions of immune cells and immune organs, resulting in an imbalance of immune responses (Fig. 6a). The accumulation of Na^+ in the skin promotes vascular endothelial growth factor C (VEGFC) release and nitric oxide (NO) [168].

4.1.2.2. Immunoregulation of sodium. Overdose of Na^+ intake can seriously impede the function of immune cells and target organs [166]. Fig. 6c illustrates changes in both the classical pathway of pro-inflammatory macrophage activation and the alternative pathway of anti-inflammatory macrophage activation under high NaCl conditions [169]. Classically activated macrophages express inflammatory cytokines such as TNF, IL-6, and IL-1β via the NF-κB and AP1 pathway, and then release NO via NOS2. In a high NaCl environment, signals upregulate the nuclear factor of activated T cells 5 (NFAT5) and heterodimeric transcription factor AP1 through the p38 pathway. This increases the production of NO and TNF beyond normal levels, exacerbating inflammation. Additionally, NaCl activates inflammasomes: NOD-like receptor thermal protein domain associated protein 3 (NLRP3) and NLRP4, which induce subsequent Caspase 1 activation and ultimately IL-1β production. These signaling pathways lead to a more inflammatory environment, thus enhancing pathogen clearance and Th17 cell differentiation through the upregulation of IL-1β. Alternatively activated macrophages, known for their tendency to produce anti-inflammatory cytokines, can suppress the expression of STAT6 by inhibiting the AKT-mTOR signaling pathway. This regulatory effect is also implicated as a contributing factor in delayed wound healing. In Fig. 6d, the polarization of Th17 and Treg cells in a high NaCl microenvironment is depicted. IL-23 and its receptor IL-23R are inhibited by the transcription factor FoxO1 through the RORγt pathway. In a high salinity environment, extracellular sodium ions enter Th17 cells and inhibit the activity of FOXO1, which allows RORγt to produce more IL-23R and promotes Th17 cell differentiation. In contrast, Treg cells are affected by a high sodium ion environment, losing their normal regulatory function and transforming into a Th1-like morphology. In a high salt environment, sodium mediates the production of the serum/glucocorticoid-regulated kinase 1 (SGK1) and inhibits its normal function by phosphorylating FOXO1 and FOXO3, thereby reducing the stability of FOXP3. Following this process, salt-stimulated Treg cells reduce IL-10 and TGF-β production, generate IFN-γ, and adopt a Th1-like phenotype [169].

4.1.2.3. Effects of sodium on bone tissue regeneration. Orthopedic implant materials containing sodium, especially alginate hydrogel, are frequently used in bone repair. However, abnormal local concentrations of Na^+, whether too high or too low, can negatively impact the healing of bone defects. Evidence suggests that chronic hyponatremia (low sodium levels) is linked to fractures, particularly in the elderly population. This

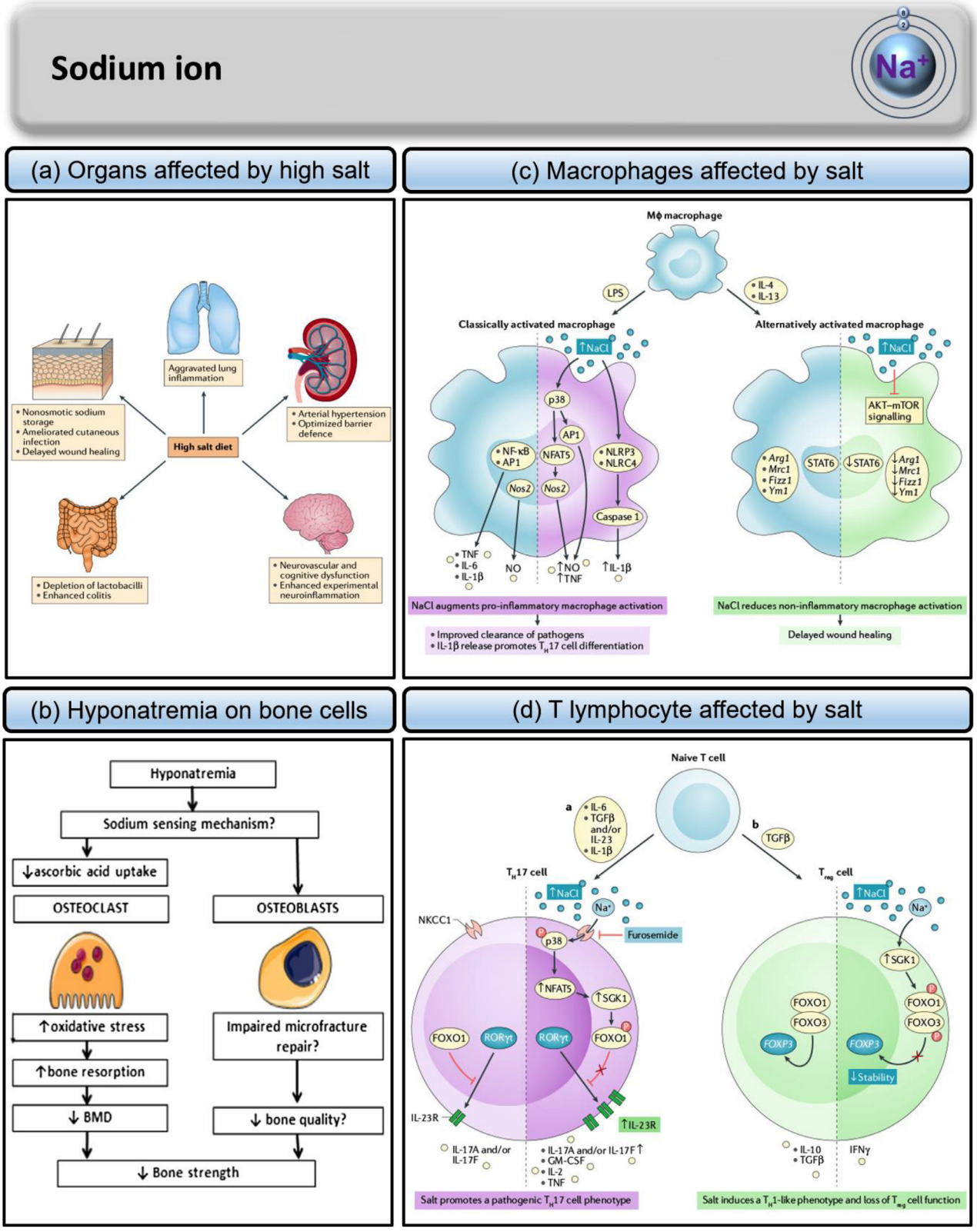

Fig. 6. Properties of sodium ion. (a) Schematic diagram of high salt (sodium chloride) diet disturbing the function of local barriers, immune cells, and epithelial cells of organs (skin, lung, kidney, central nervous system, and gut), and subsequently influencing the balance of immune responses. Adopted from ref. [168], copyright 2019, Springer Nature. (b) Flowchart illustrating how hyponatremia induces osteoclast formation and inhibits osteoblasts, hence reducing bone strength. Adopted from ref. [171], copyright 2016, Springer Nature. (c) Conceptual diagram showing macrophage differentiation in response to a high salt environment. Adopted from ref. [169], copyright 2019, Springer Nature. (d) Conceptual graph of a propensity for naive T cells to polarize into either Th17 cells or Treg cells under high salt conditions. Adopted from ref. [169], copyright 2019, Springer Nature.

may be due to hyponatremia causing mild cognitive impairment, leading to gait instability and falls, or it may directly cause osteoporosis by mobilizing sodium stores in bone tissue. Additionally, low extracellular sodium stimulation can stimulate osteoclast formation as well as bone resorption (Fig. 6b) [170–172]. High sodium intake is a recognized risk factor for osteoporosis. Cui et al. illustrated that ovariectomized rats fed a high-salt diet showed disruption in bone microarchitecture and increased urinary calcium excretion. At the same time, the expressions of sodium channel ENaCα and voltage-gated chloride channel ClC-3 were up-regulated, while the expressions of sodium-chloride cotransporter (NCC) and sodium-calcium exchanger (NCX1) were down-regulated in epithelial cells [173]. Although no direct evidence shows that degraded hydrogels or other sodium-containing materials hinder bone regeneration, the impact of changes in sodium concentration on bone suggests that the accumulation of sodium ions through a long-term utilization of these materials should not be overlooked [174–176].

4.1.3. Potassium

4.1.3.1. physicochemical and physiological properties of potassium. Potassium (K) is the second most abundant alkali metal element in humans. It possesses an atomic radius of approximately 227 picometers (pm), an ionic radius of around 152 pm, and a covalent radius of approximately 203±12 pm. These measurements provide the spatial distribution and size of potassium atoms or ions in various physiological contexts. Potassium is prone to losing its outermost electron to form potassium ions. Fig. 7a illustrates the measurement and process of potassium uptake, exchange in the body, and excretion [177]. The concentration of K^+ within the cell, which ranges from 140 to 150 mmol/L, is significantly higher than in the extracellular matrix ranging from 3.5 to 5.5 mmol/L [178]. This vast disparity is maintained by K^+ channels, which monitor and control the flow of K^+. This transfer of K^+ across the cell membrane balances fluctuations in electric potential and is key to the function of muscular, neuronal, and cardiovascular cells [179]. In addition, K^+ is largely involved in physiological activities, such as hormone secretion, maintenance of blood pressure homeostasis, gastrointestinal motility, nutrient metabolism, and water-electrolyte balance.

4.1.3.2. Potassium ion channels. There are two types of K^+ channels: Passive K^+ leak channels and active ion transport channels of Na^+/K^+-ATPase (Fig. 7b) [180]. Passive transport involves the movement of potassium ions, facilitated by the cell membrane's permeability and ionophore proteins. On the other hand, active transport is an ATP-dependent mode, typically involving Na^+/K^+-ATPase pumps. These pumps transport potassium ions from a low concentration region (the extracellular environment) to a high concentration region (the intracellular environment), thus creating a high-potassium environment within cells [181].

4.1.3.3. immunoregulation of potassium. Potassium ions and their regulation via potassium ion channels are vital for immune cell functions [182]. The K^+ concentration within immune cells is regulated by voltage-gated channels: (Kv1.3, Kv1.5), calcium-dependent channels, calcium-activated K^+ channels (KCa3.1, KCa1.1, IKCa1), and calcium release-activated channels (CRAC) [183,184]. T cells are influenced by nearby dying cells, which release more potassium ions into the microenvironment. This increased influx of K^+ into T cells via pump or leak channels inhibits T cell activation and tumor-killing ability by suppressing protein phosphatase 2A (PP2A), and Akt and mTOR protein kinase-related signaling pathways (Fig. 7c). Kv1.3 is the predominant subset of Kv channels in resting T cells, while IKCa1 is dominant in activated T cells. The apoptosis of T cells may be governed by the loss of intracellular K^+ via Kv1.3 channels [185]. Macrophages have been found to express K^+ channels (Kv1.3, Kv1.5, KCa1.1), which could serve as drug binding sites for altering their phenotypes [186]. The membrane of NK cells contains Kv1.3 channels, and the inhibition of non-specific Kv channels reduces the cytotoxicity of NK cells [187]. Memory B cells expressed around 2500 Kv1.3 channels at rest, with expression increasing upon activation [188].

4.1.3.4. Effects of potassium on bone tissue regeneration. Potassium supplementation may promote bone formation. In a clinical study of the relationship between potassium content consumption and bone mineral density (BMD), researchers divided the enrolled population into three groups according to dietary potassium intake, and people with higher dietary potassium intake showed higher BMD [189]. In exploring the mechanism of BCP in promoting osteoinduction, researchers discovered that BCP induced PP2A upregulation to dephosphorylate and prevent endocytosis of the Na^+/K^+-ATPase, thereby maintaining its activation. Activating Na^+/K^+-ATPase of mouse MSCs enhanced osteogenic gene expression and calcium deposition, improving osteogenesis [190]. Few studies have directly applied potassium ions as the major component of bone tissue engineering materials. However, potassium ions can exhibit distinctive physical and chemical properties from sodium ions in materials [191]. A 3D scaffold composed of Kappa-carrageenan, chitosan, and gelatin crosslinked with potassium chloride (KCl) was prepared for bone tissue regeneration. Compared to scaffolds without crosslinked KCl, this material demonstrated superior mechanical properties and osteogenic differentiation potential [192].

4.2. Alkaline earth metals

Alkaline earth metals make up six elements in group 2 of the periodic table: beryllium (Be), magnesium (Mg), calcium (Ca), strontium (Sr), barium (Ba), and radium (Ra). These metals show a tendency to lose electrons and thus form doubly charged positive ions because their outer S-orbitals accommodate two electrons [151]. In their respective periods, they possess the second lowest first ionization energy of elements, which is mainly attributed to their low effective nuclear charge and their ability to achieve a stable outer shell configuration via losing these two electrons [151,195]. With the exception of beryllium, all alkaline earth metals can react with halides to formulate alkaline earth metal halides, or with water to form strongly alkaline hydroxides.

These elements' relatively stable atomic orbital structure and ionic properties allow them to play a regulatory character in organisms. Deficiency of certain metal components, such as magnesium, calcium, and strontium, can induce diseases [196]. Hypomagnesemia, characterized by a decreased level of magnesium in the blood, is common in the general public, accounting for 2.5% to 15% of cases. Most patients are asymptomatic with hypomagnesemia, but symptoms of neuromuscular, cardiovascular, and metabolic dysfunction can occur [197]. Magnesium sulfate has been applied in the relief of rapid atrial fibrillation and for pain relief [198,199]. Since calcium is required for bone development, many bone-related diseases are associated with organic calcium matrices and hydroxyapatite (HA) in bone structures or tissues [200]. Conditions such as osteoporosis require additional calcium supplementation to treat the loss or deficiency of calcium, and the treatment of fractures also involves calcium supplementation to support bone formation [201]. For pharmaceutical applications, absorbable calcium compounds are more beneficial for the treatment of these diseases [202,203]. Strontium ranelate has demonstrated the potential to enhance bone growth and BMD. However, it is important to note that it can also lead to a decline in the calcium ratio within bone. The long-term biological effects of strontium ranelate are still under investigation and require further study to fully understand its comprehensive impact [204,205].

4.2.1. Magnesium

4.2.1.1. physicochemical and physiological properties of magnesium. Magnesium ion (Mg^{2+}) is the fourth most abundant cation in humans, following calcium, potassium, and sodium ions [206]. The atomic radius of magnesium is approximately 160 pm, while its ionic radius is around 86 pm. In terms of covalent radius, magnesium has a value of 141±7 pm. It typically loses two electrons to form a stable magnesium divalent

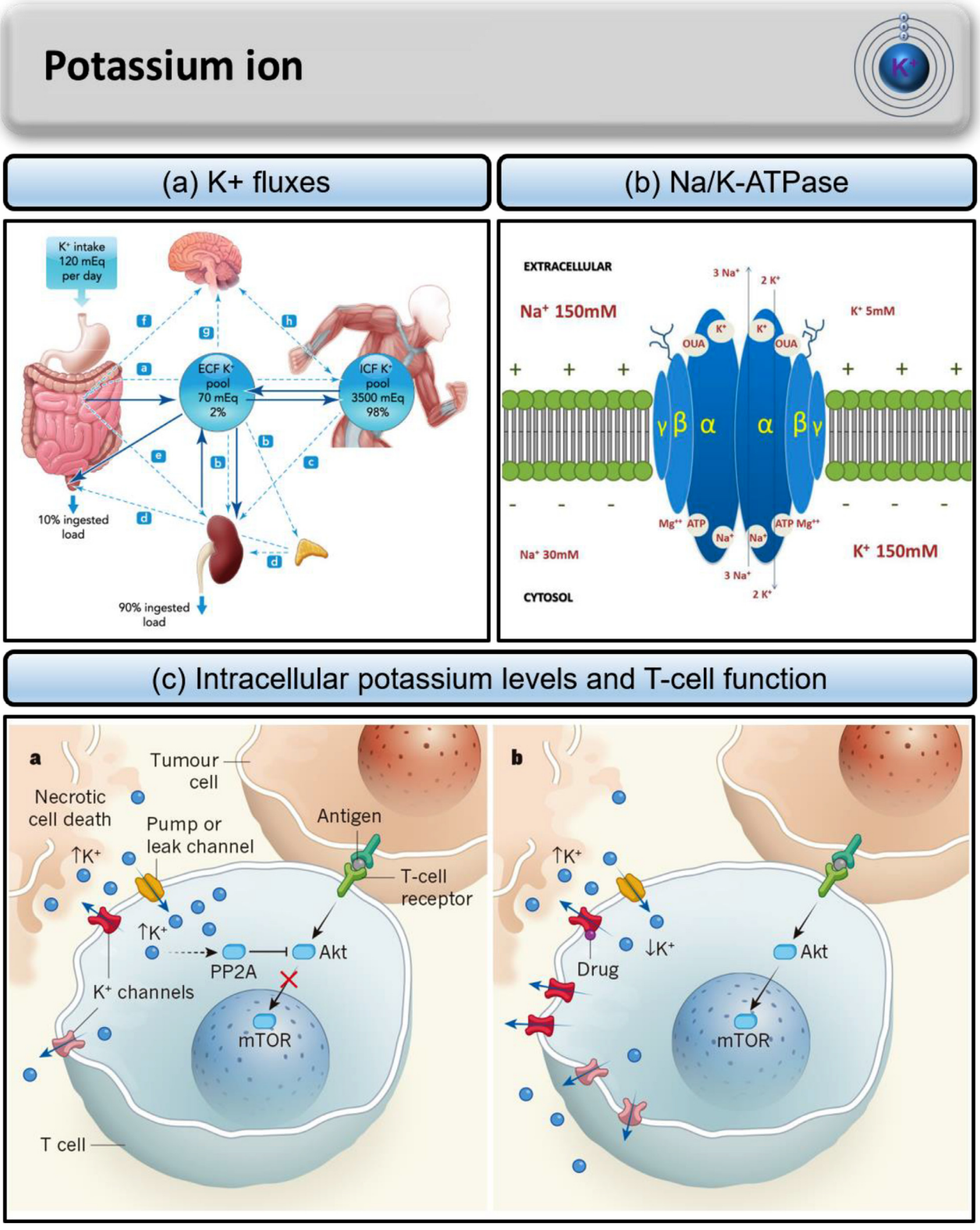

Fig. 7. Properties of potassium ion. (a) Schematic representation of the overall intersection of potassium uptake, flow, and excretion between organs. Adopted from ref. [177], copyright 2020, The American Physiological Society. (b) Scheme of Na/K-ATPase with α-subunits and cardiac glycosides. Adopted from ref. [193], copyright 2017, Frontiers Media S.A. (c) **a.** Schematic depicting tumor cells undergoing necrotic cell death releasing a high level of K^+ into the microenvironment, which contributes to a high intracellular K^+ concentration of T cells. **b.** Scheme of pharmacological stimulation for the overexpression of voltage-gated K^+ channels and calcium-activated K^+ channels, resulting in intracellular K^+ concentration decrease and normalization of T cell function. Adopted from ref. [194], copyright 2016, Springer Nature.

cation (Mg^{2+}). Approximate magnesium storage in the body is about 25 g distributed in organs and tissues, with 65% found in the bone matrix and 32% in macromolecules like nucleic acids, proteins, and lipids [207,208].

Compared to adjacent elements in the periodic table, such as Li, Na, K, and Ca, magnesium has a smaller ionic radius but larger hydration energy than calcium (0.86 vs 1.14 Å for Ca, −1922 vs −1592 kJ/mol, respectively) [206]. In the structure of hydrous $MgSO_4$ or $MgCl_2$, magnesium ions are bound to 6 or 7 molecules of H_2O, respectively, whereas calcium and beryllium ions, in the case of $CaCl_2$ or $BaCl_2$, are coordinated to 2 or 1 mol of H_2O, respectively [206]. Mg-H_2O coordination yields a typical octahedral conformation and exhibits a slower rate of exchange of H_2O molecules than other metal ions. This phenomenon makes magnesium have a larger occupancy and more stable biological properties in the organism [206]. Additionally, the hydrated radius of a magnesium ion is approximately 400 times greater than its dehydrated radius. This significant difference in size necessitates energy to dehydrate the ion before it can pass through channels and transporters. Consequently, this size disparity can hinder the potential functional role of magnesium ions in signal pathways [209].

At the cellular level, magnesium exerts profound regulatory effects on biological processes, encompassing cell proliferation, differentiation, and survival. It serves as a cofactor or activator with multiple enzymes in DNA and RNA synthesis, amino acid metabolism, as well as the intricate pathways governing sugar, protein, and lipid metabolism. Magnesium's involvement in these fundamental cellular processes underscores its indispensability for maintaining optimal cellular function, ensuring proper cellular growth and development, and facilitating the intricate interplay of metabolic pathways essential for cellular homeostasis [210]. Magnesium is a structural component of numerous biological macromolecules in stabilizing and modifying structures [211]. Additionally, magnesium is involved in energy metabolism by forming the Mg-ATP2 complex or regulating ATP distribution through the modulation of ATP-Mg/Pi carrier activity [212]. It can also act as a second messenger to transduce cell signals, mediate downstream molecule activation, and neural regulation [213], and regulate cell apoptosis [214]. In addition, magnesium ions influence ion stability of cell membranes, including regulation of ion channel activity, and resistance of calcium ions [215].

4.2.1.2. Magnesium transporters. Studies have illustrated numerous magnesium transporters on the cell membrane [216]. Magnesium transporter 1 (MagT1) is widely expressed in human cells and selectively transports Mg^{2+} with voltage-dependent and pH-dependent inward currents [217]. It has profoundly been found that immune cells (typically B and T cells) express MagT1 (spleen and thymus), mediating magnesium ion metabolism and signaling transduction [218]. SLC41A1 and SLC41A2 are part of the human solute carrier (SLC) family, which comprises over 300 transporters and more than fifty subgroups of membrane transport proteins [219]. The TRPM family is a significant part of transient receptor potential (TRP) channels, which include TRPM1-TRPM8, and are widely expressed on cells [219]. These channels participate in cellular regulatory processes, such as proliferation, metastasis, invasion, and death [220]. Among them, transient receptor potential cation channels M6 (TRPM6) and M7 (TRPM7) are characteristic, as they both possess ion channels and are permeable to Mg^{2+}, Zn^{2+}, and Ca^{2+} [221]. Studies have shown that these two channels regulate Mg ions at a cellular level, and mutations in their genes can cause diseases related to magnesium ion metabolism [222].

4.2.1.3. Immunoregulation of magnesium. Magnesium has a profound impact on the immune system, influencing a group of immune cells and mediating cell proliferation, metabolism, subtype changes, and cell death in conjunction with the above mentioned magnesium-ion-related channels [223]. Fig. 8d illustrates the magnesium transporters of immune cells and their roles in immune-receptor signaling. Magnesium signals can mediate the opening process of calcium (Ca^{2+}) channels in the endoplasmic reticulum (ER), leading to the release of Ca^{2+} into the cytoplasm and the influx of Ca^{2+} into CRAC channels. Magnesium-related channels, including MagT1, TRPM6/7, and SLC41A1/A2, are significant channels in immune cells that regulate the transport of magnesium ions in the intracellular and extracellular environment [216]. In bone marrow-derived macrophages, high TRPM7-like currents were detected due to Mg^{2+} regulation, which increased the amount of the cytokine IL-43. applying TRPM7 blockers (NS8593 and FTY720) resulted in a decline in cell proliferation, cytokine release, and the formation of M2 type macrophages [224]. Individuals with insufficient TRPM6 were found to be susceptible to seizures or even death in the absence of Mg^{2+} [225]. In experiments with human Jurkat T cells, biphasic Mg^{2+} dose-response curves were observed in the absence of TRPM7 current [226]. Magnesium via TRPM7 induces M2 subtype polarization of macrophages and promotes osteogenesis in the early stage of the experimental period [227]. A particular X-linked human immunodeficiency disease characterized by CD4 lymphocytopenia is caused by a congenital deletion of the MagT1 gene, leading to an insufficiency of magnesium influx associated with the engagement of antigen receptors upon $CD4^+$ *T* cells. This discovery underlines the role of magnesium ions as second messengers [228]. Recent research indicated that tumor cells can inhibit the typical killing capabilities of activated $CD8^+$ *T* lymphocytes by accumulating Mg^{2+} and blocking its normal metabolism, thereby proliferating and evading the immune system [229].

4.2.1.4. Osteogenic effect of magnesium. Magnesium ions have been extensively investigated in osteogenesis, angiogenesis, and anti-inflammatory processes. This has led to the exposure of innovative bone regeneration materials [230–234]. Several magnesium-based materials have been developed, leveraging the osteogenic effects of magnesium. For instance, a magnesium-containing calcium phosphate cement was proposed by Wang M. et al. They observed that the secretion level of TNF-α and IL-6 decreased when macrophages were cultured with extracts of magnesium-calcium phosphate cement (MCPC), while the expression of bone repair-related cytokine TGF-β1 increased [235]. It was also found that the influence of Mg^{2+} on macrophages is dose-dependent, with higher concentrations (20 mM) inhibiting macrophage polarization toward M1 more effectively than lower concentrations (5–10 mM) [236]. This demonstrated that Mg^{2+} might participate in the application of novel materials regulating osteogenesis and the immune response. Further, a PLGA/Mg-GA MOF scaffold was synthesized. When implanted into the defective site, the scaffold was phagocytosed by adherent cells, releasing exosomes, Mg^{2+}, and gallic acid (GA), enhancing osseointegration, angiogenesis, and anti-inflammatory ability [230]. Another study reported a porous PLGA/TCP/Mg (PTM) scaffold for bone defect repair. PTM increased blood perfusion and promoted neovascularization seen at 8 weeks after operation. After 12 weeks, PTM significantly promoted new bone formation and improved its mechanical properties [237].

Magnesium has also been reported to improve osteogenesis in an osteoimmunological manner. Following different stages of the bone healing process, Mg^{2+} regulates cytokine production by monocytes/macrophages and thereby influences the metabolic balance of osteoblasts and osteoclasts. Fig. 8c illustrates the process of Mg-mediated immune response regulating bone remodeling at the cellular and subcellular levels. In this process, magnesium ions enter cells through the TRPM7 channel, mediating the release of M7CK protein to promote the phosphorylation of H3S10, thereby promoting the transcription of inflammatory genes [227]. In another study, it was observed that magnesium exerted inhibitory effects on macrophage activation. This was evident by a notable reduction in the proportion of CCR7-positive cells, whilst the decrease of CD206-positive cells was comparatively less pronounced [238].

Based on the good osteogenic effect of Mg based materials, some articles have carried out in-depth research and discussion on the related mechanism of osteogenesis. Zhang et al. tested an ultrapure magnesium

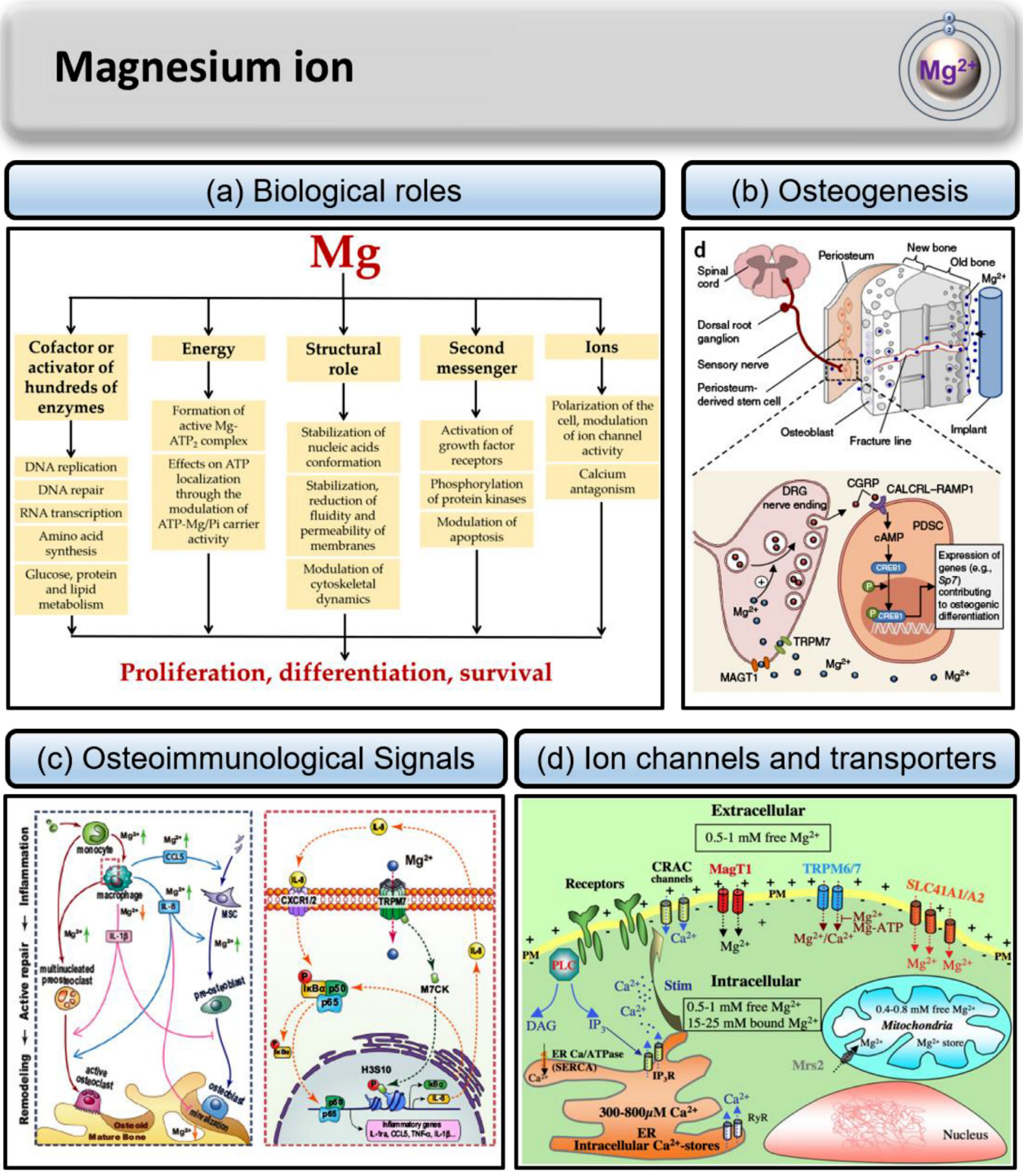

Fig. 8. Properties of magnesium ion. (a) Schematic diagram of Mg^{2+} involved in enzyme metabolism, energy conversion, macromolecular structure formation, signal transduction, and ion metabolism, ultimately affecting cell proliferation, differentiation, and survival. Adopted from ref. [240], copyright 2021, Elsevier. (b) Schematic of implant-derived Mg^{2+} entering DRG neurons via magnesium transporters or channels, promoting calcitonin gene-related peptide (CGRP) vesicles release and activating CGRP receptors within the periosteum, leading to osteogenesis-related genes expression. Adopted from ref. [239], copyright 2016, Springer Nature. (c) Schematic of macrophages and MSCs involving in the whole stages of bone repair process regulated by Mg^{2+} (left panel) and the process of magnesium entering cells through ion channels: CXC chemokine receptor 1/2 (CXCR1/2) and TRPM7, and participating in the transcriptional regulation of inflammation-related genes under the microstructure (right panel). Adopted from ref. [227], copyright 2020, Springer Nature. (d) Symbolized schematic diagram of different types of receptors, transporters, and channels on the ER, inner mitochondria, and plasma membrane of an immunocyte, and the range of Mg^{2+} concentrations in each part. Adopted from ref. [216], copyright 2012, Springer Nature.

pin in a rat model. The findings revealed a noteworthy occurrence of new bone regeneration in the cortical bone following the implantation. The increased presence of extracellular magnesium ions in ipsilateral dorsal root ganglion (DRG) neurons stimulated MagT1-dependent and TRPM7-dependent entry of magnesium ions, leading to an elevation in intracellular ATP levels and the terminal synaptic vesicles accumulation [239]. Mg ions via MagT1 or TRPM7 regulated vesica releasing at the DRG nerve ending and alter gene expression contributing to osteogenic differentiation (Fig. 8b). A study reveals a biphasic action pattern of Mg ions in bone regeneration [227]. Mg ions upregulated TRPM7 at the early stage of inflammation and promote TRPM7-dependent Mg^{2+} ion influx into the mononuclear-macrophage lineage. In the advanced phase of osteogenic healing, the prolonged presence of magnesium ions has been found to have detrimental effects. It can excessively activate the NF-κB signal pathway among macrophages, which in turn leads to an increased formation of osteoclast-like cells.

4.2.2. Calcium

4.2.2.1. physicochemical and physiological properties of calcium. Calcium is an alkaline earth metal known for its active nature with an atomic radius of 197 pm, an ionic radius of 114 pm, and a covalent radius of 176±10 pm. Calcium and magnesium belong to the same main group, sharing some basic chemical properties. Calcium has two easily losable valence electrons in its outermost *s*-orbital, making it prone to form a dipositive ion (Ca^{2+}) under most conditions. Calcium ions are among the most prevalent metal ions in humans, as a second messenger in regulating the proper functions of organs and body cells [151,241]. Ca^{2+} signaling regulates physiological processes such as blood clotting, nerve transmission, heart rhythm, and muscle contraction and relaxation (Fig. 9a). At the cellular level, calcium acts as a component of proteins and enzymes to maintain protein conformation stability and exert biological effects. Some proteins can bind calcium ions directly or chelate calcium ions with amino acid residues, including trypsin, osteocalcin, osteopontin, and bone sialoprotein [151]. Calcium regulation in vivo is controlled by thyroid hormones, and calcitonin is used to maintain calcium homeostasis in the human body [242].

4.2.2.2. Calcium transporters. Calcium ion channels and transporters control Ca^{2+} homeostasis. Typically, a specific cell type selects a distinct combination of channels that suits its biological roles. For instance, as lymphocytes polarize and activate, both the type and content of calcium channels on T cells change. The expression of calcium release-activated calcium modulator 1 (CRACM1), CRACM2, and CRACM3 on mouse double-positive lymphocytes changes as they develop into $CD4^{+}T$ cells. Meanwhile, its STIM2 expression changes from negative to positive. Human lymphocytes show similar characteristics with CRACM1 and CRACM3 expression increasing in response to $CD4^{+}T$ cell activation [243]. Fig. 9d summarizes the channels on lymphocytes that control the flux of calcium ions. On the plasma membrane, the types of channels involved in calcium transfer include SOCE, transient receptor potential channel 1 (TRPC1) (whose categorization as either SOCE or ROCE is not yet determined), non-store-operated channels, and ion exchangers. On the ER membrane, the calcium release channel, calcium pump, and STIM1 (the sensor of stored calcium) all participate in calcium transport. Calcium ion exchangers and Ca^{2+} uptake channels are shown on the mitochondrial membrane [243]. Calcium ion channels are divided into store-operated Ca^{2+} channels (SOCCs) and non-store-operated Ca^{2+} channels. SOCCs are widely observed in signaling transport in response to the "store-depletion" effect, representing the biological effects of calcium storage and release to the cytoplasm from ER [244]. CRAC channels are expressed on lymphocytes and serve as a member of the SOCC channel family. Non-store-operated Ca^{2+} channels, including P2 receptors, TRPV6, TRPM2, TRPM7, CARC channels, Ins(1,4,5)P3R, voltage-operated Ca^{2+} channels (Cav) as well, primarily facilitate non-selective cation influx. In addition, some indirect channels also control the balance of calcium ions. Operated by calcium pumps, Ca^{2+} can be pumped out of the cell to maintain a balance of Ca^{2+} concentrations in the extracellular fluid (about 1 mM) and the ER (about 100 nM) [245]. These calcium channels, pumps, and receptors interact with each other to maintain the functional integrity of cell signaling.

4.2.2.3. immunoregulation of calcium. Calcium is regulated by ion channels in immune cells and influences downstream signal transduction, leading to changes in gene expression and protein products [246]. CRAC channels manage the intracellular Ca^{2+} increase in lymphocytes [247]. Store-operated Ca^{2+} entry (SOCE), facilitated by the influx of calcium ions (Ca^{2+}) through CRAC channels, exerts profound regulatory influence on T cell dynamics by orchestrating the activation of Ca^{2+}-dependent transcription factors and finely modulating gene expression [248–250]. Beyond its impact on gene regulation, the SOCE-mediated differentiation pathways intricately shape the fate of T cells, steering them towards specific subtypes (Tfh cells, Treg cells) [251]. Fig. 9b visually encapsulates the intricate interplay of SOCE in governing the functional repertoire of conventional and murine regulatory T cells. Although thymus-derived naive T cells appear to be largely unaffected by SOCE, differentiation of peripheral naive T cells into follicular regulatory T cells (Tfr) or induced regulatory T cells (iTreg) unequivocally depends on the fine-tuned orchestration by SOCE. Furthermore, the versatile thymus-derived regulatory T cells (tTregs) demonstrate remarkable plasticity, enabling their differentiation into specialized subtypes of effector regulatory T cells, such as Tfr cells involved in germinal center responses, and tissue-resident Treg cells (tissue Treg) dedicated to the maintenance of tissue-specific organ homeostasis. These intricately modulated T cell subsets serve as pivotal gatekeepers in sculpting immune responses and ensuring immune homeostasis [252].

4.2.2.4. osteogenic effects of calcium. Calcium is vital for bone development, and many bone diseases are connected to the content of the organic calcium matrix or hydroxyapatite in bone tissue [253,254]. For instance, osteoporosis is defined as a decrease in mineral content per unit volume of bone, often caused by malabsorption, decreased intake, or increased calcium loss [201,255]; Delayed union and non-union, common complications of bone defects, are also closely tied to calcium intake. Given the structure of bone tissue, new implant materials have been developed for treating fractures or bone defects. Hydroxyapatite (HA), which contains a substantial proportion of Ca, has been used in the preparation of surgical implants [256], biological coatings of alloy materials [257], and bone replacement materials [258]. As an essential component of bone tissue, calcium ions are also involved in osteoimmunological processes. Bone extracellular fluid and plasma constantly regulate the balance of calcium ions, which also modulate the bone resorption of osteoclasts to release calcium ions and bone formation of osteoblasts to absorb calcium ions (Fig. 9c) [259]. In a tumor-associated bone defect disease model, researchers used HA nanoparticles (n-HA) to treat bone defects caused by neoplasm metastasis. The n-HA released scaffold showed significant effects in inhibiting tumor growth and osteolytic injury [260]. Additionally, tricalcium phosphate (TCP) has been extensively used due to its capacity to produce RANKL and Wnt signals in osteocytes, which stimulate the differentiation and proliferation of osteoblastic cells [261]. TCP was also found to stimulate macrophage M2 differentiation through the Ca^{2+} sensor receptor, thereby establishing an osteogenic immune microenvironment, inhibiting local inflammation, and promoting bone formation [262].

4.2.3. Strontium

4.2.3.1. physicochemical and physiological properties of strontium. Strontium (Sr), a member of the mentioned alkaline earth elements above, is highly reactive in its solid metal form when exposed to air and readily reacts with oxide, halides, and sulfide [264]. Strontium possesses an atomic radius of 215 pm, an ionic radius of 132 pm, and a covalent radius of 195±10 pm. Like the preceding two alkaline earth metals, strontium also tends to lose two electrons, forming a stable divalent state. In

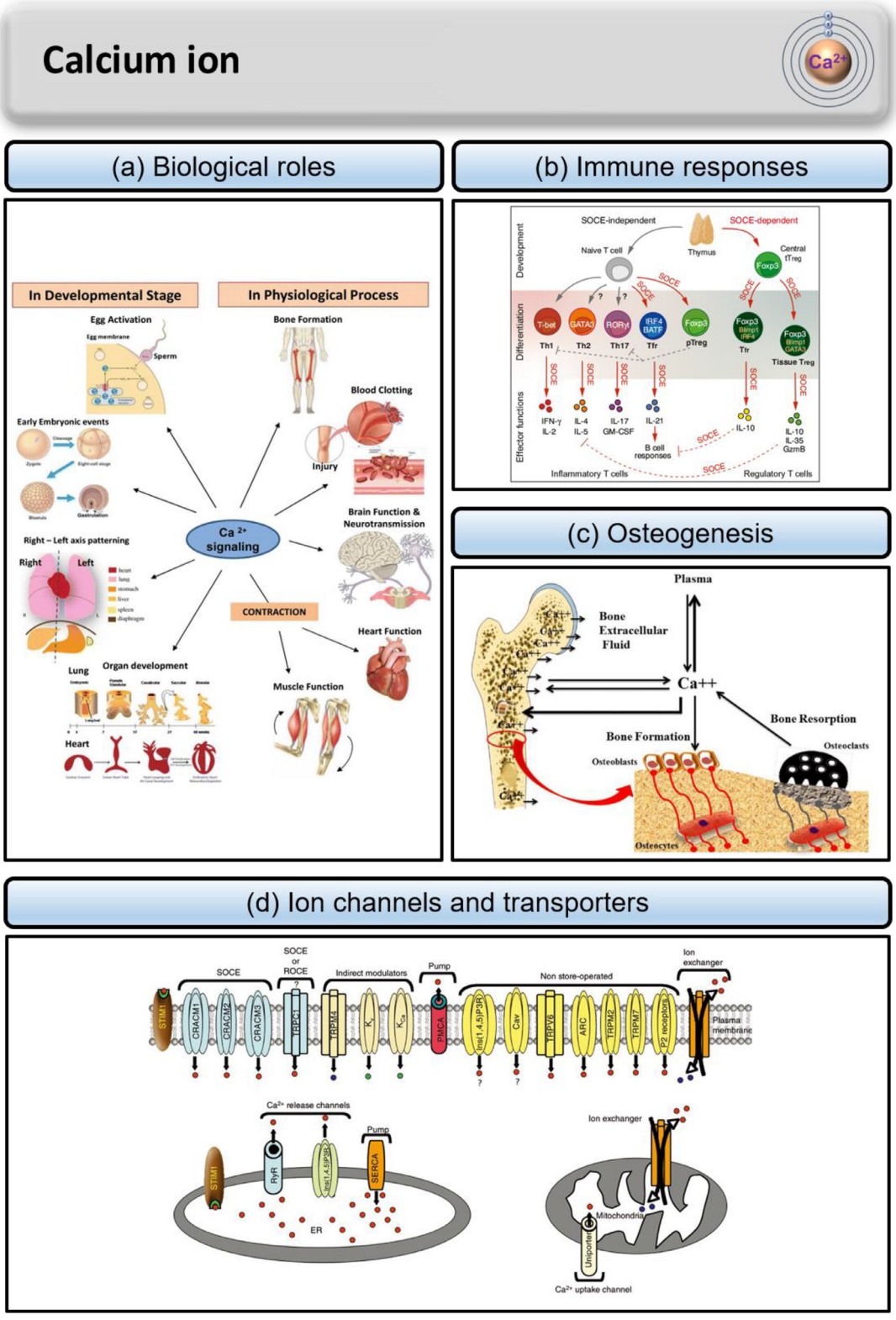

Fig. 9. Properties of calcium ion. (a) Scheming diagram of calcium signaling in the regulation of developmental stage and physiological process. During the developmental stage, calcium signaling regulates human egg activation, the occurrence of early embryonic developmental events, the right-left axis patterning of the lung, and the development of organs. In physiological processes, calcium signaling participates in bone formation, thrombosis after trauma, brain function and neurotransmission, and normal contraction of the heart and skeletal muscle. Adopted from ref. [263], copyright 2017, Springer Nature. (b) Scheming diagram of SOCE regulating the agonist-selected Treg cells' development, the production of effector functional cytokines by Th cells, and immunosuppressive molecules produced by Treg cells. Adopted from ref. [252], copyright 2020, Elsevier. (c) Schematic diagram of the interaction and balance of Ca^{2+} in bone tissue and in the extracellular matrix fluid. Calcium concentration mediates the functions of bone cells to maintain the strength and normal volume of bone mass. Adopted from ref. [259], copyright 2020, Springer Nature. (d) Symbolized diagram of Ca^{2+} channels, pumps, exchangers, and receptors on the plasma membrane, ER, and mitochondria membrane. Adopted from ref. [243], copyright 2008, Springer Nature.

the human body, strontium ions can be absorbed and stored in the bone matrix, similar to the storage mechanism of calcium [264].

4.2.3.2. immunoreguation of strontium. The immune system can be influenced by applying Sr^{2+} doped materials or Sr^{2+} therapy in vivo and in vitro, although the precise mechanism remains unclear. From the perspective of immune regulation, it has been shown that Sr^{2+}-treated human large granular lymphocytes (LGL), which include granulocytes and NK cells, significantly increase granulation and reduce killing activities [265]. Strontium-related materials and strontium ions have been demonstrated to polarize neutrophils and macrophages [266]. Tao Li et al. prepared strontium hydroxyapatite (SrHA)-containing nanofibrous gelatin scaffolds. It was shown that strontium induced the immunomodulation and pro-angiogenic functions of neutrophils via the down-regulation of the NF-κB signal pathway and the increase of STAT3 phosphorylation [267]. Another study found that after Sr-doped hydroxyapatite microspheres were implanted into the inflammatory model, the quantity of M2 macrophages in the inflammatory tissue was significantly increased. This indicated that Sr-doped hydroxyapatite microspheres could promote M2 macrophage polarization and regulate inflammatory response [268]. Fig. 10c depicts the antioxidant and immunomodulatory effects of Sr at the molecular and cellular levels, respectively. At the molecular level, strontium inhibits the hydrogen peroxide formation from oxygen with one electron by superoxide dismutase (SOD) and decomposes hydrogen peroxide by catalase (CAT). At the cellular level, strontium induced the transformation of M0 macrophages into the M2 subtype, as well as inhibited the M1 subtype transformation simultaneously [269].

4.2.3.3. osteogenic effects of strontium. Sr-related biomaterials and metals have been used in osteogenesis and show promising application prospects. N.H. Lee et al. prepared a Sr-nanocement for treating osteoporosis [270]. This material significantly increased the osteogenesis-related gene expression: OPN, Bone sialoprotein (BSP), OCN, Runx2, and suppressed osteoclast differentiation (Fig. 10a). Fig. 10b demonstrates the impact of strontium ions on osteoblasts. Strontium can mediate osteoclast apoptosis through the Wnt pathway to promote bone regeneration (Fig. 10b) [24]. A strontium-releasing composite scaffold has been demonstrated to possess osteogenic, anti-osteoclast, and immunomodulatory properties [268]. The expression of ALP from MSC increased, especially under the condition of osteogenesis and higher concentration of Sr^{2+} (1 and 3 mM Sr^{2+}). Regarding osteoclasts, the results indicated that 0.5 mM, 1 mM, and 3 mM of Sr^{2+} drew an inhibition on the ability of osteoclasts to adhere to substrates and incorporate. The Sr^{2+} release from coated titanium enhanced the activities of CAT and SOD, thereby eliminating endogenous reactive oxygen species (ROS) and conferring better osteoinductive and antioxidant properties [269]. Immunologically, Sr^{2+} can also regulate the morphology and CAT/SOD activity of macrophages, promoting the polarization of macrophages from M0 to M2. Another study demonstrated that a stereo lithography Sr-incorporated micro/nano titanium (SLA-Sr) implant released strontium ions into the microenvironment of a bone fracture site, promoting M2 polarization of macrophages, osteogenesis of MSCs and angiogenesis of human umbilical vein endothelial cells (HUVECs) (Fig. 10d) [271].

4.3. Transition metals

Transition metals are characterized by possessing either a partially filled *d* sub-shell or the capability to form cations with an incomplete *d* sub-shell. These elements can be found in groups 3 to 12 on the periodic table. Due to their multivalent nature, transition metals determine their biological effects according to their changes when they exert biological effects in organisms. Under biological conditions, transition metals commonly exhibit two or more oxidation states. For example, compounds of vanadium express various oxidation states between −1 $[V(CO)_6]^-$ and +5 (VO_4^{3-}); Iron possesses +2 or +3 oxidation states in biological conditions with the function of oxygen transport; copper is commonly found in +1 or +2 states, helping in the transfer of electrons of Fe proteins. In addition, transition metal ions are usually hydrated by six water molecules arranged in an octahedral formation, which stabilize their chemical and biological characteristics in organisms [272].

4.3.1. Vanadium

4.3.1.1. physicochemical and physiological properties of vanadium. Vanadium is classified in group VB of the periodic table. It is a reactive metal with an atomic radius of 134 pm, and it has four ionic radii depending on its ionic state. Its ionization energy at each stage is not much different, resulting in a great range of oxidation states from −3 to +7 in the human body. The polyvalent nature allows vanadium to have fundamental biological effects in the body's fluid environment (Fig. 11a) [273,274]. The +5 oxidation state of vanadium is mostly found in extracellular bodily fluids, as represented in anionic metavanadate (VO^{3-}) or orthovanadate anion (VO_4^{3-}) that resembles phosphates, while the +4 oxidation level (VO^{2+}) is predominantly found in intracellular fluid [275]. This suggests that vanadium may substitute phosphates in ATP-driven processes. In a molecule vision, [VO_4^{3-}] can be transferred into the cell and reduced by glutathione into [VO^{2+}] with an oxidation state of +4. This cation, also known as vanadyl, has a similar structure to phosphoric acid and a similar ion radius with Mg^{2+}, therefore potentially competing with them in biological processes, such as ATP phosphohydrolase.

4.3.1.2. immunoregulation of vanadium. The V ions have been found to have immunostimulatory or immune-toxic effects through BCR, TCR, NF-κB pathway, interleukin expression, or TLR (Fig. 11c) [276]. The innate immune system could be influenced by pro-oxidative responses of metal ions. Activated neutrophils, which were treated with vanadium in the distinctive valence states (+2, +3, +4), significantly increased hydroxyl radical formation [277]. CD11c and MHC-II secreted by thymic dendritic cells could be down-regulated by vanadium, thus potentially inducing dysfunction of negative selection of T cells [278]. Vanadium has been found to potentially enhance the function of $CD8^+$ helper T cells. vanadium salts have been observed to express an inhibition on the nuclear factor of activated T cells (NFAT) and impact the constitutive DNA binding activity within resting T cells [279].

4.3.1.3. osteogenic effects of vanadium. Research findings have demonstrated the significant accumulation of vanadium in bones, with levels ranging from 10 to 26 μg/g. Vanadium compounds have shown notable biological effects, including insulin and growth factor mimicking properties, as well as exhibiting osteogenic activity [280]. It has been established that vanadium-based scaffolds are involved in bone metabolism and bone regeneration. A vanadium-doped mesoporous biological glass particle has been prepared to improve osteogenic effects. In cell-based studies, vanadium ions at about 19 μM increased the osteogenic gene: BMP-2, human type I collagen (COL-1), expression, and signaling pathway genes expression: FAK, Itga 2b, pERK1/2. This suggests that vanadium ions could regulate bone regeneration through the Itga 2b–FAK–MAPK pathway (Fig. 11b) [281]. Another study evaluated the osteogenic effect of V and Mg in rats. The combined administration of V-Mg resulted in synergistic effects such as the downregulation of phosphorus and potassium levels in the femoral diaphysis (FD) and the normalization of zinc levels in FD. However, it also presented several antagonistic interactions, including the upregulation of the Na^+ level in FD, ALP activity in FD, and femoral bone surface roughness (Fig. 11d) [282].

4.3.2. Iron

4.3.2.1. physicochemical and physiological properties of iron. Iron (Fe) is the fourth most prevalent metal element on Earth and belongs to the first transition series in the periodic table. It is an active metal with a wide range of valence states, an atomic radius of 134 pm, and ions in

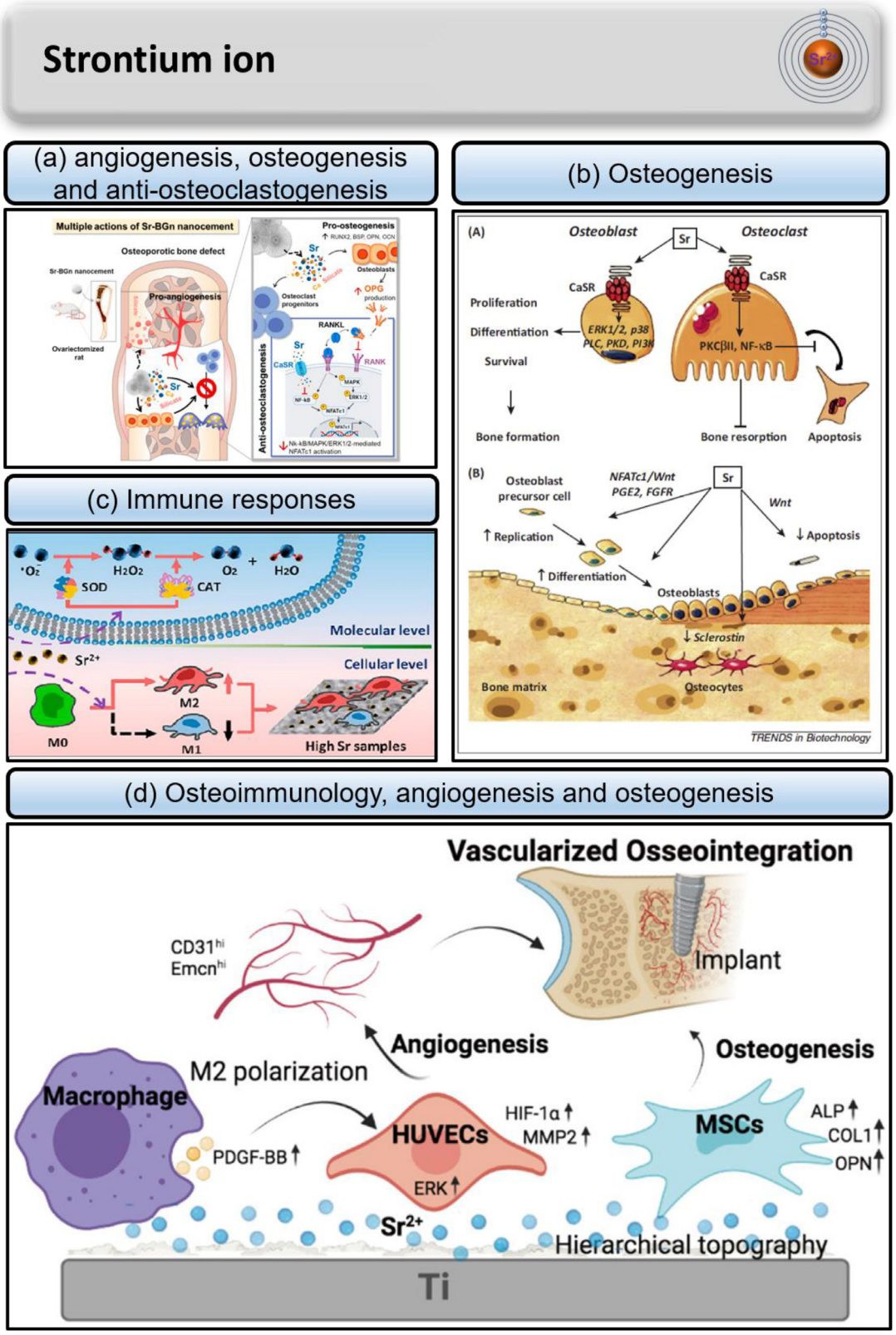

Fig. 10. Properties of strontium ion. (a) Schematic diagram of a Sr-BGn nanocement that induces pro-angiogenesis, pro-osteogenesis, and anti-osteoclastogenesis after implantation into an osteoporotic bone defect model. Adopted from ref. [270], copyright 2021, Elsevier. (b) Schematic diagram of the Sr regulation on osteoblasts and osteoclasts (A in the figure), and the proliferation, differentiation, or apoptosis of osteoblasts induced by Sr through multiple signaling pathways (B in the figure). Adopted from ref. [24], copyright 2021, Springer Nature. (c) Schematic diagram of peroxidase pathway at a molecular level and its regulatory role in the phenotypic regulation of macrophages upon high strontium samples. Adopted from ref. [269], copyright 2021, Elsevier. (d) Graphic illustration of SLA-Sr mediating the differentiation of M2 macrophages to promote angiogenesis through local release of Sr^{2+}. Adopted from ref. [271], copyright 2013, Royal Society of Chemistry.

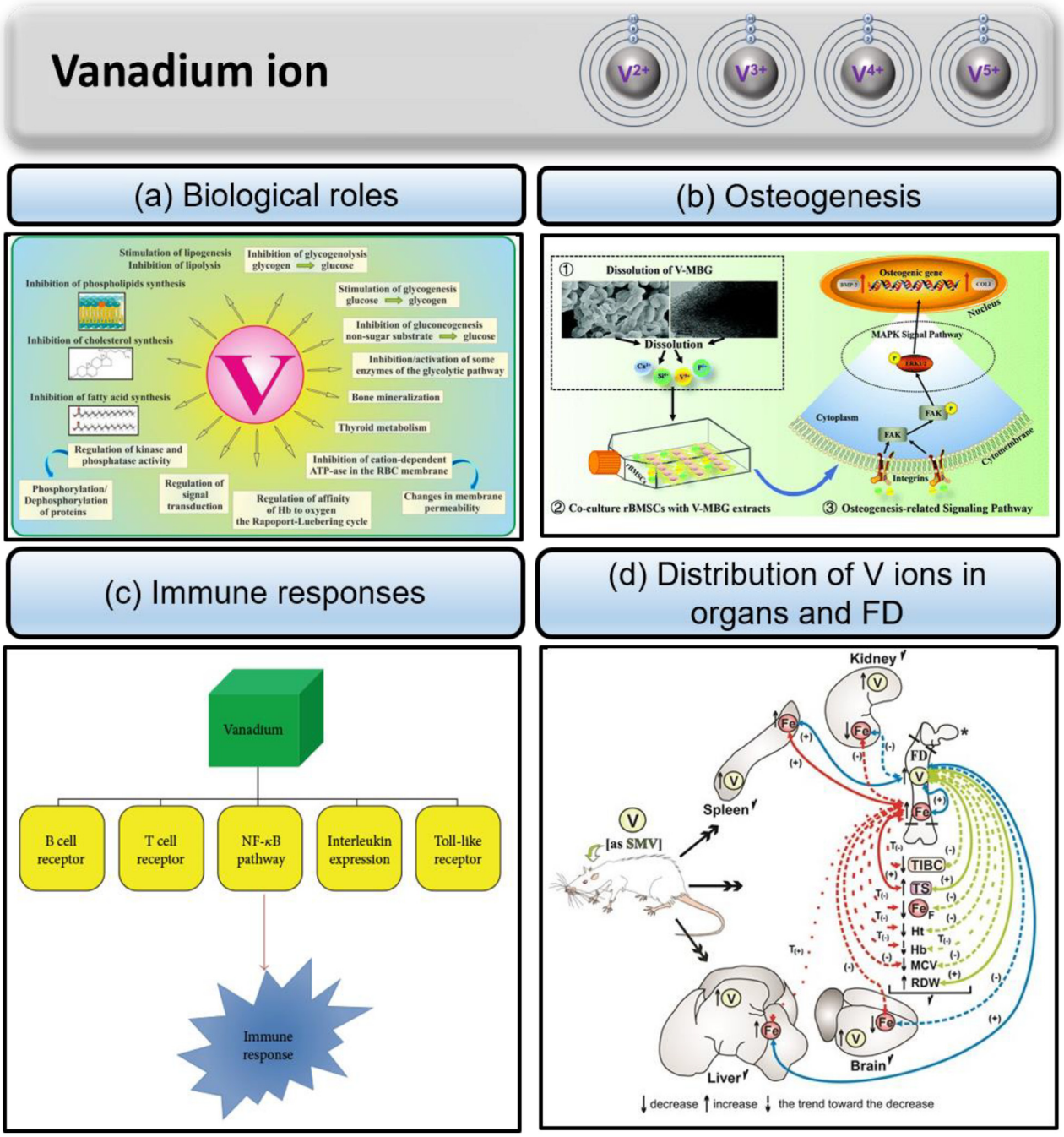

Fig. 11. Properties of vanadium ion. (a) Schematic diagram of vanadium regulating the anabolism of macromolecules and their transformation in mammals. Adopted from ref. [274], copyright 2020, Elsevier. (b) Schematic diagram of activation of osteogenic signaling pathways through culturing MSCs with V-MBG extracts. Adopted from ref. [281], copyright 2013, Royal Society of Chemistry. (c) Simplified Schematic illustrating vanadium regulates the immune response through multiple receptors, signaling pathways, and cytokines. Adopted from ref. [276], copyright 2016, Hindawi. (d) Schematic diagram of correlations of iron and vanadium ions with tested parameters between organs and FD in V exposed rats. Adopted from ref. [282], copyright 2014, Oxford University Press.

each valence state having different ionic radii. The multiple oxidation states of Fe (−4 to +7) make it amphoteric and an excellent electron exchanger [283]. Iron is widely involved in human physiological processes and metabolism [284]. The most common biological iron compounds include hemoglobin, myoglobin, metalloproteins, and transferrin In the human body [285–289]. These iron compounds participate in oxygen transport, enzyme synthesis, electron transfer, and iron absorption [284]. Hemoglobin is an iron-containing oxygen carrier involved in oxygen transport widely presented in red blood cells. Hemoglobin binds oxygen from the lungs and transports it to myoglobin [286]. Myoglobin uses oxygen to metabolize glucose to produce energy, and hemoglobin combines with carbon dioxide from metabolism to transport it back to the lungs along the veins [289]. Metalloproteins, a class of proteins with metal ion cofactors, include ferritin and erythrocyte membrane redox proteins, involved in the electron transfer of iron ions and the maintenance of Fe^{2+} and Fe^{3+} balance [290]. Many life-essential enzymes contain iron, such as CAT, lipoxygenase, and IRE binding protein (IRE-BP) [291–293]. Transferrin is a protein responsible for the storage and transportation of iron in the body. The center of transferrin has a Fe^{3+}, which is very stable and able to absorb Fe^{3+} efficiently [288].

The process of iron transport in cells can be divided into iron import, storage, and export [294]. Most cells import iron ions mainly through endocytosis mediated by transferrin receptor 1 (TFR1), TFR2, and reduced glyceraldehyde-phosphate dehydrogenase (GAPDH) receptors [295]. The transferrin receptors recognize the trivalent iron bound by transferrin, leading to a conformational change that triggers endocytosis. Within endosomes, iron is subsequently reduced to the ferrous state by reductases. Divalent metal transporter 1 (DMT1) facilitates the iron transportation from the endosome to the cytoplasm. In the cytoplasm, ferrous iron exists in a soluble and chelated state, forming an unstable iron pool with a concentration of approximately 0.001 mM. Iron within this pool is believed to bind to low-affinity compounds (phosphates, peptides, carboxylates) [296,297]; Dysfunctional ferritin may accumulate in the form of hemosiderin, forming an iron storage pool with a much higher concentration than that of the unstable iron pool (0.7–3.6 mM) [298]. Iron export involves the membrane ferroportin expressed on neurons, erythrocytes, macrophages, and enterocytes [299]. It transfers ferrous iron out of the cell assisted by ceruloplasmin and hephaestin [300,301]. Hephaestin occurs only in certain cell types (hepatocytes), and its expression is controlled at the transcriptional level, representing a link between cellular and whole-body iron homeostasis [300].

4.3.2.2. immunoregulation of iron. Iron homeostasis is related to the immunological regulation throughout the whole body. Iron is involved in the physiological activities of cells and the synthesis of biomacromolecules, but it can also produce ROS through the Fenton reaction. While the damaging effect of ROS can help immune cells kill pathogens, the imbalance of iron homeostasis and excessive ROS can damage a variety of autologous biomacromolecules, and eventually affect the normal immune regulation effect of the body [302].

Iron homeostasis is regulated by the hepcidin derived from the liver, which reduces the influx of stored iron into plasma and prevents the absorption of dietary iron by inducing the degradation of the iron-exporting protein ferroportin in its receptor cells (Fig. 12a) [303]. When the body's iron level decreases, iron regulation production decreases along with increased iron absorption. This systemic feedback loop can be disrupted by infection and inflammation, resulting in iron absorption inhibition and inducing iron sequestration in macrophages [304]. This process is also seen as a host defense function, as most microorganisms depend on exogenous iron for survival. Enhanced iron clearance and macrophage sequestration serve a dual function: to deny iron to invading microorganisms and to defend against the toxic effects of elevated iron, hemoglobin, and heme levels. This process ensures that the immune system recognizes and kills pathogens while protecting normal tissues from the damaging effects of elevated plasma iron concentrations caused by ferritin degradation [299].

Macrophage polarization is related to the iron environment. In conditions of iron sufficiency, macrophages typically tend to undergo M1 polarization, while iron deficiency often results in M2 polarization. Iron has been demonstrated in T cell activation and polarization. The uptake of iron is involved through an IL-2-dependent pathway in T cell activation mediated by transferrin receptor 1 (TfR1 or CD71). Mutations in the TfR1 gene can hinder iron endocytosis, resulting in functional deficiencies in T cells. Elevated levels of iron ions can hinder the differentiation and activity of Th1, Th2, and Th17 cells while promoting the differentiation of cytotoxic T lymphocytes (CTLs) (Fig. 12b) [305].

4.3.2.3. Influence of iron on bone homeostasis. Iron homeostasis is important for osteointegration. Iron deficiency can induce hypoxia to induce osteoclast differentiation and inhibit osteoblast differentiation, whereas iron overload produces excessive ROS to damage tissues (Fig. 12c) [303]. Under the precise control of the doses and applications of iron, iron-based materials are produced in an antibacterial way due to their ROS releasing effect [306,307]. Iron based materials have the characteristics of low biodegradation rate and insufficient biological activity. To solve this defect, Iron-based composites containing silicate-based bioceramic particles were prepared [308]. This material solved the former two shortcomings while ensuring the mechanical properties of iron-based materials, and also had certain osteogenic properties.

4.3.3. Cobalt

4.3.3.1. physicochemical and physiological properties of cobalt. Cobalt is a transition metal in the periodic table, located between iron and nickel [151]. Characterized as a ferromagnetic metal, cobalt possesses a magnetic moment between 1.6 and 1.7. Its oxidation states range from +1 to +5, with +2 and +3 being the most common. 58Co and 60Co are two cobalt isotopes that emit high-energy photons and have been extensively used in cancer treatment [151]. Cobalt is regarded as an indispensable element in organisms because it combines with vitamin B_{12} (hydroxocobalamin), which possesses a corrin ring structure and is required by almost all forms of life [310]. Other cobalt proteins, particularly non-corrin cobalt proteins, have attracted profound attention due to their chemical and biological versatility. These proteins, which include methionine aminopeptidase, nitrile hydratase, prolidase, glucose isomerase, and cobalt transporters (COT1), provide new insights into the functions of cobalt beyond its toxicity to the human body and may foster the development of innovative anti-tumor and anti-toxicosis drugs [311]. Additionally, cobalt is a component of the coenzyme of cell mitosis, neurotransmitters, and erythropoietin. However, inorganic forms of cobalt are toxic to humans and have been proven to induce chronic inflammation, excessive bone marrow activity, cardiomyopathy, and even cancer (Fig. 13a) [312].

4.3.3.2. immunoregulation of cobalt. Cobalt ions (Co^{2+}) and Chromium (Cr^{6+}) have been reported to induce apoptosis of T lymphocytes, suppressing their growth and functions [313]. Lawrence et al. pointed out that the TLR4 signaling pathway was directly responsible for the activation of cobalt ions in innate immune cells, with cobalt-induced chemokines having a migratory effect on both neutrophils and monocytes [314]. K. Chamaon et al. proposed that ROS the main toxic substance of cobalt ions. In monocytes, oxygen free radicals and superoxide in the cytoplasm are produced and secreted by the cobalt ions into the immune effector environment, leading to local cell death and tissue damage [315]. Studies have explored the regulation of cobalt ions on macrophage subtype differentiation. the polarization of macrophages can be altered by Co^{2+} depending on its concentration. After treatment with a low medical or high amount of cobalt ions, the phenotypes of macrophages altered into M1/M2 and M1, while a very high dose of cobalt ions led to cell death (Fig. 13b) [316]. One study found that treating macrophages with a high concentration of Co^{2+} for 48 h promoted TNF-α production and exceeded CD206 expression, leading to pro-inflammatory M1 differentiation [317]. In contrast, Kumanto et al. demonstrated that $CoCl_2$ increased M2 subtype differentiation and arginase-1 protein expression, but had no effect under IL-4 and IL-13 conditions, which are potential stimulants for M2 subtype polarization [318]. Co ions have also been reported to promote M1 subtype polarization by activating the iNOS/nitric oxide pathway. Salloum et al. found that Co^{2+} ions stimulated the production of ROS and mitochondrial dysfunction, therefore stimulating an inflammatory response and M1 subtype macrophage polarization [318]. Another study conducted by Yang Xiaoming et al., composed cobalt-incorporated plasma electrolytic oxidation (PEO) coatings featuring varying concentrations of cobalt. The researchers observed that the titanium coatings loaded with cobalt demonstrated pro-inflammatory subtype polarization in macrophages [317]. Xu et al. pointed out that cobalt induces ROS production and reduces RhoA expression (a Rho protein family member). The related RhoA/ROCK pathway has been proven to be involved in osteoarthritis and governs macrophage activities and cytoskeleton structure. This provides a novel method for restricting macrophage spreading, adhesion, and migration and extending chronic inflammation [319].

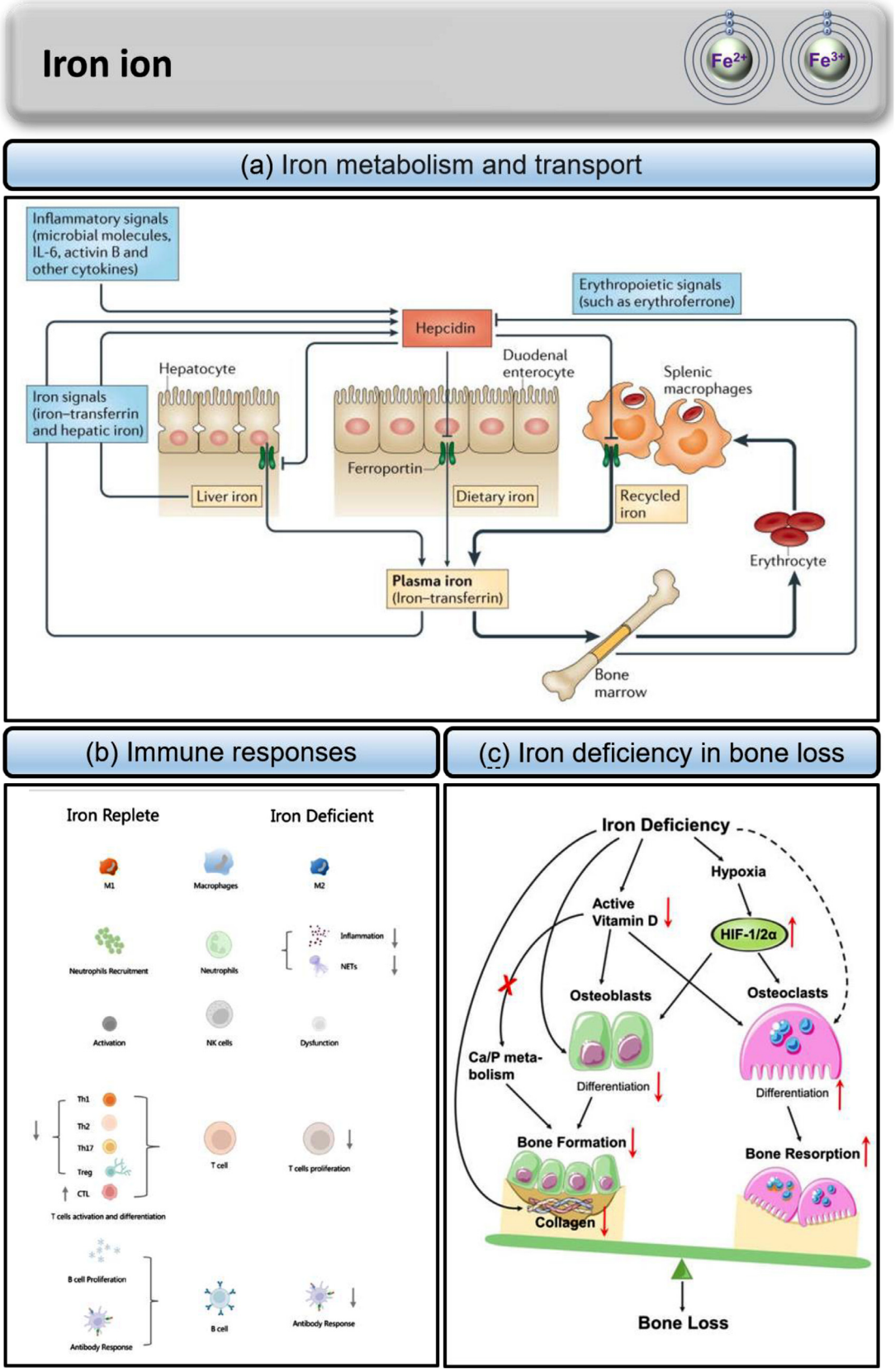

Fig. 12. Properties of iron ion. (a) Schematic of the homeostatic regulation of iron and iron in the regulation of erythropoiesis and inflammation. Adopted from ref. [309], copyright 2015, Springer Nature. (b) Symbolized Schematic diagram of the regulatory effects of iron on immune cells. Immune cell function, differentiation, and proliferation are affected in an iron-replete or iron-deficient environment. Adopted from ref. [305], copyright 2022, Frontiers Media S.A. (c) Schematic representation of potential mechanisms by which iron deficiency mediates differentiation of osteoblasts and osteoclasts to produce bone loss. Iron deficiency stimulates osteoclast differentiation and inhibits osteoblast differentiation by upregulating hypoxia-inducible factor 1/2α (HIF-1/2α) through hypoxia. Adopted from ref. [303], copyright 2023, MDPI (Basel, Switzerland).

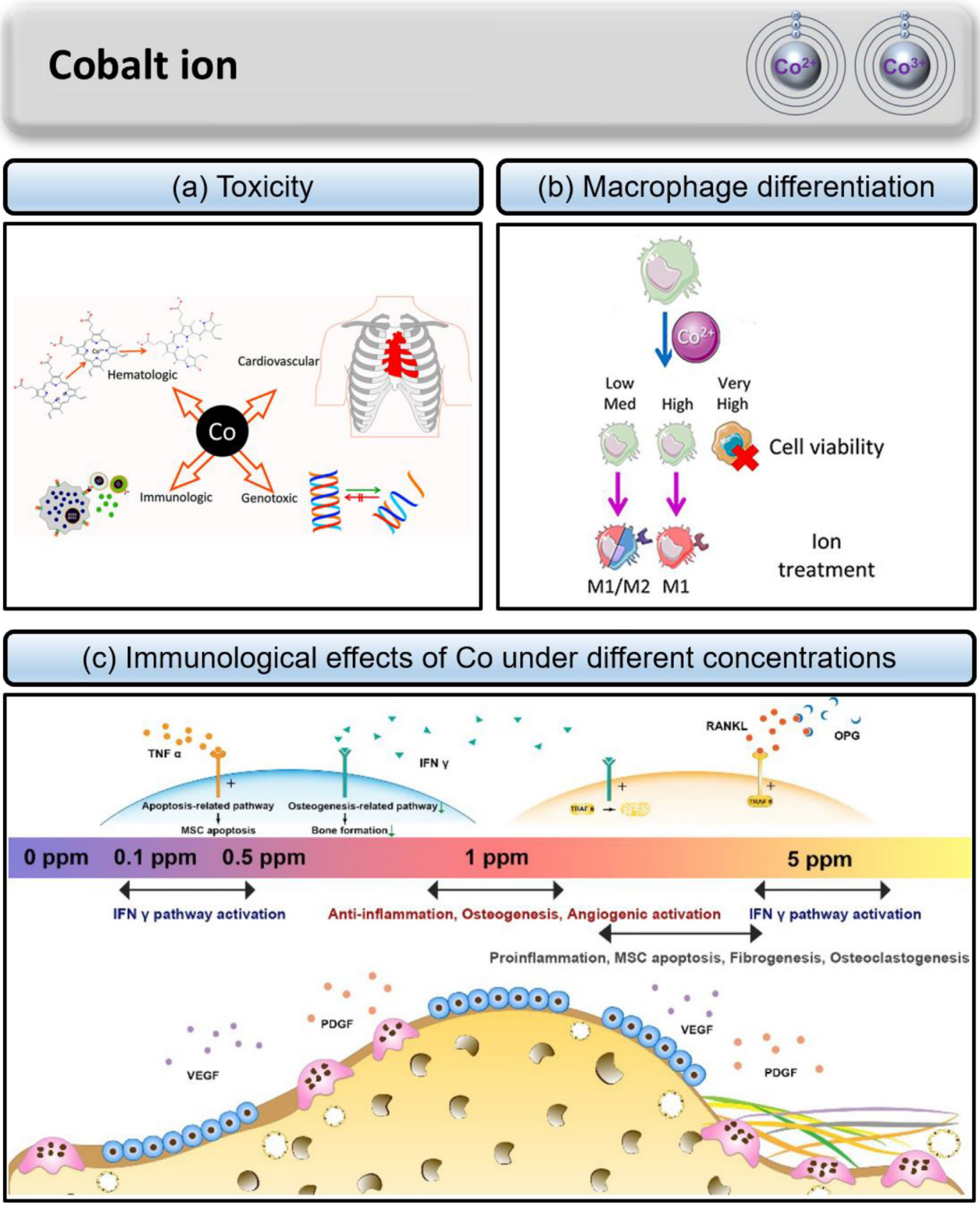

Fig. 13. Properties of cobalt ion. (a) Schematic diagram of the hematologic, cardiovascular, immunologic, and genotoxic toxicity of cobalt nanoparticles through direct or dissolution-mediated mechanisms in humans. Adopted from ref. [326], copyright 2020, De Gruyter. (b) Schematic illustration of bioactive cobalt ions mediating macrophage differentiation at various concentrations. Low doses of cobalt ions can induce the formation of M1 or M2 subtypes, high doses can induce the differentiation of M1 subtypes, and extremely high doses can cause the death of macrophages. Adopted from ref. [316] with modification, copyright 2021, Springer Nature. (c) Diagram illustrating the dose range of cobalt as an important balance factor in the application of cobalt-related materials. The relationship between osteogenesis and osteoclast system, immune response, and angiogenesis is better balanced at the dose of 1 ppm cobalt, while low or excessive cobalt can cause the activation of inflammation-related signal pathways during the bone regeneration process, which leads to adverse effects. Adopted from ref. [322], copyright 2019, Ivyspring International Publisher.

4.3.3.3. osteogenic effects of cobalt. Cobalt-based alloys and biomaterials have been proven to facilitate angiogenesis and the bone healing process. By exploiting the hypoxia-like reaction of cobalt ions, a cobalt-doped borosilicate glass scaffold was developed for bone regeneration and angiogenesis. This Co-doped system controlled the release of Co ions and exhibited significant osteogenic abilities on the 3 wt% Co bioactive glass scaffold [320]. TCP scaffolds were prepared and doped with different percentages of cobalt for the investigation of the dosage effect of cobalt on osteogenesis [321]. Among these groups, 2% and 5% Co-TCP demonstrated significant osteogenic and angiogenic effects compared to the TCP group. However, a smaller bone volume and higher vascularization rate were observed in the 5% Co-TCP than in the 2% Co-TCP, indicating that appropriate Co ions positively influenced osteogenesis within a suitable range of vascularization, while excessive Co ions suppressed bone formation. Fig. 13c demonstrated that the appropriate doses of cobalt could promote local bone regeneration, while either low or high concentrations of cobalt inhibited the proliferation of MSCs, thus delaying bone regeneration. At a concentration of 1 ppm, cobalt produces anti-inflammatory, bone regenerative, and angiogenic effects and promotes osteogenesis [322]. Cobalt stabilized hypoxia-inducible factors (HIFs) enhance angiogenesis at the implant site by producing a hypoxic environment, where activates angiogenic factors VEGF, glucose transporter-1, and erythropoietin [323,324]. Cobalt has been used in bone implant materials and alloys for a long time. Although some studies have confirmed the osteoprotective effect and compatibility of cobalt materials, long-term studies have shown that excessive exposure to cobalt brings systemic health hazards, including the nervous system, cardiovascular system, and endocrine system [325].

4.3.4. Copper

4.3.4.1. physicochemical and physiological properties of copper. Copper's ductile, malleable properties, high electrical conductivity (59.6106 S/m), and thermal conductivity (401 W/(mK)) have led to its extensive application in alloy manufacturing. Copper has an atomic number of 29 in group 11 of the periodic table [327]. Copper's oxidation state is weakly basic. Although copper can form a range of valence states from −2 to +4, it generally forms +1 or +2 to maintain ion stability. Due to the interconversion of Cu^{+} (cuprous) and Cu^{2+} (cupric), the biological function of Cu ions is to conduct electrons involved in electron transport and synthesize copper-associated proteins in biological processes [328,329]. Copper is an essential element in biological systems as a cofactor in approximately 30 different enzymes. These enzymes rely on copper for their proper functioning and catalytic activity. This is especially important in cellular redox reactions. However, the redox reaction ability of copper and its ability for protein coordination not only participate in cell metabolism but can also produce toxicity under certain amounts [330]. During absorption in the gastrointestinal tract, copper is primarily bound to ceruloplasmin (CP) in hepatocytes. CP then is secreted into the blood and is involved mainly in iron metabolism, promoting the release of iron from certain tissues (Fig. 14a) [331].

4.3.4.2. immunoregulation of copper. Copper deficiency has been shown to lead to reduced levels of IL-2, a phenomenon that may underpin the observed reduction in T cell proliferation. Under conditions of marginal copper deficiency, both T cell proliferative responses and interleukin levels are reduced. Simultaneously, neutrophils show not only a reduction in number but also a diminished capacity to produce superoxide anions and kill microorganisms during significant copper deficiency [332]. In the immune defense process, copper ions can catalyze superoxide anion radicals to produce ROS [333]. Evidence suggests that copper deficiency disrupts immune functions. Not only does copper deficiency cause neurological dysfunction, but it also induces abnormalities in the circulatory system, most commonly neutropenia and anemia [334]. Several studies have shown that a low-copper diet impairs humoral immunity and increases susceptibility to infectious diseases in animals [334–336]. These lines of evidence all point to functional defects in neutrophils and macrophages as a result of a low-copper diet or environment. Fig. 14b illustrates the potential mechanism by which macrophages are regulated by copper to act for pathogen clearance [337]. Similar to cobalt, the dosage of Cu ions impacts the macrophages' polarization. When stimulated by LPS, M2 macrophages induced by a low dose of Cu ions can be altered into the M1 type, leading to pro-inflammatory effects (Fig. 14d) [316].

*4.3.4.3. **osteogenic effects of copper**.* The synthesis and metabolism of bone require the participation of copper, since lysyl oxidase, the copper-dependent enzyme, is involved in the final step of collagen synthesis. This enzyme is copper-dependent, so copper deficiency affects bone development and repair [338,339]. A Cu-containing bioactive glass ceramic (Cu-BGC) was prepared for healing cartilage lesions and reducing local inflammation. The release of Cu^{2+} promoted the chondrocytes' maturation while elevating the differentiation of the anti-inflammatory phenotype of macrophages [340]. Copper ions also reinforce angiogenesis via stabilizing HIF-1α, as well as increasing VEGF production (Fig. 14c) [341–343]. Copper ions also exhibit antibacterial properties in bone regeneration applications [344]. These biological functions of copper facilitate the development and application of novel biomaterials [345,346]. One study fabricated an implant surface using self-assembled copper nanoparticles (CuS NP) and reduced graphene oxide (rGO) to synergize the photocatalytic antibacterial and osteogenic potentials [347]. This material not only combined photothermal therapy (PTT) to enhance the photothermal effect for eliminating bacteria, but also avoided the inactivation of biological agents caused by this effect. Simultaneously, the material, coupled with copper ions and rGO, promotes the integration of vascularized bone, showing promising bone repair and antibacterial properties. M. Shi et al. produced a Cu-incorporated TCP scaffold providing a specific concentration of Cu ions in the microenvironment, thus modulating angiogenesis and providing favorable conditions for bone repair [348]. In another study, Cu ions were combined with l-arginine to explore its osteogenic and antibacterial activity [349]. The incorporation of arginine could attenuate the copper's inhibitory effect upon MSCs' osteogenic development at 100 μM, and the synergistic effect of Cu ions and l-arginine showed stronger antibacterial activity. To combat potential bacterial contamination of stainless-steel implants, researchers incorporated bioactive glass containing copper into the implant coating. This coating exhibited antibacterial and pro-angiogenic properties while maintaining the cytocompatibility and mechanical properties of stainless steel [350].

4.3.5. Zinc

4.3.5.1. physicochemical and physiological properties of zinc. Zinc is a lustrous, diamagnetic metal with the atomic number 30 [151]. It has a hexagonal crystal structure, with each atom in its plane having six neighbors at 265.9 pm, while others are at 290.6 pm [151]. Zinc has comparatively low melting and boiling temperatures (419.5 °C and 907.7 °C, respectively) [354]. Zinc is distributed in multiple organs and tissues within the human body, but is stored in bone and skeletal muscle primarily (Fig. 15b). It is an essential ligand involved in signaling pathways regulating the metabolism of macromolecules as well as gene expression [355]. However, excessive zinc consumption may be detrimental to health, resulting in inhibition of copper and iron absorption, tissue damage, and cell death [356]. Zinc ions are involved in the modification of channel proteins, including MTs, ZnTs, and ZIP family channel proteins. These zinc-related proteins are involved in mediating signal transduction, protein modification, and gene regulation. Their imbalance affects a variety of cells and organs, potentially causing diseases (Fig. 15a) [357].

4.3.5.2. immunoregulation of zinc. Zinc participates in diverse signaling pathways of immune cells [358]. Zinc ions regulated the transcription

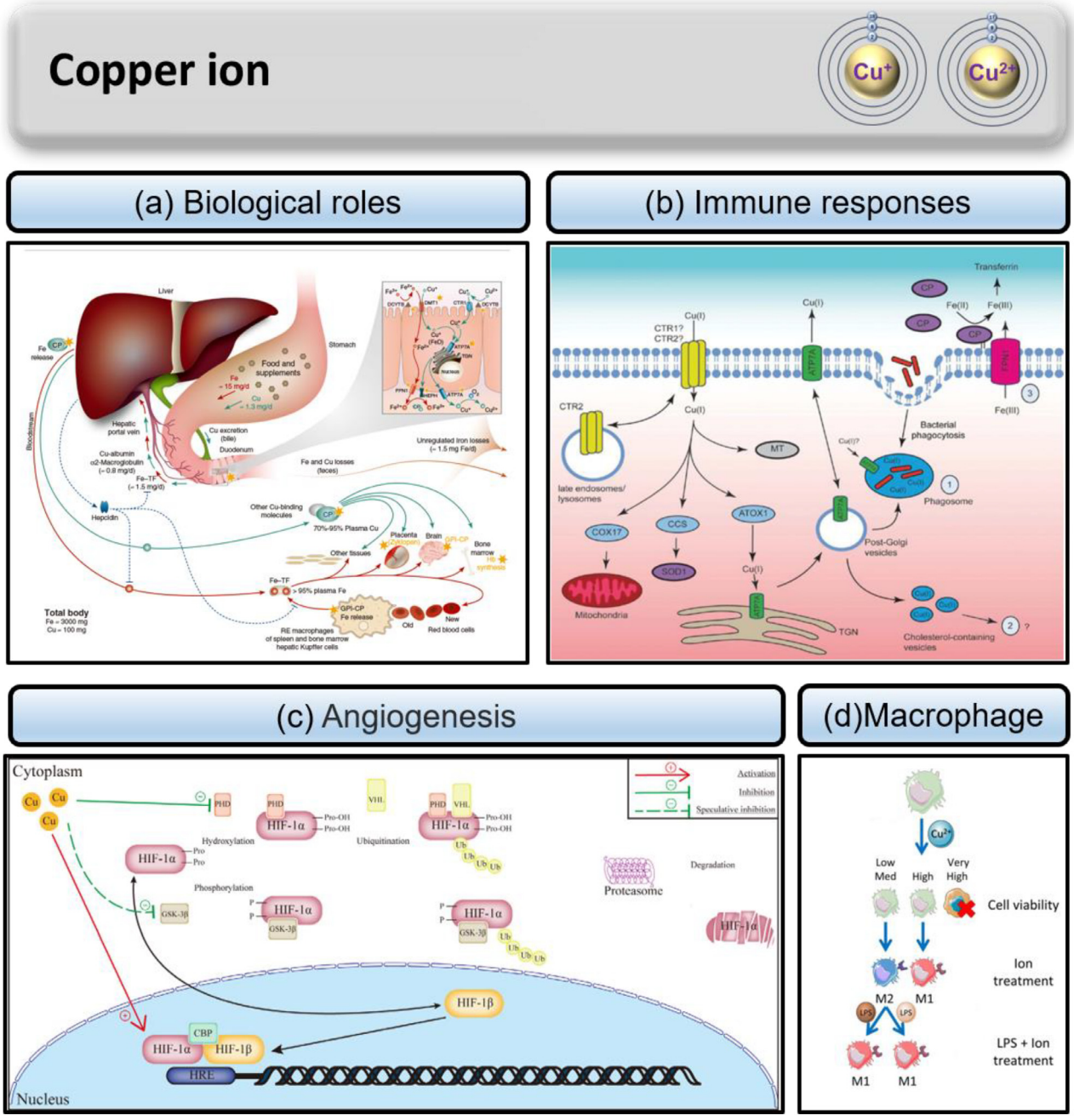

Fig. 14. Properties of copper ion. (a) Schematic of the interaction and metabolic mechanism of copper and iron as two trace elements in metabolism. Copper is synthesized by hepatocytes into ceruloplasmin, which regulates iron metabolism. Adopted from ref. [351], copyright 2018, John Wiley and Sons. (b) Illustration of copper facilitating the antimicrobial responses of macrophages. Several supposed mechanisms are given and shown in the figure: direct toxic molecules generated by the Fenton reaction; vesicular accumulation contributing to oxidative stress, or promoting the FPN1-dependent iron export and thus leading to depletion of iron within intracellular bacteria. Adopted from ref. [352], copyright 2013, Portland Press. (c) Schematic diagram of how copper promotes angiogenesis. Copper maintains the hydroxylation of prolyl residues by inhibiting HIF-1α degradation and maintains the concentration of HIF-1α to augment angiogenesis. The figure also depicts the authors' hypothesis that copper directly activates HIF-1α by down-regulating GSK-3β expression. Adopted from ref. [353], copyright 2022, Elsevier. (d) Schematic diagram of bioactive Cu^{2+} inducing differentiation of macrophages and LPS-induced further conversion of M2 subtype into M1 subtype. Adopted from ref. [316] with modification, copyright 2021, Springer Nature.

of AP1, NF-κB, and IRF3 pathways by mediating the downstream signaling molecules of TNF receptor and TLRs in monocytes/macrophages to regulate macrophage metabolism and their effector functions (Fig. 15c) [358]. Zinc also exerts a regulatory role involved in some major signaling pathways of T cells, including those mediated by the TCR, IL-1 receptor (IL-1R), IL-2R, and IL-6R with downstream molecules affected (Fig. 15d) [358]. Since Zn^{2+} deficiency decreases the differentiation, proliferation, and subsistence of numerous types of immune cells–monocytes, PMN leukocytes, NK cells, T cells, and B cells [359], Zn ions must be carefully monitored by signaling transduction and stored effectively [360,361]. Zn^{2+} signals were involved in the activation of TLR-4 by LPS in monocytes [362]. The stimulation by LPS raised the intracellular concentration of dissociative zinc ions, which activated the downstream signaling pathways (MAPKs, NF-κB), and enhanced pro-

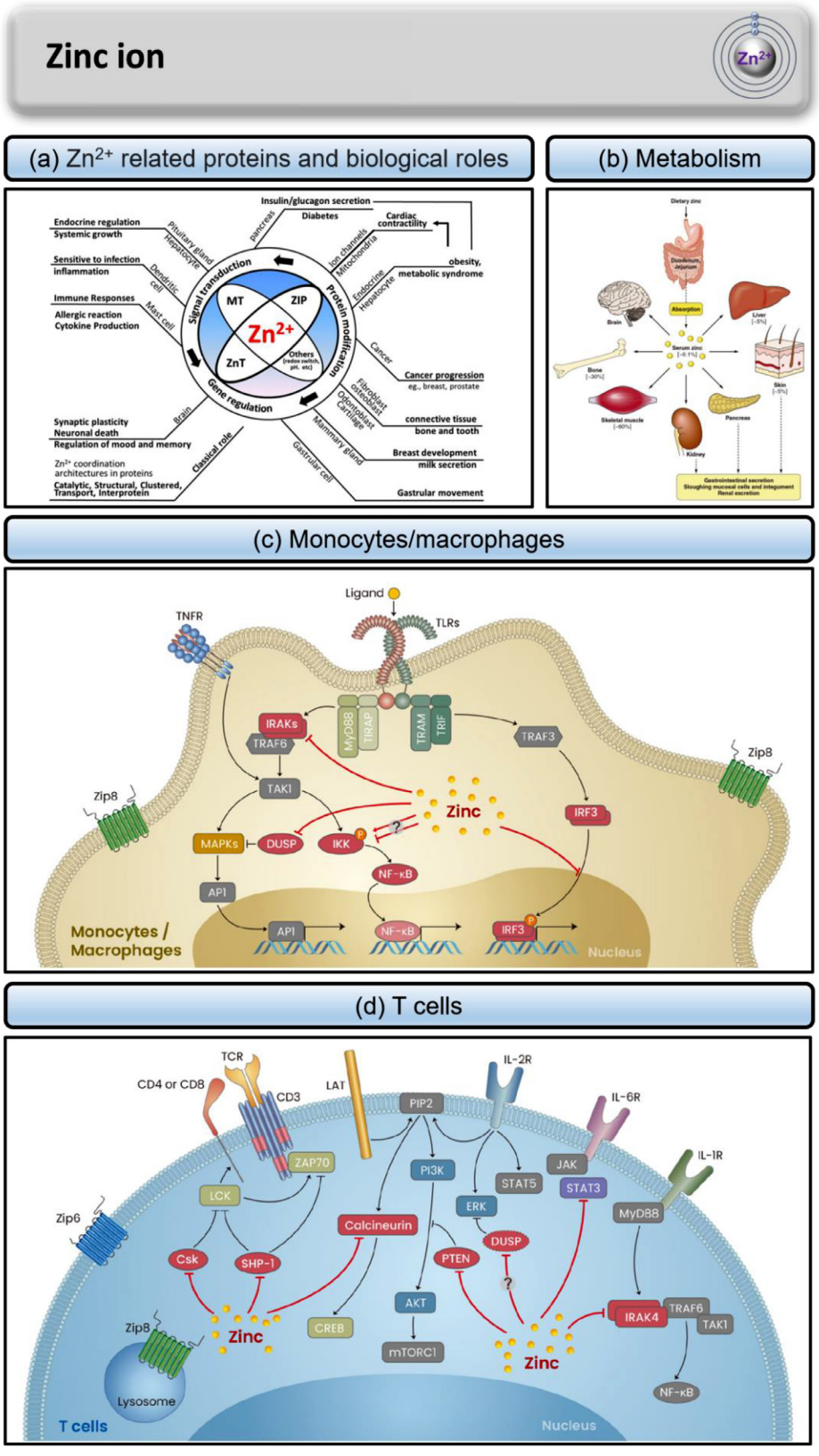

Fig. 15. Properties of zinc ion. (a) Diagram of Zn^{2+} involved in protein modification regulated by MTs, ZnTs, and ZIPs family channel proteins, thus participating in signal transduction and gene regulation under various circumstances. Adopted from ref. [357], copyright 2015, Korean J Physiol Pharmacol. (b) Schematic diagram of the proportion of free zinc in serum transported to organs or tissues of the body and the metabolic pathway of zinc ions (including the metabolism of kidney, pancreas, and skin) after absorption of zinc ions through the gastrointestinal tract into the blood. Adopted from ref. [378], copyright 2015, The American Physiological Society. (c) Schematic diagram of zinc cooperated within the signal transduction of monocytes/macrophages with receptors shown on the cell membrane. Adopted from ref. [358], copyright 2021, Elsevier. (d) Schematic diagram of zinc cooperated in some major signaling pathways of T cells, including pathways of TCR, IL-1R, IL-2R, and IL-6R. Receptors and proteins involved in these pathways are shown. Adopted from ref. [358], copyright 2021, Elsevier.

inflammatory cytokines' production [363]. Neutrophils might be attracted by membrane-induced damage in a model of zinc deficiency. Chelation of free Zn^{2+} by using zinc ion chelators has been shown to inhibit chemotaxis, oxidative burst, phagocytosis, and cytokine production in human neutrophils [364]. Zinc signals are related to the activation, degranulation, and generation of cytokines in mast cells [365]. The ZnT5 transporters were abundantly expressed on mast cells, which resulted in FcRI-mediated NF-κB pathway activation and the PKC translocation of mast cells, hence mediating cytokines' production in delayed-type allergic responses [366,367]. Zn^{2+} influences the adaptive immune

response depending on peculiar cell types. It shows that zinc depletion switched the Th1/Th2 proportion into a Th1-dominant type and inhibited the activation of Th17 cells, therefore impairing the normal function of the whole T lymphocyte subsets [368]. Lower Zn^{2+} intake decreased the IL-12 synthesis by monocytes/macrophages, resulting in impaired Th1 differentiation [369]. B cells are indirectly affected by Zn ions, since BCRs are connected to the ZIP10 transporter in signal transduction, and a ZIP10 deficit lowered B-cell generation and proliferation [370].

4.3.5.3. osteogenic effects of zinc. Most of the zinc element is stored in the bone matrix. It is involved in stabilizing the bone structure and regulating the synthesis of protein cofactors [371]. Novel zinc scaffolds have been verified in both osteogenic and angiogenic processes. Zinc alloys are applied significantly in bone implant materials since their mechanical characteristics are comparable to mammalian bone tissues, and zinc is involved in several signal pathways that influence the functioning and proliferation of osteogenic cells [372–374]. Several biomaterials incorporating Zn have been proposed. Zn ions promoted osteoblastogenesis through TGF-β/Smad signal pathways in osteoblastic cells [375]. Zn deposited on HA coating also exhibited antibacterial and osteogenesis effects [376]. A zinc scaffold demonstrates the ability to activate the P38 pathway within monocytes, leading to BMSCs' recruitment to the site of bone defect. Furthermore, after implantation, there is an observed increase in the angiogenesis-related gene expression, indicating enhanced angiogenesis in the bone regeneration process [377].

5. Conclusion

Research has shown that the immune microenvironment induced by biometal ions is important for bone tissue regeneration. These inorganic bioactive factors are cost-effective, stable, and can be easily incorporated into bioinert matrices, expanding their practical applications in bone repair. This article provided a comprehensive overview of the interaction between biometal ions, immune cells, and the skeletal system.

Although the role of metal ions in osteoimmunomodulation has been uncovered, the underlying mechanisms are not yet clear. Previous studies have mainly focused on the polarization of macrophages and metal ions released from biomaterials, given the impacts of macrophages on the inflammatory response processes during biomaterial integration. However, other cells involved in the immune response, such as natural killer cells, mononuclear phagocytes, and lymphocytes, and their impacts on biomaterial-induced bone tissue repair are also worth further investigation.

Existing research on metal ions has demonstrated various combinations. In many cases, two or more bioactive ions are introduced into materials to synergistically promote bone tissue regeneration by harnessing their unique osteo-immunomodulatory properties. While the combination of multiple ions has shown stronger reparative effects compared to the use of a single ion, comprehensive studies elucidating the underlying mechanisms of collective regulatory effects of multiple metal ions in this context are necessary.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Shubo Liu: Writing – original draft, Visualization. **Zhengjie Lin:** Writing – original draft, Funding acquisition. **Wei Qiao:** Conceptualization, Writing – review & editing, Funding acquisition. **Bin Chen:** Writing – review & editing, Supervision, Funding acquisition. **Jie Shen:** Conceptualization, Writing – review & editing, Supervision, Resources, Funding acquisition.

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