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Endogenous VEGF isoform expression regulates tumour cell motility

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Background

Vascular endothelial growth factor-A (VEGF) is produced by most cancer cells as multiple alternatively spliced isoforms, which display distinct receptor and matrix binding characteristics. In addition to being a major inducer of tumour angiogenesis, VEGF also has complex functions in angiogenesis-independent aspects of tumour growth, but the role of individual VEGF isoforms remains poorly understood. Here we investigated the effects of endogenous VEGF isoform expression on tumour cell migration and invasion.

Method

We used a panel of mouse fibrosarcoma cells we developed (fs^{188} , fs^{164} and fs^{120}) that express single VEGF isoforms (188, 164 or 120 respectively), under endogenous promoter control. We investigated adhesion to different matrices, 2D migration and invasion through 3D collagen.

Results

Fs^{188} cells, are typically mesenchymal, form ruffles, display strong integrin-dependent adhesion and express high levels of pERK1/2 and pAKT. In contrast, fs^{164} and fs^{120} cells are not typically mesenchymal in morphology; they display weak binding to collagen, lack ruffles and align longitudinally forming long multicellular chains and abundant cell-cell contacts. On 3D collagen, fs^{188} cells remain mesenchymal while fs^{164} and fs^{120} cells adopt a rounded/amoeboid and a mix of rounded/mesenchymal morphologies respectively. Cell morphology and migration are dependent on the cytoskeleton and actinomyosin contractility, to provide traction force in mesenchymal movement, and cortical contraction for rounded amoeboid motility. Consistent with their mesenchymal characteristics, fs^{188} cells migrated faster in 2D and invaded 3D collagen more efficiently than fs^{164} or fs^{120} cells. Contractility inhibitors caused fs^{164}/fs^{120} cells to switch to a mesenchymal morphology and accelerated their migration but not that of fs^{188} cells.

Conclusion

VEGF isoforms are emerging as potential biomarkers for anti-VEGF therapies. Our results suggest that individual VEGF isoforms influence the migration and invasion strategies of tumour cells thus adding to the complexity of VEGF signaling within the tumor microenvironment.

Acknowledgements

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