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CELL ADHESION

Winning mechanism for angiogenesis

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To form new blood vessels from existing ones — as occurs during tumour angiogenesis — endothelial cells must degrade the underlying basement membrane, which normally maintains quiescence of the vascular endothelium. Seano *et al.* describe the role of endothelial podosome rosettes as a focal point for basement membrane degradation and vessel branching.

Podosomes, which are cell–matrix contacts with an inherent ability to degrade extracellular matrix (ECM), can occur individually or in ring-like clusters known as rosettes in cultured endothelial cells. The percentage of podosome rosette-containing endothelial cells was increased after stimulation with vascular endothelial growth factor A (VEGFA), and the level of matrix metalloproteinase 14 (MMP14) was greater in VEGFA-stimulated endothelial cells than quiescent endothelial cells. Podosome rosettes were also observed in mouse models of tumour angiogenesis and clinical biopsies from human lung tumours. In a mouse tumour model, rosette density increased during the 'angiogenic switch', and in human lung tumours, rosette density correlated with microvessel density and VEGFA level. Thus, angiogenic endothelium is characterized by ECM-degrading podosome rosettes.

Further study showed that VEGFA strongly upregulates α6 integrin expression in endothelial cells and that this stabilizes podosome rosettes. Laminin α4, which is a ligand for α6β1 integrin and a component of the vascular basement membrane, decreased VEGFA-induced rosette formation by preventing the re-localization of α6β1 integrin from focal adhesions to podosome rosettes. Forced disassembly of focal adhesions overcame the inhibitory effect of laminin on rosette formation. So, the level of available α6β1 integrin is a limiting factor for the formation of endothelial podosome rosettes. Angiogenic growth factor stimulation overcomes the inhibitory effect of the basement membrane by increasing transcription of the gene encoding α6 integrin and hence the quantity of α6β1 heterodimer.

Live imaging studies of mouse aortic rings showed that vessel branching is always preceded by rosette formation, both of which were inhibited by genetic ablation of endothelial α6 integrin. Genetic or antibody-mediated blockade of α6 integrin in mouse tumour models impaired rosette formation and tumour vessel branching, which illustrates the therapeutic potential of targeting these structures for 'vascular normalization' in tumours.

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ORIGINAL RESEARCH PAPER Seano, G. *et al.* Endothelial podosome rosettes regulate vascular branching in tumour angiogenesis. *Nature Cell Biol.* **16**, 931–941 (2014)

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