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EDITORIAL

The vascular outsiders

A recent perspective on vessel co-option and angiotropic extravascular migratory metastasis by Lugassy et al. suggests cancers use both mechanisms sequentially during tumour growth and spread.

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MAIN

Not all cancers induce angiogenesis to sustain growth. Tumours can also grow around existing vasculature to access the sustenance they need for survival. This phenomenon, now known as vessel co-option, was first observed over 25 years ago in a subset of non-small cell lung cancers and metastasis in the lung [1], but is only recently more widely recognised as an alternative to sprouting angiogenesis as a means of blood vessel recruitment [2]. Importantly, vessel co-option helps to explain the poor clinical responses and resistance to anti-angiogenic therapies (AAT) [3].

As well as refinement in understanding of tumour blood vessel recruitment, knowledge of cancer spread has also evolved beyond the classic model of blood-borne metastases to include extravascular routes. For example, extravascular migratory metastasis (EVMM) describes a method by which cancer cells migrate along external vessel walls without ever entering the blood circulation. EVMM is not well understood. It is best described in melanoma, but has also been detected in glioma and pancreatic cancer [4]. It is generally not known how frequently this mode of metastatic spread occurs and also how far cells can migrate via this route. Nevertheless, it is an elegant concept. Why expend energy invading into and out of blood vessels, which is also a notoriously inefficient way to metastasise, when cells can piggyback on existing vascular scaffolds using them like a climbing frame in order to move around?

This thoughtful perspective on vessel co-option and EVMM is from Lugassy and colleagues, who performed much of the formative work [5]. The authors provide a compelling argument that these two mechanisms of tumour growth and spread are not necessarily discrete, but likely work in tandem (Fig. 1). This seems like a logical conclusion to draw since both processes involve colonisation of the perivascular niche and can employ similar mechanisms.

For instance, extravasating metastatic cells can colonise the brain and co-opt existing vasculature by expressing neural cell adhesion molecule L1 (L1CAM), which facilitates vascular adhesion [6]. L1CAM has also been implicated in pericyte mimicry which occurs during EVMM and is the ability of cancer cells to spread along the outside of vessels, sometimes replacing existing pericytes as they migrate along the external vessel surface [7].

Other interesting synergies include the role of serine protease inhibitors (serpins) which have long been implicated in metastatic spread [8]. While some proteolytic activity by cancer cells is necessary to promote remodelling of the tumour microenvironment and cell invasion, by limiting plasmin generation, serpins can prevent excessive proteolysis and degradation of the extracellular matrix. More recent work has shown that secretion of neuroserpin is protective as it prevents plasmin-mediated apoptosis of extravasating cells. Serpins also prevent plasmin inactivation of L1CAM, thereby promoting vessel co-option [6].

The increasing body of literature in the fields of vessel co-option and EVMM make this a timely perspective [3, 4, 9]. The authors carefully explain the terminology in common use in the fields, expand on the evidence and gaps in knowledge. Clearly, further studies will be necessary to understand the complexity of both vessel co-option and EVMM. This will be important if targeting either or both of these mechanisms will have translational promise. Identification of vascular targets in co-opted vessels may prove difficult since recent work demonstrates that both endothelial cells and pericytes are quiescent in co-opted vessels with a similar transcriptome to normal vessels [10].

While there is much more work to be done in identifying potential vascular targets, properties of cancer cells that facilitate migration towards and along the vasculature may prove more tractable as targets. Drawing on comparisons of mechanisms involved in malignant cell motility with those that occur during embryogenesis may afford opportunities for the identification of new therapeutic strategies. Possible examples include inhibitors of epithelial–mesenchymal transition (EMT), MET receptor and Wnt signalling pathways [9]. As noted by the authors, the role of basement membrane laminins may also prove pivotal to understanding altered cancer cell signalling and migration patterns along the vasculature [5].

In summary, vessel co-option by primary and secondary tumours occurs more frequently than previously appreciated. It is a mechanism of both intrinsic and acquired resistance to AAT as cancers are either inherently able to evade these treatment modalities, or can switch between angiogenic and non-angiogenic modes of vessel recruitment depending on selection pressures [3].

The challenge now will be to design and deliver effective therapeutic approaches that limit the ability of tumours to use both strategies of vessel recruitment. A greater appreciation and understanding of extravascular routes of metastatic dissemination will also expand the possibilities to limit cancer spread. The work by Lugassy et al. provides new models for tumour growth and metastasis, which will ultimately uncover further avenues of research and opportunities to inhibit cancer.

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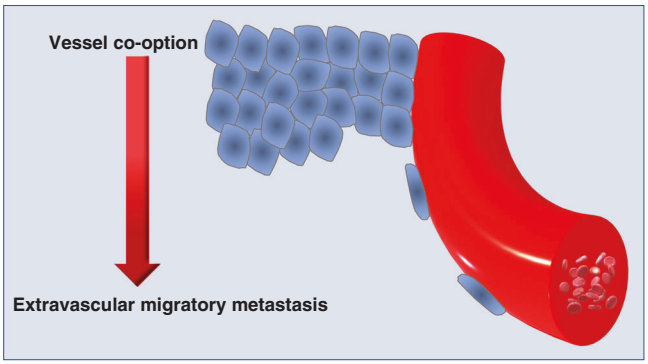

Fig. 1 Sequential tumour growth and spread by vessel co-option and extravascular migratory metastasis. Schematic of a tumour growing towards and around an existing blood vessel during vessel co-option, followed by metastatic escape of cells from the tumour which migrate along the external vessel wall during extravascular migratory metastasis.

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