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Linked in: the extracellular matrix network in tumour dissemination

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Linked Article: Caley *et al.* *Br J Dermatol* 2021; **184**:923–934.

The focus of cancer research initially lay on individual tumour cells and uncovering the cell-intrinsic hallmarks and deregulated pathways that distinguished these from their normal counterparts. However, today, cancers are investigated as entities, and include the nonmalignant cells and noncellular components of the tumour microenvironment that enable and perpetuate this corrupted cell behaviour. The extracellular matrix (ECM) comprises up to 60% of a tumour's mass.[1] This heterogeneous, but well-orchestrated, three-dimensional meshwork of proteoglycans and insoluble fibrillar proteins, such as collagens, elastins, fibronectins and laminins, imparts important biophysical and biochemical properties to tissue.[2] Far from being an inert intercellular filler, the ECM is a dynamic structure that is constantly being remodelled and is a key regulator of many crucial cellular processes. The ECM proteome, also known as the matrisome, consists of approximately 300 core and 700 associated proteins.[3] As these are interconnected via the same network, alterations in single components tend to have serious knock-on effects. Unsurprisingly, matrisome composition is altered in cancer, with significant downstream consequences for tumour progression.

In this issue of the *BJD*, Caley *et al.* uncover signalling events downstream of reduced laminin α3 expression that lead to invasive cutaneous squamous cell carcinoma.[4] Laminin α3 is a subunit of the heterotrimeric laminin-332 molecule, a specialized ECM component of the basement membrane important for epidermal–dermal cohesion. Binding to cell receptors on one end, and to ECM components on the other, laminin-332 is perfectly poised to transmit signals from the ECM to cells and can switch from being an anchoring protein to a migration-promoting factor depending on context.[5] In the context of reduced laminin α3 expression, signalling of ROCK, a key element of cell motility and metastatic cancer cell behaviour, is activated. Furthermore, the authors demonstrated that loss of laminin α3 drives the reprogramming of the immune microenvironment, enhancing recruitment of monocytes to the tumour, via TWIST-mediated increase in CCL2 secretion, and further their interleukin-13-mediated differentiation to tumour-supportive M2 macrophages.[4] The factors leading to loss of laminin α3 expression, which was shown to be associated with poor differentiation status, currently remain unclear.

Beyond an altered composition, changes in the physical ordered structure and assembly of the ECM network dictate its biophysical role. For example, collagen density influences matrix pore size, which impacts not only cell motility but also the local sequestration of signalling factors by preventing their passive diffusion.[6,7] However, the thickening and realignment of collagen fibres into linearized bundles influences stiffness, impacting cell mechanotransduction, and also provides an infrastructure for dissemination by serving as an invasion 'highway' that facilitates the directional migration of tumour cells.[8]

Given that changes in the ECM promote the stepwise progression through the metastatic cascade and contribute to therapy resistance,[1,3] comprehensive profiling of the cancer matrisome, including the resolution of spatiotemporal changes in its mechanics,[6] for the purposes of diagnostics and therapy, is a worthy undertaking and should remain a key focus of cancer research.

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