Nikki Walker

10-YEAR ANNIVERSARY

Environment dictates behaviour

Although the extracellular matrix (ECM) was originally thought to function to keep cells together, it is now widely recognized that it has a more influential and active role as it also controls cell behaviour. In the 1980s, Bissell and colleagues laid a strong foundation for studies on the role of the ECM by showing that the physical properties of the environment dictate epithelial cell differentiation and tumour induction by Rous sarcoma virus; but the functional importance and robustness of the physical properties of the ECM have only been revealed in the past decade.

In 2004, McBeath *et al.* showed that human mesenchymal stem cells (MSCs) differentiate into adipocytes or osteoblasts depending on their shape, which is determined by the density at which they are grown and thus the degree of adhesion to their substrate. The authors also showed that the mechanical cues that drive MSC differentiation are mediated by the small GTPase RHOA, which signals to the cytoskeleton.

Two years later, Engler *et al.* found that different degrees of ECM stiffness direct human MSC fate — MSCs differentiate into neuron-like cells when cultured on soft matrices, into muscle cells on stiffer matrices and into osteoblasts on rigid matrices. They also reported that this information is transmitted by focal adhesions and requires myosin II contractility. These studies showed that the mechanical properties of the environment are sensed by MSCs and can direct lineage specificity, similarly to growth factors.

More recently, Levental *et al.* showed that ECM stiffness affects tumour cell invasion. They showed that breast cancer tumorigenesis is accompanied by collagen cross-linking, which stiffens the ECM. This, in turn, promotes the formation of adhesions, which function as mechanical sensors, and integrin signalling, which induces tumour invasion.

The importance of the ECM in controlling cell behaviour has led to many studies aiming to elucidate the principles of mechanosensing, which are only now beginning to emerge. Understanding how cells respond to signals from the microenvironment should increase the efficiency of cancer and stem cell therapies and thus may have important clinical implications.

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