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The regulation of immune cell trafficking by the extracellular matrix

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The extracellular matrix (ECM) comes in different structural forms and biochemical compositions, which determine both its biophysical properties and its ability to convey specific signals to immune cells encountering or navigating through it. Traditionally, the role of the individual ECM molecules on cell migration has been investigated independent of considerations such as the tension/mechanical strength constituted by the ECM. However, more recently, this aspect has attracted considerable attention and data suggest that rigidity and molecular signals derived from the ECM define the mode of cell migration. We here review the different types of ECM encountered by migrating immune cells *in vivo*, as well as current information on how both molecular components of the ECM and their supramolecular structure can impact on modes of immune cell migration.

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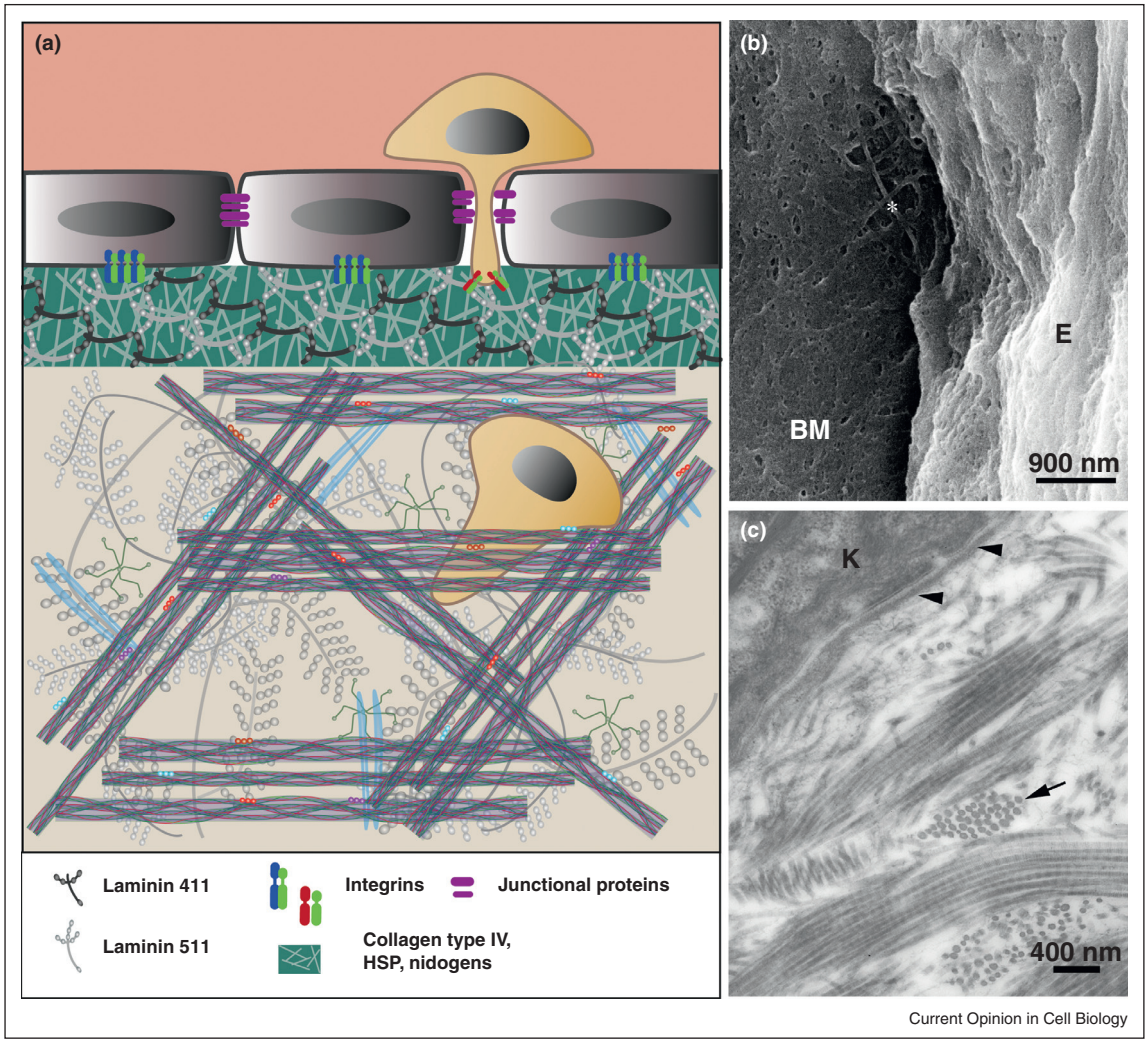
ECM composition and structure

The extracellular matrix (ECM) is composed of glycoproteins that assemble to form supramolecular structures that are specific to the organ and its function [1•]. For example, the ECM of the dermis of the skin is very different to that of the parenchyma of the central nervous system (CNS) but both are perfectly adapted to the function of the organ — flexibility and strength in the case of dermis while, in the case of the CNS parenchyma, the ability to occupy the large volume between the delicate neurons without exerting pressure on them and without impeding neural transmission. Not only are the molecular constituents different in these two tissues but so too is their supramolecular organization, both of which act concertedly to influence cell migration in these organs.

Broadly, ECMs can be divided into interstitial matrix and basement membranes (Figure 1). The interstitial matrix is composed of fibrillar collagens (mainly collagen type 1, but depending on tissue type also collagen types II, III, V, XI) [2•] which convey tensile strength, plus other non-fibrillar collagens such as collagen types VI, VIII, IX, XII and XIV, glycoproteins including fibronectin, vitronectin and the tenascins, and both large and small proteoglycans like aggrecan, veriscan, biglycan, decorin, lumican and fibromodulin that act to resist compressive forces (Table 1). Although minor components of the interstitial matrix, non-fibrillar collagens, glycoproteins and (small leucine-rich) proteoglycans control the spatial organization of collagen monomers into fibrils, fibril diameter, density and their 3D organization, hence, they control the stiffness of the interstitial matrix (Figure 2) [3•,4]. Basement membranes are biochemically more heterogeneous than interstitial matrices. They are all composed of the same four families of glycoproteins: laminins, collagen type IV, heparin sulfate proteoglycans and nidogens (Table 2). However, as each family has several isoforms they can combine differentially to form biochemically unique basement membranes. In addition, there are more than 50 other glycoproteins, including netrin-4 [5], fibulin-1 and fibulin-2 [6], BM-40 (also known as osteonectin and SPARC) [7], collagen types VII, VIII, XV and XVIII [8], that are minor components of some basement membranes but nevertheless can interact with cells and have distinct functions. The interstitial matrix forms structures that are similar to fishing nets — loose networks of collagen fibres, the size and density of which varies between tissues depending on the presence of other glycoproteins and small proteoglycans, while basement membranes are dense protein networks that form sheet-like structures that separate tissue compartments and either underlie (epithelial and endothelial cells) or encase cells (nerves, fat and muscles) (Figure 1). Despite their greater biochemical heterogeneity it is not possible to discern ultrastructural differences between the basement membranes, yet the different organization of fibrillar collagen matrices resulting from comparatively small differences in minor components are readily detectable by electron microscopy [9•]. Reticular fibre networks of lymphoid organs represent unique ultrastructures that combine interstitial matrices and basement membranes, with the characteristic flexibility and strength of the

Figure 1



(A) Schematic presentation of the basement membrane underlying an endothelial monolayer and the subjacent interstitial matrix in association with migrating cells. **(B)** Scanning electron microscopy (EM) shows the sheet-like nature of the basement membrane (BM) underlying an endothelial cell (E). A typical banded type I collagen fibril in the underlying interstitial matrix is evident through a tear in the basement membrane (marked with *). **(C)** Transmission EM of mouse skin shows sagittal sections of type I collagen fibrils revealing their typical banded pattern and linear alignment, as well as cross sections (arrow) of fibrils revealing the occurrence of different sized fibrils arranged into larger fibres. The dense basement membrane is also evident underlying keratinocytes (K) (arrowheads). HSP is heparin sulphate proteoglycans; SLRP is small leucine rich proteoglycans.

interstitial matrix and the barrier properties of basement membranes [10]. Such matrices are similar to the provisional matrix that occurs at sites of injury that are readily invaded by immune cells during wound healing, but which will not be dealt with here.

Interstitial matrices

Conventionally, cell migration has been studied on 2D surfaces coated with purified individual ECM molecules. Even though they do not reflect the complexity or 3D organization of the ECM *in vivo*, such studies provide valuable information on adhesive substrates for specific cell types, the nature of surface receptors required for recognition of a particular ECM molecule, and molecular mechanisms of integrin receptor activation [1•,11••,12]. They were also the first to demonstrate that highly adhesive substrates are less conducive to cell migration than less adhesive substrates and elucidated intracellular signalling pathways induced by a defined ECM-receptor interaction leading to cytoskeletal rearrangements required for directed migration [13,14].

More recently, the use of 3D extracellular matrices for cell migration have revealed that the mechanical properties of the ECM influence whether or not defined integrins and signal transduction pathways are actually