

P035 Syndecan-4-dependent GTPase regulation determines directional migration in response to the extracellular matrix
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Cell migration in wound healing and disease is critically dependent on integration with the extracellular matrix, through the simultaneous engagement of receptors, integrin $\alpha5\beta1$ and syndecan-4, by matrix ligands such as fibronectin. The coordinated cycles of membrane protrusion and cytoskeletal contraction, which facilitate cell translocation, require convergence of signals downstream of integrin and syndecan-4, and also divergence of adhesive signals to alternately regulate the small GTPases Rac1 and RhoA. Using nano-engineered fibronectin surfaces and cell-derived matrices, we identify synergy between integrin and syndecan-4 as the key determinant of directional migration. In wild-type fibroblasts, syndecan-4 mediates matrix-induced, PKC α -dependent activation of Rac1 and suppression of RhoA, localising active Rac1 to the leading edge of the cell, and resulting in persistent migration. By contrast, syndecan-4-null fibroblasts migrate randomly due to high, delocalised Rac1 activity, while cells expressing a syndecan-4 cytodomain mutant deficient in PKC α regulation fail to localise active Rac1 to points of matrix engagement and consequently fail to recognise and respond to topographical changes in the matrix. These experiments define syndecan-4 as a matrix sensor that regulates the migratory response of individual cells to the matrix environment.