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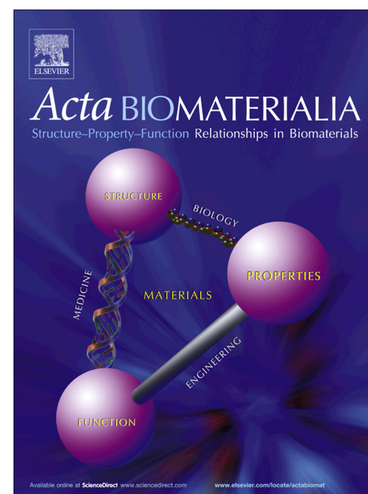

Full length article

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Engineering Interfacial Migration by Collective Tuning of Adhesion Anisotropy and Stiffness

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Abstract

Interfacial migration is central to multiple processes including morphogenesis and wound healing. However, the sensitivity of interfacial migration to properties of the interfacial microenvironment has not been adequately explored. Here, we address this question by tracking motility of 3T3 fibroblasts at the interface of two hydrogels. By sandwiching cells between two adhesive gels (composed of methacrylated gelatin) or between an adhesive and a non-adhesive gel (composed of gellan), we show that cells are more motile in case of the latter. By tuning the bulk stiffness of the gellan gel, we then show that motility is tuned in a stiffness-dependent manner. Fastest motility observed in case of the stiffest gel was associated with increased cell height, suggestive of stiffness-mediated cytoskeletal assembly. Inhibition of cell motility by contractile agonists and actin depolymerizing drugs is indicative of a mode of migration wherein cells combine contractile tractions exerted at their base and actin-based pushing forces on the top surface to propel themselves forward. Together, our results suggest that dorso-ventral adhesion anisotropy and stiffness can be collectively tuned to engineer interfacial migration.

Introduction

Cell migration is a complex and organized process observed both in physiological and in pathological processes including tissue morphogenesis [16, 30, 34], wound healing [19, 34], immune surveillance [20], and cancer invasion [36]. It is increasingly appreciated that cell migration is shaped both by cell intrinsic as well as by cell extrinsic factors. The extracellular matrix (ECM), which constitutes the bulk of the cell microenvironment, represents the single most important cell extrinsic factor influencing cell migration. ECM physicochemical properties including ligand type [26, 38, 40], ECM density [13], ECM stiffness, ECM topography and ECM dimensionality [7] have been shown to influence cell shape and cell motility across multiple different cell types. The relative importance of each of these individual attributes and their effect is dependent on the nature of cell migration, i.e., two-dimensional (2D) versus interfacial versus three-dimensional (3D). For example, studies have shown opposite effects of ECM stiffness on cell motility in 2D versus 3D, with increased ECM stiffness promoting cell motility in 2D, but inhibiting cell motility in 3D [33]. Additionally, the molecular mechanisms utilized for cell migration in these different microenvironments also differs [10]. For example, 2D cell motility involves actin-based protrusion at the leading edge, formation of focal adhesions, and contractility-dependent retraction of the trailing edge. In 3D environments, while cells are capable of migrating without forming focal adhesions, contractility-mediated nuclear squeezing is critical in dense matrices [14]. While much is known about 2D and 3D cell migration, relatively less importance has been paid towards understanding interfacial migration, which applies to peritoneal layers lining the organs, cells that migrate at the linear interface of basement membranes and bed of ECM proteins [27].

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