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Mechanosensing of matrix by stem cells: from matrix heterogeneity, contractility, and the nucleus in pore-migration to cardiogenesis and muscle stem cells *in vivo*

Running title: Mechanosensing by stem cells

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Abstract

Stem cells are particularly 'plastic' cell types that are induced by various cues to become specialized, tissue-functional lineages by switching on the expression of specific gene programs. Matrix stiffness is among the cues that multiple stem cell types can sense and respond to. This seminar-style review focuses on mechanosensing of matrix elasticity in the differentiation or early maturation of a few illustrative stem cell types, with an intended audience of biologists and physical scientists. Contractile forces applied by a cell's acto-myosin cytoskeleton are often resisted by the extracellular matrix and transduced through adhesions and the cytoskeleton ultimately into the nucleus to modulate gene expression. Complexity is added by matrix heterogeneity, and careful scrutiny of the evident stiffness heterogeneity in some model systems resolves some controversies concerning matrix mechanosensing. Importantly, local stiffness tends to dominate, and 'durotaxis' of stem cells toward stiff matrix reveals a dependence of persistent migration on myosin-II force generation and also rigid microtubules that confer directionality. Stem and progenitor cell migration in 3D can be further affected by matrix porosity as well as stiffness, with nuclear size and rigidity influencing niche retention and fate choices. Cell squeezing through rigid pores can even cause DNA damage and genomic changes that contribute to de-differentiation toward stem cell-like states. Contraction of acto-myosin is the essential function of striated muscle, which also exhibit mechanosensitive differentiation and maturation as illustrated *in vivo* by beating heart cells and by the regenerative mobilization of skeletal muscle stem cells.

(244 words)