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Extracellular matrix elasticity directs stem cell differentiation

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Stem cell differentiation is regulated by a variety of cues including growth factors and extracellular matrix (ECM), although the role that the ECM has in this process is less understood. Here we provide examples of how the composition, concentration, and elastic modulus of matrix as well as its temporal and spatial location plays a key role in regulating cell fate. Natural variation of matrix elasticity (Figure 1A), ranging from soft brain tissue to calcified bone, plays an important developmental role for tissues: muscle cells want compliant matrix such that they can deform it during contractions whereas bone cells want a less compliant matrix which they can mineralize. Differentiation of naïve mesenchymal stem cells (MSCs) in a microenvironment with a controlled elastic modulus (Figure 1B) mirrors tissue-level elasticity: soft matrices that mimic brain are neurogenic, stiffer matrices that mimic muscle are myogenic, and comparatively rigid matrices that mimic collagenous bone prove osteogenic (Figure 1C). Responses are observed at all levels from RNA to protein production to morphology and cell stiffness. Inhibition of elasticity-directed lineage specification in MSCs and ES cells occurs when non-muscle myosin-II is blocked - without strongly perturbing many other aspects of cell function and shape. However, such responses act synergistically with chemical factors where only the combination of both results in differentiation marker expression similar to that of differentiated cell lines.

Although growth factors likely have increased influence earlier in development compared to matrix as they signal to cells to produce matrix, ECM maintains the ability to stimulate similar cell responses in embryonic stem (ES). Over the initial week of ES cell differentiation, expression of Nanog, a self-renewal gene, drops 10-fold and is followed by a 3-fold up-regulation in ECM, suggesting an inverse relationship between matrix expression and self-renewal. This is supported by co-localization of matrix and germ layer markers (e.g., GATA4, SOX1, etc.) along with decreased levels of matrix and Nanog. When the elasticity of this matrix was increased by the introduction of cross-linking agents, loss of self-renewal and germ layer commitment is accelerated. Taken together, it appears that stem cells can be significantly influenced by *both* the chemical and physical aspects of their microenvironment, which should be considered for therapeutic uses of stem cells.

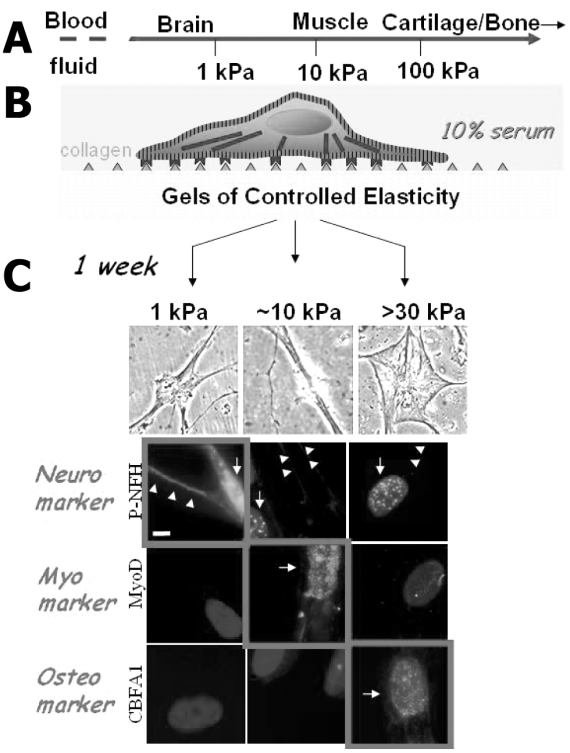

Figure 1. Natural tissue variation induces differentiation marker expression in stem cells.

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