Cell-Matrix-Mechanics Dictates Cell Fate via Cytoskeleton Structure

Florian Rehfeldt

Institute of Physics, Biophysics
Georg-August-University, Göttingen

Abstract:

The mechanical properties of microenvironments in our body are very diverse and are as important to cells as biochemical cues. An especially striking experiment of this *mechano*-sensitivity demonstrated that systematic variation of the Young's modulus *E* of the substrate can direct the lineage differentiation of human mesenchymal stem cells (hMSCs).

To elucidate the complex interplay of physical and biochemical mechanisms of cellular *mechano*-sensing, well-defined extracellular matrix (ECM) models are essential. While elastic substrates made of poly-acrylamide (PA) are widely in use, they have the potential drawback that the precursors are cytotoxic and therefore do not allow for 3D culture systems.

Here, a novel biomimetic ECM model based on hyaluronic acid (HA) was successfully established that exhibits a widely tuneable and well-defined elasticity *E*, enables 2D and 3D cell culture and enables us to mimic a variety of distinct *in vivo* microenvironments.

Quantitative analysis of the structure of acto-myosin fibers of hMSCs on elastic substrates with an order parameter *S*, reveals that the stress fiber morphology is an early morphological marker of *mechano*-guided differentiation and can be understood using a classical mechanics model. Furthermore, the cytoskeleton also dictates the shape of the nucleus and lends support to a direct mechanical matrix-myosin-nucleus pathway.

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Room PH 127

Contact: Hendrik Dietz, dietz@tum.de, phone: 089-289-11615