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# COMBATING MECHANO-DRIVEN STEM CELL FATE WITH ADVANCED BIOMATERIALS TO ENHANCE TISSUE REPAIR AND FUNCTIONAL RECOVERY

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## SUMMARY

Crucial to their survival and function as reparative cells within all tissues, perivascular-derived mesenchymal stromal cells (MSCs) actively sense and respond to variations in extracellular matrix (ECM) composition and changes in the mechanics of their local microenvironment. We have previously confirmed that by mimicking these biophysical and biochemical cues in vitro, variations in matrix mechanics, ligand type and nano-spatial organization of adhesive ligands can not only invoke, but be deterministic of changes in MSC proliferation, migration and differentiation. These insights are important to consider, especially when one reflects on the fact that in a wounded or diseased microenvironment, the composition and status of the ECM, and hence the mechanical properties of the tissue, are not the same as in healthy tissues! In our most recent works, we have sort to develop new approaches to overcome the impacts of these 'corrupted' microenvironments on MSC behavior and function, and still effect functional tissue repair. We firstly identified differentially expressed microRNAs produced by MSCs in response to varying matrix stiffness and RhoA activity, or post activation in an injury site in tissues. Thereafter, using hydrogels and self-assembling nanoparticles, we have shown that modulating these mechanosensitive miRNAs (through targeted delivery) when delivering MSCs can overcome local 'soft' mechanical cues to drive commitment to stiffer tissues (e.g. bone), or suppress the creation of 'stiff' fibrotic tissue within an injured 'soft' tissue which can negatively impact endogenous MSCs and their fate. The outcomes of these recent studies provide new understanding of the complex mechanisms regulating MSC mechanosensing, mechanotransduction and differentiation, but also a novel strategy with which to manipulate MSC fate and significantly impact tissue engineering and regenerative medicine applications that focus on their exogenous use or endogenous manipulation.