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UNRAVELLING THE IMPACT OF LOCAL FORCE TRANSMISSION AT THE NANOSCALE ON STEM CELL FATE CHOICE

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SUMMARY

The exquisite sensitivity of tissue resident mesenchymal stem cells (MSCs) to nanoscale variations in adhesive ligand spacing *in vivo* is made clear and present by pathological conditions that prevail within our musculoskeletal tissues, with perturbations in the ability of extracellular matrix (ECM) molecules to create requisite tertiary structures, such as the 67nm banding periodicity in collagen fibres, or the nanoscale organisation of the epitopes on fibronectin fibres, being responsible for the onset or persistence of disease states (such as osteogenesis imperfecta). Given the sensitivity of MSCs to such small variations in ligand lateral spacing, and the potential for dysfunctional spacings in tissues of pathogenic states (e.g. post injury or disease), a greater understanding of the molecular mechanisms underlying the impacts of ligand lateral nanospacings on human MSC fate choice is required. In this work we utilised a range of real time cellular biosensors to investigate how human MSCs sense defined variations in lateral nanospaced ligands, showing that changes in lateral spacing of adhesion motifs affects the activation of critical mechanotransduction signalling pathway modulators, ultimately leading to bias in cell fate commitment. This new insight can be used to not only guide researchers to design directive biomaterials for stem cell culture and regenerative medicine applications that support normal phenotypes, but also to understand how perturbations in ECM conformation (with injury or disease), and hence ligand availability and spacing, can lead to dysfunctional stem cell behaviours post injection to site of injury.