MECHANOTRANSDUCTION

Lamin A for tension relief

The extracellular tension (or stress) that a cell experiences influences its behaviour, for example during differentiation. Discher and colleagues have identified the nuclear envelope protein lamin A as a 'mechanostat' factor that is upregulated in response to physical stress and alters the properties of the nucleus as well as gene expression.

The authors reasoned that specific factors must respond to changes in extracellular matrix (ECM) stiffness and so analysed the proteomes of different human and mouse tissues to identify possible candidates. They observed that levels of lamin A (but not B-type lamin) globally increased in stiff tissues relative to soft tissues and scaled with tissue elasticity (equivalent to stiffness). Mass spectrometry analysis also showed that the conformation and phosphorylation of lamin A changed in response to altered extracellular stress, the latter of which would be consistent with reduced lamin A turnover.

Next, the authors asked whether the changes in lamin A that occur in response to altered ECM stiffness are relevant for cell differentiation. It is known that matrix elasticity can determine mesenchymal stem cell (MSC) lineage differentiation, with a soft matrix favouring the formation of fat and a stiff matrix the formation of bone. After depletion of lamin A, the formation of fat on soft matrix increased, whereas overexpression of lamin A on stiff matrix increased osteogenesis.

The authors also identified the serum response factor (SRF) pathway (which affects the actin cytoskeleton) and the transcription factor Yes-associated protein 1 (YAP1) as potential effectors of lamin A.

LMNA transcription in this context was found to be controlled by retinoic acid signalling, as chromatin immunoprecipitation analysis showed that retinoic acid nuclear receptors bound to *LMNA*. Moreover, lamin A levels responded to changes in retinoic acid signalling, an effect that was increased in cells on stiff matrix relative to soft matrix and was important for MSC differentiation control. Lamin A knockdown also reduced the levels and nuclear translocation of retinoic acid receptors, suggesting that it might participate in its own negative feedback control.

Interestingly, increased lamin A levels prevented distortion of the nucleus in response to physical stress and increased nuclear viscosity. Thus, the authors conclude that lamin A acts as a mechanostat factor in cells, and that its increased levels in response to extracellular tension makes the nucleus more resistant to deformation. This might ensure that chromatin organization is not perturbed when tissues experience stress and may be fundamental for normal development.

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