Nature Reviews Molecular Cell Biology | Published online 21 Mar 2018; doi:10.1038/nrm.2018.21

MECHANOTRANSDUCTION

Kindlin' the fate of mesenchymal stem cells

> "kindlin-2 controls … the levels and activity of YAP1 and TAZ and osteogenesis"

Mesenchymal stem cells (MSCs) can give rise to several cell lineages, including osteoblasts and adipocytes, and it is known that adhesive and mechanical cues from the microenvironment control cell fate decisions. In the *Journal of Cell Biology*, Guo *et al.* now report that kindlin-2 regulates MSC differentiation through the mechanosensitive transcription co-regulators YAP1 and TAZ.

Kindlin-2 is an integrin- and actin-binding protein that regulates the actin cytoskeleton and integrin bidirectional signalling. The authors first found that, in MSCs derived from human placenta, the levels of kindlin-2 increase during osteogenic differentiation and decrease during adipogenic differentiation. Low and high expression in adipose cells and in bone, respectively, were confirmed by immunostaining of mouse femur bone sections. Moreover, knockdown of kindlin-2 in human MSCs induced spontaneous adipogenic differentiation and reduced their capacity to differentiate into osteocytes when cultured in an osteogenic differentiation-induction medium, indicating that reduced expression of kindlin-2 is sufficient to induce adipogenic differentiation of MSCs.

Ablation of kindlin-2 in mice caused severe limb shortening and defects throughout the skeleton, which were accompanied by reduced expression of osteogenic markers and an increase in adipogenic markers. Thus, kindlin-2 plays a crucial part in the control of MSC cell fate decision *in vivo*, promoting osteogenic differentiation and inhibiting adipogenesis, which is in agreement with previous reports of osteogenesis and adipogenesis being inversely correlated.

Next, in cultured human MSCs, the authors found that, similar to kindlin-2, the expression levels of YAP1 and TAZ, which are known regulators of MSC differentiation, were increased during osteogenic differentiation and reduced during adipogenic differentiation. Importantly, YAP1 and TAZ mRNA and protein levels were markedly reduced following kindlin-2 knockdown in cultured cells and in mice, and were restored upon kindlin-2 re-expression in cells. Thus, kindlin-2 regulates YAP1 and TAZ levels *in vitro* and *in vivo*.

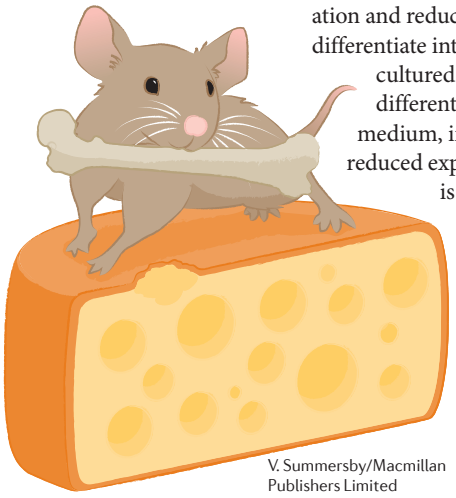
To test whether kindlin-2 regulates MSC differentiation via YAP1 and TAZ, the authors overexpressed YAP1 and TAZ in MSCs in which the gene encoding kindlin-2 was knocked out. Indeed, this forced expression restored MSC differentiation into osteocytes and reduced adipogenic differentiation. So what are the mechanisms linking kindlin-2 to YAP1 and TAZ and to MSC fate?

Kindlin-2 interacts with and activates integrins. Expression of kindlin-2 mutants that lack either integrin-binding or actin-binding capacity failed to restore YAP1 and TAZ mRNA and protein levels in cells depleted of kindlin-2. Moreover, they were less effective in inducing osteogenic differentiation and suppressing adipogenic differentiation than wild-type kindlin-2, suggesting that kindlin-2 must bind to integrin and actin to regulate YAP1 and TAZ.

Mechanical cues play an important role in the regulation of MSC fate through YAP1 and TAZ, which translocate to the nucleus in response to high matrix stiffness. When MSCs were plated on stiff matrices, but not on soft matrices, kindlin-2 interacted with myosin light chain kinase and activated RHOA, promoting myosin light chain phosphorylation, the formation of stress fibres and focal adhesion assembly, which promote nuclear localization of YAP1 and TAZ. Moreover, kindlin-2 reduced the levels of the AIP4 ubiquitin ligase, increasing YAP1 and TAZ protein levels and nuclear localization.

This study indicates that kindlin-2 controls MSC differentiation in response to mechanical inputs by promoting actin stress fibre formation at integrin adhesions, increasing the levels and activity of YAP1 and TAZ and osteogenesis. These findings have important medical implications as an imbalance between osteogenesis and adipogenesis is the cause of many bone diseases.

Kim Baumann



V. Summersby/Macmillan Publishers Limited

ORIGINAL ARTICLE Guo, L. *et al.* Kindlin-2 regulates mesenchymal stem cell differentiation through control of YAP1/TAZ. *J. Cell Biol.* https://doi.org/ 10.1083/jcb.201612177 (2018)
FURTHER READING Panciera, T. *et al.* Mechanobiology of YAP and TAZ in physiology and disease. *Nat. Rev. Mol. Cell Biol.* **18**, 758–770 (2017)