STEM CELLS

Mitochondria unite

> mitochondrial dynamics regulates stem cell expansion and differentiation

Mitochondrial networks are dynamically remodelled through fusion and fission. These dynamic fusion–fission events regulate mitochondrial function in physiology and disease, but how these processes influence cell biology remains poorly understood. In two independent studies, Zhong et al. and Wu et al. now show that mitochondrial dynamics regulates stem cell expansion and differentiation.

Previous studies suggested that mitochondrial dynamics regulate stem cell potency. Using previously established mouse induced pluripotent stem cell (iPSC) lines with different degrees of pluripotency (partial versus full pluripotency), Zhong et al. observed pronounced mitochondrial fusion upon differentiation of fully pluripotent iPSCs. By contrast, partially pluripotent iPSCs had increased numbers of small, fragmented mitochondria and increased expression of fission genes; this was accompanied by decreased differentiation potential in vitro and an inability to support embryonic development in tetraploid complementation assays. Furthermore, ectopic expression of mitochondrial fission regulators interfered with the differentiation potential of fully pluripotent iPSCs and mouse embryonic stem cells (mESCs) in vitro, whereas silencing of mitochondrial fission factor (*Mff*) promoted the differentiation of partially pluripotent iPSCs. In addition, embryos generated by tetraploid complementation using *Mff*-overexpressing mESCs had pronounced developmental alterations. Thus, excess mitochondrial fission interferes with cell differentiation in vitro and in vivo.

Cytosolic Ca^{2+} was increased in partially pluripotent iPSCs and this was dependent on *Mff* expression. Increased Ca^{2+} elevated the activity of Ca^{2+}/calmodulin-dependent kinase II (CaMKII), which in turn was responsible for decreasing the levels of β-catenin, an important regulator of stem cell potency and differentiation. Accordingly, *Camk2* knockdown restored the differentiation potential of partially pluripotent iPSCs and that of *Mff*-overexpressing fully pluripotent iPSCs or mESCs. In conclusion, increased mitochondrial fission elevates cytosolic Ca^{2+}, which activates CaMKII, leading to the degradation of β-catenin and decreased stem cell potency.

Wu et al. investigated the connection between mitochondrial dynamics and epithelial–mesenchymal transition (EMT), which was previously implicated in the acquisition of stem-cell-like properties and stem cell maintenance. Induction of EMT in mammary epithelial cells promoted mitochondrial fusion by increasing expression of fusion-regulating genes, including mitofusin 1 (*MFN1*) and its upstream transcription regulator PGC1α; this was caused by downregulation of a PGC1α-targeting microRNA, miR-200c. EMT induction promoted the asymmetrical division and expansion of stem cells in vitro. Increased stem cell expansion was also induced by inhibiting or silencing the fission regulator DRP1 and could be prevented by *MFN1* knockdown. In addition, mice in which *Pgc1a–Mfn1* expression was induced by *Mir-200c* deletion had hyperplastic mammary glands that harboured increased numbers of stem cells with augmented self-renewal potential. Thus, increased mitochondrial fusion downstream of EMT induction promotes stem cell expansion in vitro and in vivo through asymmetrical cell division.

In asymmetrically dividing cells, fused mitochondria were retained in the stem cell progeny. This retention depended on MFN1 binding to the polarity factor PKCζ, which was in turn required for PKCζ-mediated phosphorylation of the differentiation determinant NUMB and its partitioning away from the stem cell progeny. In addition, fused mitochondria promoted the biosynthesis of a key antioxidant molecule, glutathione (GSH). Inhibition of GSH interfered with in vitro stem cell expansion induced by mitochondrial fusion, and the induction of EMT was associated with lower levels of mitochondrial reactive oxygen species (ROS). Overall, mitochondrial fusion promotes stem cell maintenance by modulating cell polarity cues associated with asymmetrical cell division and by promoting ROS removal in stem cell progeny.

These studies provide new insights into the role of mitochondrial dynamics in the regulation of stem cell biology and have broad implications for the development of iPSC-based regenerative therapies as well as therapies against cancer.

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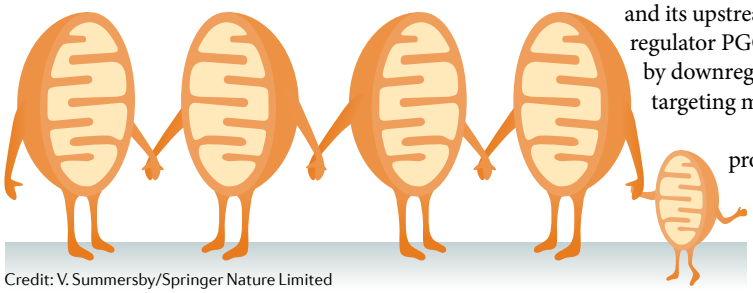

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ORIGINAL ARTICLES Zhong, X. et al. Mitochondrial dynamics is critical for the full pluripotency and embryonic developmental potential of pluripotent stem cells. *Cell Metab.* https://doi.org/10.1016/j.cmet.2018.11.007 (2018) | Wu, M.-J. et al. Epithelial–mesenchymal transition directs stem cell polarity via regulation of mitofusin. *Cell Metab.* https://doi.org/10.1016/j.cmet.2018.11.004 (2018)