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METABOLISM

A metabolic switch of fate

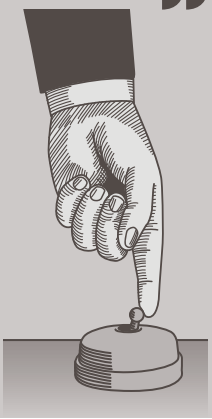
Endothelial–mesenchymal transition (EndoMT) involves acquisition of fibroblast-like characteristics in endothelial cells, including loss of cell–cell contacts and tissue barrier function, and gain of migratory potential. EndoMT occurs during development, for example, to form heart valves (in particular mitral and triscupid), and in adults it has been linked to various pathologies, including pulmonary hypertension, atherosclerosis, tumour dissemination and tissue fibrosis. EndoMT is induced by transforming growth factor β (TGFβ), but the execution and regulation of EndoMT is poorly understood. Xiong *et al*. now show that fatty acid oxidation (FAO) — by modulating acetyl-CoA levels — suppresses EndoMT.

Metabolomic profiling of human pulmonary microvascular endothelial cells (HPMVECs) revealed a marked reduction in the utilization of long-chain fatty acids (LCFAs) following EndoMT induction. This was accompanied by reduced expression of carnitine *O*-palmitoyltransferase 1 (CPT1A), which is a rate-limiting enzyme in FAO. Induction of EndoMT in HPMVECs resulted in a decline in FAO and impaired metabolic response to LCFAs. Moreover, constitutive expression of CPT1A interfered with EndoMT induction, whereas CPT1A knockdown promoted EndoMT. Thus, FAO suppresses EndoMT and is inhibited in response to EndoMT induction.

Induction of EndoMT in HPMVECs was associated with decreased cellular acetyl-CoA. Increasing acetyl-CoA levels by acetate treatment prevented EndoMT, whereas inhibition of enzymes involved in acetyl-CoA synthesis from citrate facilitated EndoMT induction. Because FAO has previously been shown to regulate acetyl-CoA levels, these results suggested that FAO suppresses EndoMT by maintaining high cellular levels of acetyl-CoA.

SMAD7 is a potent antagonist of TGFβ signalling and its stability is regulated by lysine acetylation. Increasing or decreasing acetyl-CoA levels resulted in corresponding changes in SMAD7 protein levels and acetylation. Thus, acetyl-CoA promotes SMAD7 acetylation and stability, thereby suppressing TGFβ signalling and, consequently, the EndoMT programme.

> “FAO suppresses EndoMT by maintaining high cellular levels of acetyl-CoA”



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CPT2 together with CPT1A is required for FAO. Accordingly, FAO was impaired and acetyl-CoA levels were decreased in endothelial cells derived from endothelium-specific *Cpt2* knockout ($Cpt2^{E\text{-}KO}$) mice. Notably, $Cpt2^{E\text{-}KO}$ mice showed thickening of the mitral valve and increased vascular permeability in the kidneys, spleen and lungs, suggesting that impairment of FAO and acetyl-CoA maintenance *in vivo* augments both developmental and adult EndoMT. In the future, it would be interesting to explore the potential of modulating FAO in the context of human diseases associated with aberrant EndoMT.

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ORIGINAL ARTICLE Xiong, J. *et al.* A metabolic basis for endothelial-to-mesenchymal transition. *Mol. Cell* https://doi.org/10.1016/j.molcel.2018.01.010 (2017)