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POST-TRANSLATIONAL MODIFICATION

ES cells have a sweet tooth

O-linked β-D-*N*-acetylglucosamine (*O*-GlcNAc) modification has recently emerged as a key regulator of cell physiology, controlling aspects such as nutrient sensing and cell cycle progression. Youn and colleagues reveal that this is not restricted to differentiated cells; *O*-GlcNAcylation also regulates embryonic stem (ES) cell pluripotency.

Previous studies suggested that ES cell maintenance may be regulated by *O*-GlcNAcylation, in particular by reporting that the levels of glucose in medium affect whether ES cells differentiate or self-renew. Consistent with these observations, the authors found that loss of *O*-GlcNAc transferase (OGT; which mediates *O*-GlcNAcylation) led to reduced proliferation and self-renewal of ES cells as well as decreased reprogramming efficiency of induced pluripotent stem (iPS) cells. By contrast, overexpression of OGT or depletion of *O*-GlcNAcase (OGA; which removes *O*-GlcNAc) increased reprogramming efficiency and decreased differentiation, respectively. These findings indicate that *O*-GlcNAcylation promotes ES cell self-renewal and inhibits differentiation.

ES cell self-renewal is regulated by a pluripotency network comprising OCT4 (also known as POU5F1 and OCT3), SOX2, KLF4 (Krüppel-like factor 4) and NANOG, so the authors hypothesized that *O*-GlcNAc may be modifying some of these factors. Indeed, OCT4 and SOX2 were *O*-GlcNAcylated, and this modification decreased following ES cell differentiation. Moreover, OCT4 *O*-GlcNAcylation depended on the OCT4 residue Thr228, as mutation of this residue decreased *O*-GlcNAc levels in ES cells. Importantly, mutation of OCT4 at Thr228 resulted in reduced reprogramming efficiency of mouse embryonic fibroblasts and defective self-renewal of ES cells, which suggests that *O*-GlcNAcylation of OCT4 is required to maintain pluripotency.

But how is this achieved? Because OCT4 *O*-GlcNAcylation did not affect protein stability or cell localization, the authors postulated that it may regulate OCT4 activity as a transcription factor. Using a luciferase reporter assay, the authors confirmed that *O*-GlcNAcylation increases the transcriptional activity of OCT4. Further analysis indicated that *O*-GlcNAcylated OCT4 directly regulates the transcription of 29 genes, including pluripotency-related genes such as *Nanog* and *Klf4*.

Together, these findings reveal that OCT4 *O*-GlcNAcylation acts as a key regulator of pluripotency, adjusting the transcription of pluripotency-related genes according to external signals.

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ORIGINAL RESEARCH PAPER Jang, H. *et al.* *O*-GlcNAc regulates pluripotency and reprogramming by directly acting on core components of the pluripotency network. *Cell Stem Cell* 17 May 2012 (doi:10.1016/j.stem.2012.03.001)

FURTHER READING Hanover, J. A., Krause, M. W. & Love, D. C. Bittersweet memories: linking metabolism to epigenetics through *O*-GlcNAcylation. *Nature Rev. Mol. Cell Biol.* **13**, 312–321 (2012)

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