STEM CELLS

Sweetening pluripotency

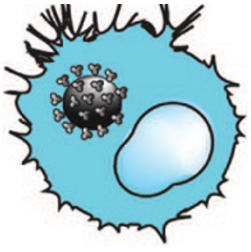
Cell Stem Cell, published online 17 May 2012, doi:10.1016/j.stem.2012.03.001

Somatic cells can be reprogrammed into pluripotent cells called induced pluripotent stem cells by a combination of transcription factors, including Oct-4 and Sox2. Glucose conditions in culture also affect pluripotency, but a molecular explanation for this observation has been lacking. Now Jang *et al.* report that Oct-4 is modified with an *O*-linked *N*-acetylglucosamine (*O*-GlcNAc) in stem cells. Chemical or genetic inhibition of *O*-GlcNAcase (OGA), the enzyme that removes *O*-GlcNAc, reduced reprogramming efficiency as well as embryonic stem cell (ESC) maintenance in culture. The authors used succinylated wheat germ agglutinin and free GlcNAc to pull down and elute GlcNAc-modified proteins, which included Oct-4 and Sox2. Treatment with β-N-acetyl-hexosaminidase, an enzyme that removes O-linked glycans, confirmed the O linkage in Oct-4 and Sox2. Follow-on analyses revealed that Oct-4 was modified at Thr228 and that mutation of this site reduced reprogramming efficiency and ESC self-renewal. The authors also showed that chemical inhibition of OGA in differentiating ESCs, which lose O-GlcNAc on Oct-4, restored the Oct-4 modification and Oct-4–dependent reporter gene expression. Gene expression analysis and ChIP-seq, to reveal promoters occupied by and regulated by Oct-4, identified specific pluripotency genes whose expression was sensitive to the Oct-4 modification. Taken together, these data provide a direct molecular connection between O-GlcNAcylation and the activation of a pluripotency network. *AD*

VIROLOGY

HIV-1 gets attached

PLoS Biol. **10**, e1001315 (2012)



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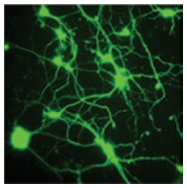
HIV-1 has evolved numerous strategies to promote viral transmission, including subverting the antiviral activity of these antigen-presenting cells of the immune system, dendritic cells (DCs). However, little is known about the molecular mechanisms underlying viral uptake by DCs. On the basis of previous work using glycosphingolipid biosynthesis inhibitors, Izquierdo-Useros *et al.* hypothesized that gangliosides on the outer monolayer of the viral membrane could act as viral attachment factors to allow recognition and capture by DCs. Captured viruses and lab-generated virus-like particles (VLPs) could then be transmitted to susceptible T cells in a process called *trans*-infection. To explore this idea, the authors showed that uptake of VLPs and of large unilamellar vesicles mimicking the size and lipid composition of HIV-1 required membrane gangliosides and involved similar trafficking within the DCs. Only gangliosides with exposed sialic acids attached to a lactose group (sialyllactose) could support uptake activity by DCs and facilitate subsequent viral *trans*-infection. These results demonstrate a new role for sialylated glycosphingolipids as new molecular recognition determinants for specific capture by DCs. *MB*

NEURODEGENERATION

Aβ peptides go mad

Nature, published online 2 May 2012, doi:10.1038/nature11060



JUSTIN NUSSBAUM

Toxic oligomeric forms of amyloid β (Aβ) peptides, including $Aβ_{1–42}$ and the N-terminally truncated pyroglutamated (pE) $Aβ_{3(pE)–42}$ peptides, are linked to Alzheimer's disease (AD) pathology. Nussbaum *et al.* now uncover a molecular mechanism by which $Aβ_{3(pE)–42}$ peptides exert their cytotoxic effects. The authors observed that the $Aβ_{3(pE)–42}$ peptides or a mix of $Aβ_{3(pE)–42}$ and excess $Aβ_{1–42}$ peptides oligomerized more slowly than $Aβ_{1–42}$ alone and were more toxic and metastable. Fractionation of the $Aβ_{3(pE)–42}$–$Aβ_{1–42}$ hybrid oligomers and cytotoxicity assays showed that the toxic species were low-molecular-weight oligomers. They observed that serial dilutions of $Aβ_{3(pE)–42}$–$Aβ_{1–42}$ oligomers with monomeric $Aβ_{1–42}$ led to the formation of toxic $Aβ_{1–42}$ oligomers without further addition of $Aβ_{3(pE)–42}$, suggesting that $Aβ_{3(pE)–42}$ indeed has prion-like activity; it induces misfolding and aggregation of other peptides. Importantly, $Aβ_{3(pE)–42}$ oligomers were detected in brain lysates of patients with AD, and transgenic mice with increased amounts of $Aβ_{3(pE)–42}$ showed AD-like pathology. In agreement with the observations that $Aβ_{3(pE)–42}$ peptide has prion-like activity, injection of hybrid $Aβ_{3(pE)–42}$–$Aβ_{1–42}$ oligomers into the brains of mice with AD led to faster accumulation of Aβ plaques. This study provides evidence that the pE-Aβ peptides can prime the formation of toxic Aβ oligomers and function as prion-like species. *AC*

MECHANISM OF ACTION

Cyclins lost in translation

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Metformin, an activator of AMP kinase and a widely used antidiabetic drug, has been associated with antiproliferative effects through interference with the mammalian target of rapamycin complex 1 (mTORC1) anabolic pathway. Larsson *et al.* now explore the mechanisms by which metformin counteracts the mTORC1 pathway. The authors treated MCF7 cells with metformin or two known mTORC1 inhibitors and observed inhibition of the translational regulator 4E-BP and concomitant reduction in the rate of translational initiation. Although the drugs had minimal effects on gene expression and total cytoplasmic mRNA levels, genome-wide analyses of polysome-associated mRNAs present in metformin- or mTORC1 inhibitor–treated cells showed a dramatic decrease in the levels of some translated mRNAs. Gene ontology analyses of the affected mRNAs revealed a partial overlap between metformin- and mTORC1 inhibitor–treated cells. The overlapping mRNAs were enriched for those encoding proteins with cell-cycle functions. The authors verified the effects of the drugs on the translation of specific cell cycle regulators, cyclin E2 and ornithine decarboxylase 1 (ODC1). 4E-BP knockout cells were partially resistant to metformin-mediated inhibition of proliferation and translation of cell cycle regulators. In sum, the authors showed that metformin specifically inhibits the translation of mRNAs that regulate cell cycle through inhibition of the 4E-BP translation protein. *AC*

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