STEM CELLS

Food for renewal

Nature doi:10.1038/nature13981

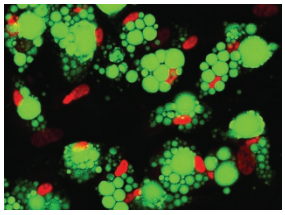
The culturing of mouse embryonic stem (ES) cells requires the right mix of conditioned media, serum and cytokines to ensure self-renewal and pluripotency maintenance. ES cells have traditionally been grown in serum-containing media, but these conditions lead to heterogeneity both in the morphology and expression of pluripotency factors. Culturing ES cells in a serum-free medium (termed '2i'), which includes kinase inhibitors for MEK and GSK-3b that block differentiation signals, has been shown to reduce this heterogeneity and is currently thought to best represent the naive ground state. High-resolution genome-wide transcriptome analysis comparing ES cells cultured in serum or 2i conditions further revealed that cells grown in 2i conditions contained elevated transcripts for genes encoding metabolic functions as well as reduced H3K27me3 epigenetic marks on promoters. Carey *et al.* predicted that these metabolic and epigenetic outcomes might be caused by inhibition of MEK and GSK-3. To understand whether these kinases are involved in this pluripotency ground state, the authors compared the metabolism of ES cells grown in 2i or serum conditions. 2i-cultured cells contained elevated levels of the TCA cycle metabolite α-ketoglutarate (α-KG) with diminished amounts of downstream TCA metabolites, such as succinate and malate. Using metabolic tracing experiments, they found that the metabolic flux was altered with α-KG being rerouted to produce glutamate instead of progressing through the TCA cycle. The resultant high α-KG/succinate ratio observed in 2i-cultured ES cells could also explain the epigenetic observations, as this is known to promote histone demethylase activity. Indeed, inhibition of the H3K27me3 demethylase using GSK-J4 produced a greater enhancement of H3K27me3 in 2i-cultured cells versus serum-cultured cells. Finally, the authors found that the addition of α-KG to ES cells induced germline-associated gene expression and promoted the increased self-renewal of serum-treated ES cells. Although these findings implicate α-KG in the epigenetic regulation of stem cells, further experiments are needed to determine how the inhibition of GSK-3B and MEK directly alter TCA cycle flux to increase α-KG levels. *GM*

FAT DEVELOPMENT

BATting the WAT

Nat. Cell. Biol. **17**, 57–67 (2015)

NATURE CELL BIOLOGY



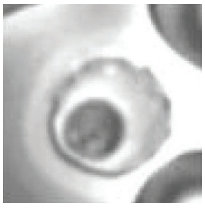
Brown adipose tissue (BAT) differs from white adipose tissue (WAT) in cellular morphology, gene expression and metabolic function. BAT contains multiple small lipid droplets and expresses uncoupling protein 1 (UCP1), which disrupts the respiratory chain to release heat, whereas WAT contain large lipid droplets whose primary function is to store energy. As promoting increased thermogenesis to burn excess calories has been thought of as a potential therapeutic treatment to combat obesity and type 2 diabetes, researchers have searched for strategies that increase the amount of BAT. Considering that thermogenic stimuli such as cold exposure or β-adrenergic stimulation promote the appearance of brown adipocytes in white depots in both mice and humans, Moisan *et al.* envisioned that small molecules might perform the same task to convert WAT into BAT. They applied an annotated collection of small molecules in human pluripotent stem cell–derived adipocytes (PSC-WAs) using UCP1 expression as a readout of BAT identity. Some of the most effective candidates were inhibitors of Janus kinase (JAK)-STAT signaling that promoted changes in morphology consistent with brown-like adipocytes. Although these adipocytes were genetically similar to WAT, they exhibited BAT features, such as increased mitochondrial content, oxygen consumption and lipid catabolism. To determine the mechanism of these changes, Moisan *et al.* performed RNA-seq analysis of JAK-inhibited adipocytes and detected changes in interferon (IFN)-responsive and Sonic Hedgehog (SHH) target genes. IFN-γ treatment of PSC-WA promoted a WAT phenotype that was blocked by the JAK inhibitors, whereas treatment with the SHH inhibitor cyclopamine blocked the JAK inhibitors' effects. Although JAK inhibition can also alter immune response, these findings may inspire development of a modified JAK inhibitor that is effective on adipocytes for treatment of obesity and type II diabetes while sparing immune function. *GM*

DRUG DISCOVERY

Death by sodium

Proc. Natl Acad. Sci. USA **111**, E5455–E5462 (2014)

PNAS



Malaria remains one of the largest disease burdens in humans, resulting in almost 700,000 deaths and 220 million nonfatal infections per year. For this reason, a cheaply manufactured, oral, high-efficacy drug that does not induce resistance is desperately needed. A chemical screen had identified SJ733 for further characterization as a potential preclinical compound. Jimenez-Diaz *et al.* now show that *ex vivo*, the (+)-enantiomer is significantly more potent than the racemic mixture and is active against both asexual and sexual stages; its potency and efficacy were replicated in a mouse model. The pharmacokinetics in all preclinical model species were sufficiently encouraging that it seemed this compound had the desired fast clearance component and might be a single-exposure radical cure and prophylaxis (SERCaP) drug. By sequencing drug-resistant strains, the authors identified the Na^+-efflux ATPase, PfATP4, as the target of (+)-SJ733. The PfATP4 mutation caused the parasite to become less robust. Using a structural homology model, the resistance mutations were found to cluster near the ion-transporting channel in the putative drug-binding region. PfATP4 was thought to keep $[Na^+]_i$ levels low, and treatment with (+)-SJ733 increases $[Na^+]_i$ in the parasite. Resistance strains, however, have a higher basal $[Na^+]_i$; this may account for their poor fitness. *In vivo*, (+)-SJ733 promotes rapid clearance of the parasites—even faster than in infected erythrocytes. By altering cytosolic $[Na^+]$, the drug induces a stress that leads to changes in erythrocyte morphology, arrest of parasite development and eryptosis or senescence specifically in parasite-infected erythrocytes. The specificity of the drug's targeting to infected cells, the multiple changes induced in the infected host cell itself and in the parasite, the rapid clearance of either the parasite or the entire infected cell and the correlation between resistance mutations and loss of fitness make (+)-SJ733 a promising lead for front-line malaria treatment. *AKE*

Written by Mirella Bucci, Angela K. Eggleston, Joshua M. Finkelstein, Catherine Goodman and Grant Miura