Nature Reviews Molecular Cell Biology | AOP, published online 18 January 2012; doi:10.1038/nrm3273

BRANDX

STEM CELLS

Making fat

Human embryonic stem (ES) cells and induced pluripotent stem (iPS) cells have the potential to produce patient-specific *in vitro* cell models to study disease. However, converting these cells into relevant adult cell types remains a challenge. Cowan and colleagues now report an efficient and consistent protocol for differentiating ES and iPS cells into white and brown adipocytes.

First, the authors generated mesenchymal progenitor cells (MPCs), which are adipocyte precursors, from human ES and iPS cells. ES and iPS cell lines were differentiated into embryoid bodies, which were then plated on culture dishes to obtain replicative fibroblast-like cells that could be expanded for 10–12 passages. These cells were termed fibroblast-like MPCs, owing to their transcription profiles and to their capacity to differentiate into osteoblasts, chondrocytes and adipocytes.

> “human ES and iPS cells can be efficiently programmed into white and brown adipocytes”

Next, the authors sought to programme these MPCs into white and brown adipocytes. To obtain white adipocytes, MPCs were transduced with a lentiviral construct that enabled the inducible expression of the transcription factor peroxisome proliferator-activated receptor γ2 (PPARγ2), a key regulator of adipogenesis. Approximately 88% of cells differentiated into white adipocytes after 16 days of PPARγ2-induced expression, whereas only 9% of non-transduced MPCs differentiated into white adipocytes when cultured in adipogenic media. Furthermore, PPARγ2-programmed cells maintained the features of mature white adipocytes when cultured for an additional 4 weeks after PPARγ2 expression had been switched off. Thus, exogenous expression of PPARγ2 is sufficient to initiate the fate switch of MPCs to white adipocytes, but it is not required to sustain white adipocytes. Similarly, MPCs were programmed to efficiently differentiate into brown adipocytes using two transcription factor combinations: PPARγ2–C/EBPβ (CCAAT/enhancer-binding protein-β) and PPARγ2–C/EBPβ–PRDM16 (PR domain-containing 16).

To assess the similarity between programmed white adipocytes and primary white adipocytes, Cowan and colleagues generated and analysed transcript profiles for these cells using several methods. They found that these profiles were strikingly similar, indicating that PPARγ2-induced programming is a reliable method for the production of white adipocytes. In addition, programmed brown adipocytes expressed known brown adipose tissue markers and had transcript profiles that were distinct from those of white adipocytes.

White adipose tissue specializes in energy storage, whereas the primary function of brown adipose tissue is to produce heat. Importantly, both programmed cell types exhibited the functional properties of mature cells. For example, programmed white adipocytes could carry out lipolysis and storage and synthesis of fatty acids, and they could respond to insulin. Programmed brown adipocytes could also carry out lipolysis and had significantly increased mitochondrial activity, which is characteristic of this cell type. Furthermore, transplantation of programmed white and brown adipocytes into mice yielded tissues that were morphologically and functionally similar to the corresponding primary tissues.

Together, these results show how human ES and iPS cells can be efficiently programmed into white and brown adipocytes, which could be used to model human adipose-related diseases.

Kim Baumann

ORIGINAL RESEARCH PAPER Ahfeldt, T. *et al.* Programming human pluripotent stem cells into white and brown adipocytes. *Nature Cell Biol.* 15 Jan 2012 (doi:10.1038/ncb2411)