Eosinophils in adipose tissue energy expenditure

A.J. Knights,[1] E.J. Vohralik,[1] P.J. Houweling,[2] K.L. Hoehn,[1] M. Crossley[1] and K.G.R. Quinlan ,[1] [1]School of Biotechnology and Biomolecular Sciences, UNSW Sydney, NSW 2052, Australia and [2]Murdoch Children's Research Institute, The Royal Children's Hospital, Melbourne, VIC 3052, Australia.

Obesity is a global problem and represents a significant health and economic burden. Our research concentrates on understanding the hormones and molecular pathways that drive obesity. Recently a new category of brown fat-like cells, so-called "beige" cells residing within white fat, has been identified. These cells burn fuels to generate heat and therefore may reduce obesity by burning rather than storing excess fuels. Cells of the immune system – macrophages, innate lymphoid cells and recently eosinophils – appear to be essential to the beiging of white adipocytes.

While studying mice with a deletion in the gene encoding the transcription factor Kruppel-like Factor 3 (KLF3) we made a serendipitous discovery: these mice are lean and are protected from diet-induced obesity. Interestingly, these mice show evidence of an increased capacity for thermogenesis even when not housed in cold conditions. The adipocytes were not responsible for this phenomenon so to test the involvement of adipose-resident blood cells, we performed a bone marrow transplantation study and were able to confer the lean beige phenotype on wild type mice. This suggested that KLF3 deficiency in cells of the haematopoietic lineage may drive leanness in this mouse model. We interrogated different types of adipose-resident immune cells and discovered that there are three times as many eosinophils in KLF3-deficient adipose tissue than in adipose tissue from wild type littermate mice.

We also performed genome-wide expression analyses on eosinophils isolated from white adipose tissue and uncovered widespread gene expression differences, suggesting that not only is the number of eosinophils in adipose tissue different in the absence of KLF3, but their gene expression profiles and several biological pathways are also altered. This suggests that KLF3 is an important regulator of gene expression and activity within eosinophils. Interestingly, we saw expression of a number of genes that encode secreted proteins known for their role in beiging. Our data suggest that eosinophils may contribute to beige fat activation by secreting these factors. The eosinophils from KLF3 knockout mice, where we see enhanced beiging, expressed higher levels of these secreted proteins. We also detected expression of a number of novel secreted proteins in adipose tissue-derived eosinophils. We are now testing whether these novel secreted proteins are able to induce beiging and energy expenditure in cell culture and *in vivo* models.

Our data suggest that adipose tissue-resident eosinophils secrete important factors that drive beiging of adipose tissue. This emphasises the importance of eosinophils in the activation of beige fat. Our study of these factors may provide a platform for the development of new therapeutic agents to drive beiging and combat obesity.