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# How does fat transition from white to beige?

**Marc L. Reitman**[1,*]

[1]Diabetes, Endocrinology, and Obesity Branch, National Institute of Diabetes and Digestive and Kidney Diseases, NIH, Bethesda, MD 20892, USA

Fischer et al (2017) recently reported that interleukin-4 (IL-4) does not increase adipose thermogenesis and that activated macrophages do not synthesize catecholamines. These findings are unexpected because IL-4 activation of macrophages has been proposed to have a pivotal role in cold-induced thermogenesis by stimulating macrophage catecholamine production to recruit thermogenic beige/brite fat.

Since maintaining body temperature is essential for survival of the individual and species, robust immediate and long-term mechanisms for ensuring adequate adaptive thermogenesis have evolved. Small mammals maintain a warm body temperature by using both heat conservation and dedicated heat generation, known as cold-induced or adaptive thermogenesis. For a laboratory mouse at 22 °C, adaptive thermogenesis can account for ⅓ to ½ of total energy expenditure, thus cold exposure elicits a massive, coordinated, whole-body response. The major effector tissue for adaptive thermogenesis is brown adipose tissue (BAT), which uses uncoupling protein-1 to dissipate the energy in the mitochondrial electrochemical gradient as heat, rather than harnessing it for ATP generation. Two discoveries have elevated interest in thermogenic adipose tissue. One is the realization that there is an inducible form of thermogenic adipose tissue, termed beige or brite adipose tissue, with a transcriptional profile and developmental origin distinct from BAT (Wu et al., 2012). Another is that humans have measurable brown/beige adipose tissue, which can be activated by drugs or cold (Cypess et al., 2015). There is great interest in elucidating if beige fat or BAT activation can be used successfully as a component of drug therapy for obesity.

The classic view of BAT physiology is that sensation of cold is transmitted to the brain, through which it eventually causes sympathetic neurons to release norepinephrine, stimulating β-adrenergic receptors on the brown adipocytes (Morrison et al., 2014). The BAT activation process also includes glucose and lipid mobilization, with greatly increased blood flow to the BAT in order to both supply these fuels and remove and distribute the heat that is generated (Cannon and Nedergaard, 2004).

Intriguing insights into cold-induced thermogenesis and the beiging process were provided by the observations that cold exposure caused recruitment of eosinophils to adipose depots, where they secreted type 2 cytokines (interleukin 4/13) that act on the IL-4 receptor, thereby increasing alternatively activated M2 macrophages in adipose tissue (Nguyen et al., 2011; Qiu et al., 2014). These M2 macrophages produced and secreted catecholamines, increasing

*Correspondence: marc.reitman@nih.gov.

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local beiging and the capacity for full cold-induced thermogenesis. Supporting evidence included the observations that mice genetically lacking eosinophils, IL4/13, STAT6, macrophage IL-4 receptor, macrophage recruitment, or myeloid tyrosine hydroxylase (Th, required for catecholamine synthesis) showed defects in these processes. Treatment of mice with IL-4 increased beiging and energy expenditure.

Now a collaboration of six laboratories in four continents has carefully examined this pathway, including the role of IL-4, macrophages, and macrophage-derived catecholamines (Fischer et al., 2017). They avoided germline deletion, which might contribute developmental effects, by inducing *Th* deletion only in hematopoietic cells reconstituted by bone marrow transplantation. No phenotype was observed upon hematopoietic *Th* deletion in adult mice. In contrast, *Th* deletion in all peripheral tissues impaired cold thermogenesis, possibly from loss of tyrosine hydroxylase in sympathetic ganglion neurons. The paper also included evidence that *Th* is not expressed in macrophages.

Next, Fischer et al used *in vitro* studies to show that cells with macrophage markers were not needed for primary adipocyte differentiation or browning. *In vitro*, treatment with IL-4 indeed stimulated M2 marker levels but did not cause detectable levels of catecholamines in either bone marrow-derived macrophages or the culture medium. In addition, the conditioned medium did not increase markers of browning in cultured adipocytes. *In vivo*, treatment for 12 days with IL-4 produced the expected M2 macrophage polarization, but had no effect on energy expenditure, body weight, or catecholamine levels, compared to control cold-exposed mice.

One can suggest possible additions to Fischer et al, such as including quantification of the level of *Th* deletion in reconstituted bone marrow and investigation of whether macrophages can take up catecholamines rather than synthesize them. A potential caveat is that the 9-kb rat promoter driving the $Th^{Cre}$ transgene that was used to assess the presence or absence of Th expression in macrophages may not replicate the full expression pattern of endogenous mouse *Th*. Another is that *in vitro* adipocyte cultures may miss contributions from other ligands (Table 1) and/or cells that are present *in vivo* and contribute to browning. However, it is clear that both the earlier (Nguyen et al., 2011; Qiu et al., 2014) and recent (Fischer et al., 2017) studies contain convincing yet conflicting data.

The differences between the Fischer, Nguyen, and Qiu papers and the discussions that ensue are a ‘win’ for science and the scientific process. Innovative, novel science is difficult. Since one does not know what to expect, further investigation may uncover inconsistencies, whether due to different reagents, experimental conditions, stochastic processes, or alternative interpretations. The observation that at least three of six commercial anti-tyrosine hydroxylase antibodies appear to be unusable (Fischer et al., 2017) provides a cautionary example. Innovative science is not a linear process, no matter how logical it sounds in the final paper, review article, or popularized summary.

A mechanistic explanation reasonably consistent with the recent (Fischer et al., 2017) and previous (Nguyen et al., 2011; Qiu et al., 2014) data is that, as an element of the wholebody response to cold exposure, local adipose catecholamines increase, but not via direct

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catecholamine synthesis by macrophages. Many local mechanisms that can stimulate beiging or BAT activation exist, implicating multiple endogenous small molecule and protein ligands, their receptors and signaling pathways (see Table 1) (Pfeifer and Hoffmann, 2015; Whittle et al., 2013). Could one or more of these pathways be induced by cold exposure, possibly interact with type 2 cytokine signals, and increase norepinephrine release from sympathetic neurons or other cells? Despite the relative sparsity of sympathetic innervation to WAT, methods exist to study the neural input (Zeng et al., 2015) and the role of the sympathetic nervous system in beiging, which needs to be reevaluated. How do the sympathetic nervous and immune systems interact? More research is needed to determine where the catecholamines are coming from and the roles and importance of other ligands in beiging.

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**Table 1.**

Ligands that increase beiging or BAT activation

| Ligand | Type | Reference |
|---|---|---|
| β-adrenergic agonists | endogenous small molecule | Bartness et al., 2010 Int J Obes (Lond) 34 Suppl 1, S36–42 |
| PPARγ agonist (eg thiazolidinediones) | endogenous small molecule | Tai et al., 1996 J Biol Chem 271, 29909–29914 |
| Adenosine 2A agonist | endogenous small molecule | Gnad et al., 2014 Nature 516, 395–399 |
| GPR120 agonist | endogenous small molecule | Quesada-Lopez et al., 2016 Nat Commun 7, 13479 |
| $PGI_2$ (prostacyclin receptor agonist) | endogenous small molecule | Vegiopoulos et al., 2010 Science 328, 1158–1161 |
| thyroid hormone (TRβ agonist) | endogenous small molecule | Lin et al., 2015 Cell Rep 13, 1528–1537 |
| retinaldehyde (RAR agonist) | endogenous small molecule | Kiefer et al., 2012 Nat Med 18, 918–925 |
| bile acids (TGR5 agonist) | endogenous small molecule | Watanabe et al., 2006 Nature 439, 484–489 |
| 12,13-diHOME (unknown target) | endogenous small molecule | Lynes et al., 2017 Nat Med 23, 631–637 |
| FGF21 | protein or peptide | Fisher et al., 2012 Genes Dev 26, 271–281 |
| bone morphogenetic protein 4 | protein or peptide | Gustafson et al., 2015 Diabetes 64, 1670–1681 |
| bone morphogenetic protein 7 | protein or peptide | Tseng et al., 2008 Nature 454, 1000–1004 |
| bone morphogenetic protein 8B | protein or peptide | Whittle et al., 2012 Cell 149, 871–885 |
| irisin | protein or peptide | Bostrom et al., 2012 Nature 481, 463–468 |
| slit2-C protein | protein or peptide | Svensson et al., 2016 Cell Metab 23, 454–466 |
| lipocalin 2 | protein or peptide | Zhang et al., 2014 J Biol Chem 289, 22063–22077 |
| cardiac natriuretic peptides | protein or peptide | Bordicchia et al., 2012 J Clin Invest 122, 1022–1036 |
| TLQP-21 (VGF-derived peptide) | protein or peptide | Bartolomucci et al., 2006 Proc Natl Acad Sci U S A 103, 14584–14589 |
| meteorin-like | protein or peptide | Rao et al., 2014 Cell 157, 1279–1291 |
| parathyroid hormone | protein or peptide | Kir et al., 2016 Cell Metab 23, 315–323 |
| adiponectin | protein or peptide | Hui et al., 2015 Cell Metab 22, 279–290 |
| celastrol, activator of HSF1 | exogenous small molecule | Ma et al., 2015 Cell Metab 22, 695–708 |
| roscovitine, CDK inhibitor | exogenous small molecule | Wang et al., 2016 Cell Metab 24, 835–847 |
| amlexanox, TBK1/IKKε inhibitor | exogenous small molecule | Reilly et al., 2013 Nat Med 19, 313–321 |
| TGF-β/SMAD3 blockade | neutralizing antibody to TGF-β | Yadav et al., 2011 Cell Metab 14, 67–79 |

Table includes endogenous ligands believed to act on adipocytes or precursors. Exogenous molecules without a specific, non-redundant molecular target are not included. This Table is not exhaustive.