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Type 2 immune regulation of adipose tissue homeostasis

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Chronic and low-grade inflammation is a hallmark of obesity and type 2 diabetes, and is primarily derived from the adipose tissue. Type 1 immunity plays a disruptive role in metabolic tissues such as heart, liver and fat in the context of metabolic dysfunction. However, emerging evidence suggests that type 2 immunity has a supportive role for metabolic homeostasis. In this review, we summarize the recent advances on cellular and molecular mechanisms by which type 2 immunity orchestrates adipose tissue development and function. In addition, we touch upon therapeutic implications of these new findings.

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Introduction

Obesity and overweight have become global epidemics across industrialized nations as well as developing countries [1]. This prevalence of obesity and overweight gives rise to a huge financial burden on health care system because obesity is highly and positively associated with many major diseases such as type 2 diabetes, cardiovascular diseases, inflammation-related disorders, and even certain types of cancer [2,3]. Simply speaking, obesity is primarily an accumulation of adipose tissue due to chronic imbalance between energy intake and energy expenditure. Thus it is of the essence to thoroughly understand adipose tissue development, function, and metabolism. The adipose tissue is composed of many types of cells including adipocytes, preadipocytes, adipocyte progenitors, fibroblasts, endothelium, and most abundantly—immune cells, the latter of which plays a central role in adipose tissue biology [4].

Over the past two decades, immunometabolism has been emerged as an interdisciplinary field that can be divided into two subdisciplines: cellular immunometabolism and tissue immunometabolism [5•]. The cellular immunometabolism topic has been excellently reviewed by Pearce *et al.* [6]. In this review, we focus on one of the frontiers of the tissue immunometabolism, which is type 2 immune regulation of adipose tissue metabolism. And we discuss the therapeutic implications of these new findings and propose alternative treatment approaches against obesity and its associated disorders through balanced modulations of type 1 and type 2 immunity.

Three types of adipocytes: white, brown, and beige

Adipocyte is the major cell component of fat tissues. It can be divided into three cell types: white, beige, and brown. Most white and beige adipocytes develop from $Pax7^{-}/Myf5^{-}$ mesenchymal precursors, while brown adipocytes come from $Pax7^{+}/Myf5^{+}$ precursors [7]. A subset of adipocytes, including white, beige, and brown, may derive from $Myf5^{-}$ precursors [8]. In terms of energy homeostasis, white adipocytes are specialized to store energy as fat in lipid droplets, whereas both brown and beige adipocytes are dedicated to dissipate energy as heat through UCP-1-dependent or UCP-1-independent adaptive thermogenesis [9]. White adipose tissue (WAT) shows a UCP-1-negeative staining and a monolocular structure immunohistochemically, whereas both beige and brown fat have a UCP-1-positive multilocular morphology [7]. In addition, beige adipocytes are inducible and reversible upon environmental cold or warm exposure [10].

Brown and white adipocytes locate in brown adipose tissue (BAT) and WAT respectively, while beige adipocytes intersperse mainly in subcutaneous depots of WAT (scWAT). Visceral depots of WAT (vsWAT) are resistant to different beiging stimuli [7]. This reflects distinct physiologic function between visceral and subcutaneous depots of WAT, although they have overlapping ones, for example, both serve as nutrient reservoir and endocrine organ [11]. scWAT and vsWAT play quite dissimilar roles in the pathogenesis of metabolic disorders, for example, visceral obesity has a positive correlation with type 2 diabetes development, while subcutaneous obesity is neutral or even benign [12]. This regional differences might attribute to: 1) unique local microenvironment shaped by diverse neuronal innervation and its relationship with circulation; 2) distinct cell-autonomous programs determining different responses and outputs [4,13]. Deletion of PRDM16 in adipocytes causes a subcutaneous to visceral fat switch, exhibiting less thermogenic capacity, increased inflammatory gene expression and more

macrophage accumulation [14]. This result indicates that PRDM16 can sustain a transcriptional program to maintain the tissue fate identity as subcutaneous fat, which involves inflammatory pathways.

M1 versus M2 macrophage activation and their consequences on adipose metabolism

Chronic and low-grade inflammation, also termed 'metaflammation', is a hallmark of obesity and type 2 diabetes, which is mediated by pro-inflammatory type 1 immunity [15]. Hotamisligil *et al.* made the groundbreaking finding that obese WAT produced pro-inflammatory cytokines, such as tumor necrosis factor (TNF), which could induce local and systemic insulin resistance [16]. Another seminal finding came from Weisberg *et al.* and Xu *et al.*, who independently demonstrated that those pro-inflammatory cytokines were mainly produced by the adipose tissue macrophages instead of the adipocytes themselves [17,18]. These findings elicit explosive follow-up studies, many of which focus on macrophages as it is the most populous immune cell in the fat pad. Several other pro-inflammatory cytokines, such as interleukin-6 (IL-6) and IL-1β, were subsequently identified in obese fat pad [19].

Furthermore, obesity induces an activation switch from anti-inflammatory to pro-inflammatory state in adipose tissue macrophages [20]. Thus macrophages can be experimentally classified into two types: classically activated macrophages (CAMs) and alternatively activated macrophages (AAMs), also termed M1 and M2 macrophages [21]. M1 macrophages can be induced by lipopolysaccharides (LPS), saturated free fatty acid or type 1 cytokines such as interferon-γ (IFN-γ) to produce pro-inflammatory cytokines like TNF-α, IL-6, and IL-1β, which further deteriorate insulin resistance of metabolic tissues via paracrine or endocrine effects. In contrast, M2 macrophages are induced by type 2 cytokines such as IL-4 and IL-13 to secret anti-inflammatory cytokines like IL-10, which can maintain insulin sensitivity in the lean state [19]. The major signaling pathways were revealed to mediate the M1 activation, including pro-inflammatory kinases such as IκB kinase β (IKKβ) and JUN N-terminal kinase (JNK), inositol-requiring enzyme 1α (IRE1α) and their associated transcriptional factors including nuclear factor κB (NF-κB), c-JUN, interferon regulatory factor 3 (IRF3) and IRF5 [22,23•]. The predominant signaling components were identified for M2 activation and maintenance, including IL-4R, and transcriptional factors such as signal transducer and activator of transcription 6 (STAT6), peroxisome proliferator-activated receptor γ (PPARγ), PPARδ, Krüppel-like factor 4 (KLF4), IRF4, and HIF1α [22]. It warrants more detailed cellular and molecular mechanism studies to depict the crosstalk network among M1/M2 macrophages and their client adipocytes, and how the network responds to and is shaped by metabolic fluctuations.

Type 2 immune regulation of adipose development and function

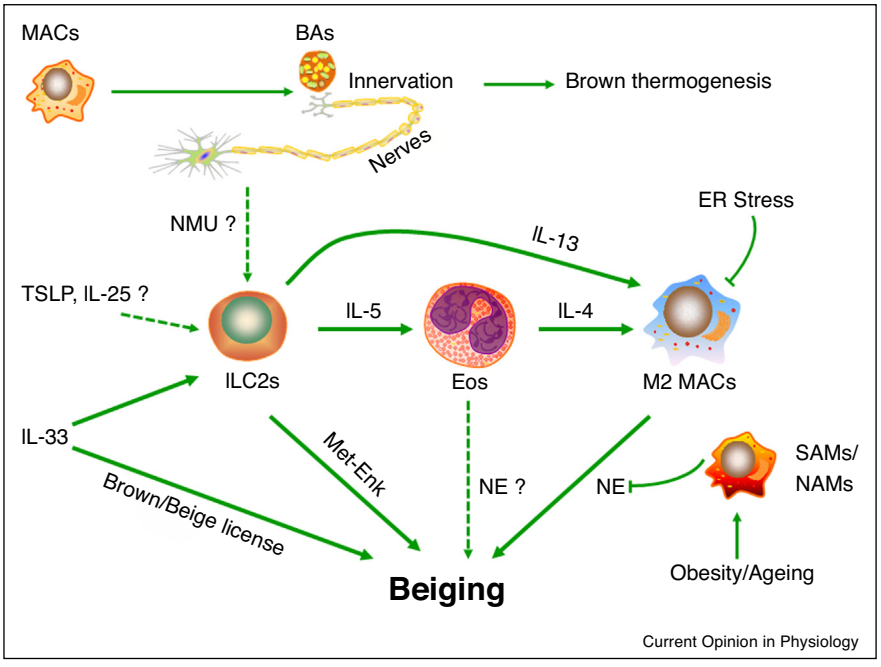
Almost all kinds of immune cells have been observed in adipose tissues, including innate immune cells, B cells and T cells [24]. Most of these cells can be categorized into two groups: type 1 and type 2 immune cells. Accordingly, type 1 immune cells and their corresponding cytokines are referred to as type 1 immunity, while type 2 immune cells and their associated cytokines are termed type 2 immunity [25]. Type 1 immune cells including M1 macrophages, $CD11c^+$ cells, B cells, CD4 Th1 cells, CD8 T cells and natural killer (NK) cells, are recruited and activated to exert a pro-inflammatory response in the obese state [24,26]. By contrast, type 2 immune cells including M2 macrophages, regulatory B (Breg) cells, CD4 Th2 cells, regulatory T (Treg) cells, invariant NKT (iNKT) cells, eosinophils and group 2 innate-like lymphoid cells (ILC2s), are resident or recruited and activated to present an anti-inflammatory response in the lean state [24]. Similar to the M2 to M1 activation switch of macrophages, obesity reduces the ratio of type 2 over type 1 immune cells in adipose tissues, leading to impaired insulin sensitivity and metabolic fitness. This raised an intriguing question whether and how type 2 immunity regulates adipose tissue homeostasis.

Most type 2 responses converge on M2 macrophage activation in adipose tissues. M2 macrophages are traditionally considered to be involved in tissue repair by disposing of dead cells and promoting angiogenesis and extracellular matrix remodeling [27]. However, M2 macrophages sustain adipose tissue homeostasis in multiple aspects. First, they promote insulin sensitivity by directly secreting IL-10 or indirectly restraining type 1 immune responses [20]. Second, they communicate with adipocytes to modulate insulin sensitivity by secreting extracellular vehicles (EVs) [28]. Third, they reduce adipocyte ion-overload to relieve insulin resistance by sequestering and processing excess ion in WAT [29]. Fourth, M2 macrophages activate adaptive thermogenesis in both brown and beige fat. We discuss the fourth part in great detail. In 2011, Nguyen *et al.* demonstrated that M2 macrophages could coordinate adaptive thermogenesis upon cold exposure by producing and secreting catecholamines in BAT and WAT. The secreted catecholamines, majorly norepinephrine, directly stimulate adaptive thermogenesis in brown adipocytes and lipolysis in white adipocytes as well [30]. However, Fischer *et al.* and Spadaro *et al.* recently reported opposite results that WAT macrophages do not express tyrosine hydroxylase (TH) to produce catecholamines [31,32]. In contrast, supportive evidence also accumulates, including: 1) Flierl *et al.* reported that exposure of phageocytes to lipopolysaccharide induces TH expression to produce and release catecholamines [33]; 2) Qiu *et al.* demonstrated that cold exposure recruits eosinophils to adipose tissues to secrete IL-4 which alternatively activates macrophages for

catecholamine production and resultant beige fat development [34]; 3) Luo *et al.* found that TH is expressed and phosphorylated by CaMKII in adipose-resident macrophages to produce catecholamines for adaptive thermogenesis [35]; 4) Zhao *et al.* reported that exosomes derived from adipose-derived stem cells induce macrophage alternative activation to increase TH expression and resultant catecholamine release [36]; 5) Staedtke *et al.* demonstrated that oncolytic bacteria and lipopolysaccharide elicit a self-amplifying loop of catecholamine expression in macrophages, which is inhibited by myeloid-specific deletion of tyrosine hydroxylase [37]. The source for the discrepancy is unknown. Interestingly, Pirzgalska *et al.* and Camell *et al.* found that sympathetic neuron-associated macrophages (SAMs) and nerve-associated macrophages (NAMs) uptake and catabolize catecholamines to modulate thermogenesis and lipolysis under obese or aged state respectively [38••,39••]. These findings raise two important questions: whether there is an alternative activation of SAMs/NAMs, and whether this M2 activation inhibits the expression and/or activity of norepinephrine-degrading enzymes like MAO since obese SAMs show higher M1 but lower M2 marker expression when compared to lean SAMs [39••]. If it is the case, then it may add another regulation axis on thermogenesis/lipolysis upon M1/M2 activation of a subset of macrophages via modulating catecholamine pool in BAT and WAT, which are secreted by sympathetic nerves. Both the macrophage-autonomous and macrophage-non-autonomous pathways may operate independently or synergistically under different contexts such as cold exposure, obesity and ageing. Supplementing another regulation layer, ER stress sensor IRE1α functions as a critical switch of macrophage M1/M2 activation to control BAT activity and beiging [23•].

Eosinophils are primarily associated with helminth immunity and allergic inflammation until Wu *et al.* implicated them in WAT homeostasis. They found that eosinophils are the major IL-4 source in WAT to induce M2 activation and maintain glucose homeostasis, and eosinophil deficiency impairs glucose tolerance while helminth-induced adipose tissue eosinophilia enhances it [40]. Qiu *et al.* demonstrated that cold exposure recruits eosinophils to secret IL-4 and then stimulate alternative macrophage activation, which promotes local catecholamine production and beige adipogenesis in an IL-4R dependent manner [34]. Unexpectedly, this efferent beige fat

Figure 1



Type 2 immunity boosts brown and beige adipose tissue development and function.
Cold exposure triggers sympathetic nerves to induce brown and beige adipose activation and development. Type 2 immunity forms a core immune-thermogenic circuit to complement this response. The circuit is composed of type 2 immune cells (ILC2s, eosinophils and M2 macrophages) and type 2 cytokines (IL-33, IL-5, IL-13 and IL-4), and it converges on M2 macrophages to secret NE and promote thermogenesis. Three additional regulation axes are supplemented, including: 1) obesity and/or ageing-induced SAMs/NAMs activation inhibits beiging via degrading NE imported from sympathetic nerves; 2) ER stress-induced IRE1α activation suppresses M2 activation and the attendant BAT activation and beging; 3) macrophages sustain brown adipocyte innervation and local norepinephrine production to maintain homeostatic thermogenesis, which may work in beige adipocyte innervation as well. Three potential upstream stimuli for ILC2s activation in the setting of thermoregulation are suggested: TSLP, IL-25 and neuropeptide neuromedin NMU.

thermogenic circuit by eosinophils-M2 macrophages axis might be a common pathway in response to different physiological stimuli. To support this notion, resistance exercise drives muscle to secret meteorin-like hormone, while cold exposure induces adipocytes to secret this hormone as well, and then the meteorin-like activates eosinophils-M2 macrophages axis to drive beiging [41]. In addition, microbiota depletion or caloric restriction increases and activates eosinophils-M2 macrophages axis to promote beige fat growth as well [42,43]. Moving upstream further, exogenous IL-33 or cold exposure induces eosinophils and ILC2s production of IL-4 and IL-13, respectively, which triggers the proliferation and commitment of adipocyte precursors toward the beige lineage [44]. ILC2s, a recently identified innate immune cell type, are the major cell source of IL-5 and IL-13 [45]. For the maintenance of WAT homeostasis, ILC2s can secret IL-5 to regulate the proliferation, activation and survival of eosinophils and then sustain adipose tissue M2 macrophage activation to promote beige fat growth [46]. However, Brestoff *et al.* found that exogenous IL-33 activates ILC2s to produce methionine-enkephalin peptides, primary endogenous ligands of the δ-opioid receptor, which directly promote beiging and limit obesity [47]. Recently, Odegaard *et al.* found an unexpected role of IL-33 and its receptor ST2, which functions as a developmental switch to license brown and beige fat for uncoupled respiration during the perinatal period [48•]. So far, a core immune-thermogenic circuit has been established, which is IL-33→ILC2s→IL-5/13→eosinophils→IL-4→M2 macrophages→thermogenesis (Figure 1).

Although the core immune-thermogenic axis is nicely structured, it is not the end of the story. Another significant advance on this topic came from Wolf *et al.* who found that macrophages are required for brown adipocyte sympathetic innervation and local norepinephrine production to maintain homeostatic thermogenesis [49••]. And Withers *et al.* identified eosinophils as a novel cell source of catacholamines in the regulation of normal perivascular adipose tissue (PVAT) anti-contractile function, which may supplement another regulation aspect for eosinophils-mediated beiging [50]. IL-33, IL-25 and thymic stromal lymphopoietin (TSLP) have been demonstrated to activate ILC2s to protect the host from helminth infection but promote allergy inflammation when dysregulated [51]. It would be interesting to examine whether these additional type 2 cytokines play a role in brown/beige fat development and function. This hypothesis is supported by a recent study posted on bioRxiv, which proposed that IL-25 induces beiging in WAT by releasing IL-4/IL-13 to activate M2 macrophages and then enhance nerve-beige adipocyte innervation just like what macrophages do in BAT innervation (https://www.biorxiv.org/content/10.1101/474288v1). With regard to the immune-neuronal circuits, three recent studies have demonstrated that the neuropeptide neuromedin U (NMU) stimulates ILC2s-driven type 2 inflammation in lung and intestine [52–54]. It is worthy of exploring whether NMU expresses in fat tissues and this NMU-ILC2s axis also functions in the regulation of WAT and BAT homeostasis.

Therapeutic implications

From a point view of energy homeostasis, when energy intake chronically exceeds energy expenditure, the remained energy is stored as fat and obesity ensues. Thus, at the level of an individual, we have two fundamental ways of fighting against obesity: to decrease energy intake or to increase energy expenditure. Current anti-obesity drugs aim to reduce energy intake by either suppressing appetite or inhibiting fat absorption. However, most of them have been associated with different degree of psychiatric and/or cardiovascular side effects, urging a search for alternative approaches [55]. In accordance with what we have learned above, we may consider three related alternative approaches, aiming at increasing energy expenditure via fine modulation of type 1 and type 2 immunity.

The first alternative approach is to improve insulin sensitivity in a proper way of controlling type 1 immunity but not just simply to inhibit it. Since pro-inflammatory responses impair insulin sensitivity, many efforts have been put to search anti-inflammatory agents to treat insulin resistance and type 2 diabetes, however this strategy has largely been disappointing [56]. This is because pro-inflammatory responses exhibit beneficial roles on the metabolic homeostasis under certain conditions by disposing of dead adipocytes to avoid necrosis and the attendant M1 activation or promoting healthy expansion and proper remodeling of WAT [5•,57].

The second approach aims to increase BAT/beige fat mass and activity. People typically thought that BAT only presents in infants and disappears in adults, until several studies demonstrated that adults do have active BAT/beige fat upon mild cold exposure, and a 10-day cold acclimation in humans increases non-shivering thermogenesis by recruiting human brown fat [58]. Since type 2 immunity is capable of promoting brown and beige fat development and thermogenesis, it is a rational strategy to increase the BAT/beige fat mass and activity by boosting an anti-inflammatory microenvironment in fat tissues.

The third one is to leverage the 'good' characteristics of scWAT for metabolic fitness. As mentioned above, the functional differences between subcutaneous and visceral adipose tissue may ascribe to distinct cell-autonomous programs and unique microenvironment shaped by neuronal innervation. Immune party might be a key contributor to the unique microenvironment of scWAT, as

scWAT are prone to beiging compared with vsWAT. This notion is also supported by an observation that beige adipocytes are enriched in the middle region of scWAT near the lymph nodes [59,60]. In addition, PRDM16 deletion in adipocytes generates a pro-inflammatory microenvironment and leads to a subcutaneous to visceral fat switch, which indicate anti-inflammatory microenvironment plays a key role in maintaining scWAT identity [14]. It would not be surprised if one could improve metabolic fitness by enhancing the 'good' characteristics of subcutaneous WAT.

Conflict of interest statement

Nothing declared.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, Mullany EC, Biryukov S, Abbafati C, Abera SF *et al.*: **Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the global burden of disease study 2013**. *Lancet* 2014, **384**:766-781.

2. Cawley J, Meyerhoefer C: **The medical care costs of obesity: an instrumental variables approach**. *J Health Econ* 2012, **31**:219-230.

3. Cao Y: **Adipose tissue angiogenesis as a therapeutic target for obesity and metabolic diseases**. *Nat Rev Drug Discov* 2010, **9**:107-115.

4. Rosen ED, Spiegelman BM: **What we talk about when we talk about fat**. *Cell* 2014, **156**:20-44.

5. • Man K, Kutyavin VI, Chawla A: **Tissue immunometabolism: development, physiology, and pathobiology**. *Cell Metab* 2017, **25**:11-26.

This review divides immunometabolism into two subdisciplines: cellular immunometabolism and tissue immunometabolism. And it defines the concept and characteristics of tissue immunometabolism by outlining general principles governing how accessory cells support parenchymal cells for metabolic homeostasis.

6. Buck MD, Sowell RT, Kaech SM, Pearce EL: **Metabolic instruction of immunity**. *Cell* 2017, **169**:570-586.

7. Wu J, Cohen P, Spiegelman BM: **Adaptive thermogenesis in adipocytes: is beige the new brown?** *Genes Dev* 2013, **27**:234-250.

8. Sanchez-Gurmaches J, Hung CM, Sparks CA, Tang Y, Li H, Guertin DA: **PTEN loss in the Myf5 lineage redistributes body fat and reveals subsets of white adipocytes that arise from Myf5 precursors**. *Cell Metab* 2012, **16**:348-362.

9. Ikeda K, Maretich P, Kajimura S: **The common and distinct features of brown and beige adipocytes**. *Trends Endocrinol Metab* 2018, **29**:191-200.

10. Rosenwald M, Perdikari A, Rulicke T, Wolfrum C: **Bi-directional interconversion of brite and white adipocytes**. *Nat Cell Biol* 2013, **15**:659-667.

11. Gesta S, Tseng YH, Kahn CR: **Developmental origin of fat: tracking obesity to its source**. *Cell* 2007, **131**:242-256.

12. Lee MJ, Wu Y, Fried SK: **Adipose tissue heterogeneity: implication of depot differences in adipose tissue for obesity complications**. *Mol Aspects Med* 2013, **34**:1-11.

13. Tran TT, Kahn CR: **Transplantation of adipose tissue and stem cells: role in metabolism and disease**. *Nat Rev Endocrinol* 2010, **6**:195-213.

14. Cohen P, Levy JD, Zhang Y, Frontini A, Kolodin DP, Svensson KJ, Lo JC, Zeng X, Ye L, Khandekar MJ *et al.*: **Ablation of PRDM16 and beige adipose causes metabolic dysfunction and a subcutaneous to visceral fat switch**. *Cell* 2014, **156**:304-316.

15. Hotamisligil GS: **Inflammation, metaflammation and immunometabolic disorders**. *Nature* 2017, **542**:177-185.

16. Hotamisligil GS, Shargill NS, Spiegelman BM: **Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance**. *Science* 1993, **259**:87-91.

17. Xu H, Barnes GT, Yang Q, Tan G, Yang D, Chou CJ, Sole J, Nichols A, Ross JS, Tartaglia LA *et al.*: **Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance**. *J Clin Invest* 2003, **112**:1821-1830.

18. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW Jr: **Obesity is associated with macrophage accumulation in adipose tissue**. *J Clin Invest* 2003, **112**:1796-1808.

19. Chawla A, Nguyen KD, Goh YP: **Macrophage-mediated inflammation in metabolic disease**. *Nat Rev Immunol* 2011, **11**:738-749.

20. Lumeng CN, Bodzin JL, Saltiel AR: **Obesity induces a phenotypic switch in adipose tissue macrophage polarization**. *J Clin Invest* 2007, **117**:175-184.

21. Gordon S: **Alternative activation of macrophages**. *Nat Rev Immunol* 2003, **3**:23-35.

22. Qiu Y, Shan B, Yang L, Liu Y: **Adipose tissue macrophage in immune regulation of metabolism**. *Sci China Life Sci* 2016, **59**:1232-1240.

23. • Shan B, Wang X, Wu Y, Xu C, Xia Z, Dai J, Shao M, Zhao F, He S, Yang L *et al.*: **The metabolic ER stress sensor IRE1alpha suppresses alternative activation of macrophages and impairs energy expenditure in obesity**. *Nat Immunol* 2017, **18**:519-529.

IRE1α acts as a critical switch of macrophage M1/M2 activation to control BAT activity and beiging.

24. Mathis D: **Immunological goings-on in visceral adipose tissue**. *Cell Metab* 2013, **17**:851-859.

25. Gieseck RL 3rd, Wilson MS, Wynn TA: **Type 2 immunity in tissue repair and fibrosis**. *Nat Rev Immunol* 2018, **18**:62-76.

26. Wensveen FM, Jelencic V, Valentic S, Sestan M, Wensveen TT, Theurich S, Glasner A, Mendrila D, Stimac D, Wunderlich FT *et al.*: **NK cells link obesity-induced adipose stress to inflammation and insulin resistance**. *Nat Immunol* 2015, **16**:376-385.

27. Wynn TA, Vannella KM: **Macrophages in tissue repair, regeneration, and fibrosis**. *Immunity* 2016, **44**:450-462.

28. Gao X, Salomon C, Freeman DJ: **Extracellular vesicles from adipose tissue-A potential role in obesity and type 2 diabetes?** *Front Endocrinol (Lausanne)* 2017, **8**:202.

29. Orr JS, Kennedy A, Anderson-Baucum EK, Webb CD, Fordahl SC, Erikson KM, Zhang Y, Etzerodt A, Moestrup SK, Hasty AH: **Obesity alters adipose tissue macrophage iron content and tissue iron distribution**. *Diabetes* 2014, **63**:421-432.

30. Nguyen KD, Qiu Y, Cui X, Goh YP, Mwangi J, David T, Mukundan L, Brombacher F, Locksley RM, Chawla A: **Alternatively activated macrophages produce catecholamines to sustain adaptive thermogenesis**. *Nature* 2011, **480**:104-108.

31. Fischer K, Ruiz HH, Jhun K, Finan B, Oberlin DJ, van der Heide V, Kalinovich AV, Petrovic N, Wolf Y, Clemmensen C *et al.*: **Alternatively activated macrophages do not synthesize catecholamines or contribute to adipose tissue adaptive thermogenesis**. *Nat Med* 2017, **23**:623-630.

32. Spadaro O, Camell CD, Bosurgi L, Nguyen KY, Youm YH, Rothlin CV, Dixit VD: **IGF1 shapes macrophage activation in response to immunometabolic challenge**. *Cell Rep* 2017, **19**:225-234.

33. Flierl MA, Rittirsch D, Nadeau BA, Chen AJ, Sarma JV, Zetoune FS, McGuire SR, List RP, Day DE, Hoesel LM *et al.*: **Phagocyte-derived catecholamines enhance acute inflammatory injury**. *Nature* 2007, **449**:721-725.

34. Qiu Y, Nguyen KD, Odegaard JI, Cui X, Tian X, Locksley RM, Palmiter RD, Chawla A: **Eosinophils and type 2 cytokine signaling in macrophages orchestrate development of functional beige fat**. *Cell* 2014, **157**:1292-1308.

35. Luo Y, Liu B, Yang X, Ma X, Zhang X, Bragin DE, Yang XO, Huang W, Liu M: **Myeloid adrenergic signaling via CaMKII forms a feedforward loop of catecholamine biosynthesis**. *J Mol Cell Biol* 2017, **9**:422-434.

36. Zhao H, Shang Q, Pan Z, Bai Y, Li Z, Zhang H, Zhang Q, Guo C, Zhang L, Wang Q: **Exosomes from adipose-derived stem cells attenuate adipose inflammation and obesity through polarizing M2 macrophages and beiging in white adipose tissue**. *Diabetes* 2018, **67**:235-247.

37. Staedtke V, Bai RY, Kim K, Darvas M, Davila ML, Riggins GJ, Rothman PB, Papadopoulos N, Kinzler KW, Vogelstein B *et al.*: **Disruption of a self-amplifying catecholamine loop reduces cytokine release syndrome**. *Nature* 2018, **564**:273-277.

38. •• Camell CD, Sander J, Spadaro O, Lee A, Nguyen KY, Wing A, Goldberg EL, Youm YH, Brown CW, Elsworth J *et al.*: **Inflammasome-driven catecholamine catabolism in macrophages blunts lipolysis during ageing**. *Nature* 2017, **550**:119-123.

Ageing upregulates the expression of catecholamine-degradation enzyme MAOA of nerve associated macrophages (NAMs) to impair lipolysis in adipose tissues, in an inflammasome-driven manner.

39. •• Pirzgalska RM, Seixas E, Seidman JS, Link VM, Sanchez NM, Mahu I, Mendes R, Gres V, Kubasova N, Morris I *et al.*: **Sympathetic neuron-associated macrophages contribute to obesity by importing and metabolizing norepinephrine**. *Nat Med* 2017, **23**:1309-1318.

Sympathetic neuron-associated macrophages (SAMs) express SLC6A2 and MAOA to uptake and degrade NE respectively. And obesity increases the proportion of SAMs in the SNS. Both references 38 and 39 reveal novel neuro-immune signallings to mediate catecholamine resistance and its associated metabolic dysfunction upon obesity and ageing.

40. Wu D, Molofsky AB, Liang HE, Ricardo-Gonzalez RR, Jouihan HA, Bando JK, Chawla A, Locksley RM: **Eosinophils sustain adipose alternatively activated macrophages associated with glucose homeostasis**. *Science* 2011, **332**:243-247.

41. Rao RR, Long JZ, White JP, Svensson KJ, Lou J, Lokurkar I, Jedrychowski MP, Ruas JL, Wrann CD, Lo JC *et al.*: **Meteorin-like is a hormone that regulates immune-adipose interactions to increase beige fat thermogenesis**. *Cell* 2014, **157**:1279-1291.

42. Suarez-Zamorano N, Fabbiano S, Chevalier C, Stojanovic O, Colin DJ, Stevanovic A, Veyrat-Durebex C, Tarallo V, Rigo D, Germain S *et al.*: **Microbiota depletion promotes browning of white adipose tissue and reduces obesity**. *Nat Med* 2015, **21**:1497-1501.

43. Fabbiano S, Suarez-Zamorano N, Rigo D, Veyrat-Durebex C, Stevanovic Dokic A, Colin DJ, Trajkovski M: **Caloric restriction leads to browning of white adipose tissue through type 2 immune signaling**. *Cell Metab* 2016, **24**:434-446.

44. Lee MW, Odegaard JI, Mukundan L, Qiu Y, Molofsky AB, Nussbaum JC, Yun K, Locksley RM, Chawla A: **Activated type 2 innate lymphoid cells regulate beige fat biogenesis**. *Cell* 2015, **160**:74-87.

45. Artis D, Spits H: **The biology of innate lymphoid cells**. *Nature* 2015, **517**:293-301.

46. Molofsky AB, Nussbaum JC, Liang HE, Van Dyken SJ, Cheng LE, Mohapatra A, Chawla A, Locksley RM: **Innate lymphoid type 2 cells sustain visceral adipose tissue eosinophils and alternatively activated macrophages**. *J Exp Med* 2013, **210**:535-549.

47. Brestoff JR, Kim BS, Saenz SA, Stine RR, Monticelli LA, Sonnenberg GF, Thome JJ, Farber DL, Lutfy K, Seale P *et al.*: **Group 2 innate lymphoid cells promote beiging of white adipose tissue and limit obesity**. *Nature* 2015, **519**:242-246.

48. • Odegaard JI, Lee MW, Sogawa Y, Bertholet AM, Locksley RM, Weinberg DE, Kirichok Y, Deo RC, Chawla A: **Perinatal licensing of thermogenesis by IL-33 and ST2**. *Cell* 2016, **166**:841-854.

IL-33 and ST2 are required for an appropriate splicing of Ucp1 mRNA and thus functional UCP1 protein expression to license thermogenesis during the perinatal period, surprisingly in a MyD88 independent manner.

49. •• Wolf Y, Boura-Halfon S, Cortese N, Haimon Z, Sar Shalom H, Kuperman Y, Kalchenko V, Brandis A, David E, Segal-Hayoun Y *et al.*: **Brown-adipose-tissue macrophages control tissue innervation and homeostatic energy expenditure**. *Nat Immunol* 2017, **18**:665-674.

BAT macrophages control innervations between brown adipocytes and sympathetic nerves, which sustains normal local titers of norepinephrine to maintain homeostatic thermogenesis.

50. Withers SB, Forman R, Meza-Perez S, Sorobetea D, Sitnik K, Hopwood T, Lawrence CB, Agace WW, Else KJ, Heagerty AM *et al.*: **Eosinophils are key regulators of perivascular adipose tissue and vascular functionality**. *Sci Rep* 2017, **7**:44571.

51. Hammad H, Lambrecht BN: **Barrier epithelial cells and the control of type 2 immunity**. *Immunity* 2015, **43**:29-40.

52. Cardoso V, Chesne J, Ribeiro H, Garcia-Cassani B, Carvalho T, Bouchery T, Shah K, Barbosa-Morais NL, Harris N, Veiga-Fernandes H: **Neuronal regulation of type 2 innate lymphoid cells via neuromedin U**. *Nature* 2017, **549**:277-281.

53. Klose CSN, Mahlakoiv T, Moeller JB, Rankin LC, Flamar AL, Kabata H, Monticelli LA, Moriyama S, Putzel GG, Rakhilin N *et al.*: **The neuropeptide neuromedin U stimulates innate lymphoid cells and type 2 inflammation**. *Nature* 2017, **549**:282-286.

54. Wallrapp A, Riesenfeld SJ, Burkett PR, Abdulnour RE, Nyman J, Dionne D, Hofree M, Cuoco MS, Rodman C, Farouq D *et al.*: **The neuropeptide NMU amplifies ILC2-driven allergic lung inflammation**. *Nature* 2017, **549**:351-356.

55. Dietrich MO, Horvath TL: **Limitations in anti-obesity drug development: the critical role of hunger-promoting neurons**. *Nat Rev Drug Discov* 2012, **11**:675-691.

56. Esser N, Paquot N, Scheen AJ: **Anti-inflammatory agents to treat or prevent type 2 diabetes, metabolic syndrome and cardiovascular disease**. *Expert Opin Investig Drugs* 2015, **24**:283-307.

57. Kusminski CM, Bickel PE, Scherer PE: **Targeting adipose tissue in the treatment of obesity-associated diabetes**. *Nat Rev Drug Discov* 2016, **15**:639-660.

58. Betz MJ, Enerback S: **Targeting thermogenesis in brown fat and muscle to treat obesity and metabolic disease**. *Nat Rev Endocrinol* 2018, **14**:77-87.

59. Chi J, Wu Z, Choi CHJ, Nguyen L, Tegegne S, Ackerman SE, Crane A, Marchildon F, Tessier-Lavigne M, Cohen P: **Three-dimensional adipose tissue imaging reveals regional variation in Beige fat biogenesis and PRDM16-dependent sympathetic neurite density**. *Cell Metab* 2018, **27**:226-236.e223.

60. Chen Y, Ikeda K, Yoneshiro T, Scaramozza A, Tajima K, Wang Q, Kim K, Shinoda K, Sponton CH, Brown Z *et al.*: **Thermal stress induces glycolytic beige fat formation via a myogenic state**. *Nature* 2019, **565**:180-185.