The role of innate immunity in the regulation of brown and beige adipogenesis

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Abstract

The adipose tissue (AT) is multifunctional, acting as an endocrine tissue and participating in the regulation of the organism's homeostasis. Metabolic, endocrine and inflammatory mechanisms are tightly intertwined within the AT, regulating its function. Disruption of the equilibrium among these mechanisms leads to pathologies, the most common being obesity-related insulin resistance. Two types of AT exist, the white and the brown AT. Traditionally the white AT (WAT) was thought to store energy in the form of lipids, while the brown AT (BAT) was known to mediate heat generation. Recently, the 'brite' or 'beige' AT was identified, which is localized predominantly in subcutaneous WAT, but shares functional features with the BAT and is capable of heat production. The major stimulus triggering beige and brown adipogenesis is cold exposure and catecholamine signalling. However, several further signals and mechanisms exist, which can orchestrate and fine-tune beige and brown AT function. Immune cells and inflammation have emerged as regulators of beige and brown AT function. The present review will focus on the recently identified crosstalk between innate immunity and the regulation of beige and brown adipogenesis.

1. White, brown and beige adipose tissue

Adipose tissue (AT) has long been considered as a sole energy storage organ and thermal insulator. Recent accumulating evidence has refuted the idea of AT being a silent energy store. The current view of the AT is that of a dynamic endocrine organ that exerts several metabolic and endocrine as well as immune functions [1-4]. The AT in fact contributes to the metabolic equilibrium and homeostasis of the whole organism [3,4].

In mammals two types of AT exist, the white and the brown AT (WAT and BAT, respectively) [3,4]. The WAT underlies the skin throughout almost the whole body surface (subcutaneous WAT), as well as surrounds internal organs, such as the gastrointestinal tract (mesenteric, retroperitoneal, omental), the gonads (gonadal), the heart (pericardiac) or the kidneys (perirenal); the WAT surrounding internal organs is called visceral WAT [5,6]. WAT comprises mostly adipocytes, which display a large single lipid droplet and store triglycerides [7]. These lipids may be used as an energy source at states of low food availability; this is achieved via beta-oxidation of fatty acids [7]. Furthermore, white adipocytes secrete a number of humoral factors (adipokines), such as leptin, resistin and adiponectin, which regulate energy homeostasis through different actions including regulation of appetite, eating, glucose uptake and fatty acid breakdown (reviewed in [1,8]). Additionally, white adipocytes can, especially in obesity, secrete inflammatory mediators, such as Interleukin-6 (IL-6) or Tumor Necrosis Factor (TNF), and chemoattractants such as Monocyte Chemoattractant Protein-1 (MCP-1), thereby attracting monocytes/macrophages to the obese AT [1,2,8].

In contrast to the WAT, the BAT, situated in adult humans mainly in the area of the neck and the supraclavicular area, is responsible for non-shivering heat production primarily in neonates as well as in adults upon cold exposure [3,9-12]. This is achieved by uncoupling of the electron chain of the inner mitochondrial membrane thereby decreasing ATP production during oxidative phosphorylation. This function is attributed to thermogenin or Uncoupling protein 1 (UCP-1), which mediates the re-entry of H+ protons from the mitochondrial intramembrane space to the mitochondrial matrix, thus promoting heat generation [11,13]. Under normal temperature conditions, UCP-1 expression is abundant in BAT, while it is low to undetectable in white adipocytes [4,14,15]. However, upon cold exposure or activation of sympathoadrenergic signalling by catecholamines, UCP-1 expression is up-regulated in the BAT and seemingly induced in the WAT [4,14,15]. WAT expressing UCP-1 and acquiring characteristics reminiscent of those of BAT is designated ‘beige’ or ‘brite’ AT [4,14]. Interestingly, beige adipocytes are present in both subcutaneous and visceral WAT, yet they are more abundant in the former [14,15]. Brown and beige adipocytes share similar cell morphology. In contrast to white adipocytes, brown and beige adipocytes are multilocular cells that display multiple small lipid droplets and more mitochondria [4,15]. However, the similarities between brown and beige adipocytes should not result in the interpretation that beige adipocytes are simply brown adipocytes that appear within the WAT [4,14]. In fact, several differences with regards to their origin and gene expression profile have been identified thus far. For instance, brown adipocytes are thought to originate from Myogenic factor 5+ (Myf5+) progenitors (as do skeletal muscle cells), which is not the case for beige adipocytes in the WAT, induced by cold exposure or adrenergic stimulation [4,16]. For the origin of beige adipocytes, two hypotheses have been formulated: according to the first, beige adipocytes derive from PDGFRa+ resident progenitors, which can give rise to both white or beige adipocytes [17], while, according to the second hypothesis, beige adipocytes could derive from white adipocytes through a bi-directional interconversion or transdifferentiation [18]. The transcriptional regulator PRDM16 (PR-domain-containing 16) may exert distinct actions on beige and brown AT. PRDM16 was shown to be a key molecular factor in the differentiation of brown adipocytes [4,16] and is highly expressed in BAT [19]. However, later studies demonstrated that adipocyte-specific deletion of PRDM16 did not affect cold- or

beta-adrenergic signalling-induced thermogenic gene expression in BAT [19], while it strongly suppressed generation and function of beige AT [20]. Additionally, different molecular signatures have been described for brown and beige adipocytes: Ebf3, Eva1, Fbxo31, Zic1 represent human and murine brown adipocyte markers, while beige adipocytes are characterized by high expression of Tmem26, Tbx1 and CD137 (TNFSF9) [4,15,21-23].

The remarkable thermogenic capacity of brown and beige adipocytes relies on their metabolic profile, including enhanced glucose and lipid uptake, elevated mitochondrial biogenesis and a strong oxidative metabolism [4,24-26]. It was shown in humans that cold exposure induces glucose uptake in BAT [26]. Upon cold exposure, noradrenalin, deriving from the activated sympathetic nervous system, interacts with beta3 adrenergic receptors present on the surface of brown/beige adipocytes [4,27]. This triggers a substantial increase in intracellular cAMP levels, which stimulates lipolysis in a manner that involves induction of hormone-sensitive lipase (HSL), adipose triglyceride lipase (ATGL) and monoacylglycerol lipase (MGL), that collectively catalyse triglyceride breakdown to free fatty acids (FFA) and glycerol [28]. FFA on the one hand allosterically activate UCP-1, while, on the other hand, they contribute to thermogenesis through beta-oxidation [13]. Additionally, adrenergic stimulation induces *UCP-1* gene expression through the cAMP-PKA-p38 MAPK pathway [29,30]. These molecular mechanisms promote glucose and lipid uptake and utilisation in the BAT and beige adipocytes, and facilitate the maintenance of the body's temperature, especially during exposure to cold [4,13,16,24,26].

Many recent studies have demonstrated that BAT exists not only in human infants [12,23], as it has been thought for long [31], but also in adult individuals, in the supraclavicular area and the neck region [9,23,32,33]. By ^{18}F-fluoro-2-deoxy-D-glucose-PET-CT analysis, van Marken Lichtenbelt et al. and Cypess et al. showed that BAT exists in adult humans. BAT is however inactive under thermoneutral conditions and its activity negatively correlates with body mass index (BMI) and age [32,33]. Extensive analysis of the molecular signature of BAT has shown that the infant BAT is more similar to the murine BAT, as it highly expresses the murine BAT marker ZIC1, while having lower expression of the beige AT marker Tbx1, as compared to the adult human supraclavicular BAT [12,23]. On the contrary, adult neck BAT displays resemblance with both mouse beige AT and BAT [23,32,34]. The expression of beige or brown markers depends on the anatomical localization of the human adult neck AT. In particular, superficial neck AT expresses WAT markers, such as leptin and HOXC9, while the deeper neck fat depots express the BAT markers UCP-1, ZIC1 and LHX8. Beige AT markers, such as CD137 or TMEM26, are present in both superficial and deep human neck AT depots [32]. As in the murine system, human subcutaneous AT has beige/brown adipogenesis capacity, demonstrated by cold exposure [10]. In an interesting study, 2-hour long cold exposure at 17°C on a daily basis for a total of 6 weeks decreased the body fat mass and improved glucose tolerance [35]. This finding was not unexpected, given the previous studies in mice, which had shown that thermogenesis and insulin sensitivity are closely intertwined with each other [36]. Overexpression of UCP-1 under the control of the aP2 promoter led to body weight reduction in mice with genetically induced obesity [37]. Furthermore, mice with genetic depletion of BAT developed obesity without exhibiting any hyperphagia [38], while BAT transplantation elicited improved glucose tolerance, enhanced insulin sensitivity and decreased total body weight as well as fat mass [36].

2. Regulation of brown and beige adipogenesis

Although adrenergic signalling is a major regulatory mechanism of thermogenesis, it is not the only one. Accumulating evidence suggests that a complex network integrating several signals deriving from different cells and organs regulates the thermogenic capacity of beige and brown AT [4]. Here we will briefly describe such mechanisms, emphasizing predominantly on the role of innate immunity in the regulation of beige and brown AT function.

Although administration of high caloric diet for a short period of few days may trigger thermogenesis in a manner dependent on activation of the sympathetic nervous system [39,41], BAT activity in humans inversely correlates with body-mass index [9], whereas diet-induced obesity in rodents resulting from high caloric diet for longer periods correlates with suppression of beige adipocytes [40-42]. Obesity may induce 'whitening' of the BAT owing to fat accumulation, associated with reduced thermogenesis [43-44]. A factor, which could negatively regulate UCP-1 expression and thermogenesis, is inflammation [45]; consistently, inflammation is a hallmark of obesity induced by long-term high fat diet feedings [45-49].

Fibroblast Growth Factor 21 (FGF21) is produced by the liver and reaches the AT through the blood [50]. It potently induces beige adipogenesis by stabilizing the peroxisome proliferator-activated receptor-gamma (PPARgamma) coactivator-1alpha (PGC1a) [51], which is a central regulator in the expression of UCP-1 and other thermogenic genes [4,52,53]. Additionally, FGF21 is produced by brown adipocytes, thereby promoting locally BAT thermogenesis in an autocrine fashion [54]. Moreover, the thyroid hormone 3,3,5-triiodothyronine (T3) is an important inducer of *UCP-1* gene expression through direct regulation of thyroid hormone response elements (TREs) in the promoter of the *UCP-1* gene [55]. On the other hand, T3 may act synergistically with adrenergic signalling in brown adipocytes thereby further enhancing BAT thermogenesis [56]. Additionally, cardiac natriuretic peptides were shown to induce lipolysis and thermogenic gene expression through a cGMP-PKG-dependent pathway [57,58]. A further factor deriving from cardiomyocytes is cardiotrophin-1, which, in an AMPKa2-dependent manner, induces lipid oxidation, mitochondrial biogenesis and expression of BAT genes in the WAT, thereby increasing insulin sensitivity [59].

Recently, a myokine produced by the muscles upon exercise, which was named irisin, was identified as a novel regulator of beige adipogenesis in the WAT. Irisin was shown to induce *UCP-1* expression and a number of other BAT-related genes in the WAT, thus enhancing energy expenditure [60]. Moreover, meteorin-like (Metrnl), which is released by muscles upon exercise and by the AT during cold exposure, was shown to induce beige adipogenesis in the WAT [61].

Furthermore, bone morphogenic protein 7 (BMP7) is regarded a crucial inducer of BAT, as it stimulates differentiation of progenitor cells to brown adipocytes, increases expression of factors linked to brown adipogenesis, like PRDM16, PGC-1a, PPARgamma, CCAAT/enhancer-binding proteins (C/EBPs) and UCP-1 and induces mitochondrial biogenesis [62,63]. Finally, adenosine was recently demonstrated to activate, through A_{2A} receptors, brown and beige adipocytes and to induce thermogenesis. Adenosine is produced by the BAT and therefore confers endogenous control of thermogenesis, while treatment of mice, subjected to diet-induced obesity, with an A_{2A} agonist counteracted obesity and improved glucose tolerance [64].

3. The immune system: A central player in the regulation of beige and brown adipose tissue function

The AT and the immune system are closely intertwined through a network of mechanisms in physiology and pathology. That inflammation is causally linked to insulin resistance is known for 20 years now [47,65]. In the meantime, several immune cell subpopulations, including M1 and M2 polarized macrophages, $CD4^+$, $CD8^+$ T cells, regulatory T cells (Tregs), neutrophils, eosinophils, natural killer cells (NKT) cells, mast cells and B cells have been identified in the AT and contribute to metabolic regulation [2,48,66,67]. Depending on the state of the AT, lean or obese, these populations can dynamically change: in the lean state, Tregs and cell types associated to type 2 immunity, such as alternatively activated (M2) macrophages, eosinophils, and type 2 innate lymphoid cells (ILC2) predominate and may regulate AT homeostasis, including beige and brown adipogenesis [66-68], while in obesity, inflammatory cell types accumulate, such as classically activated (M1) macrophages or $CD8^+$ cells [2,48,69-73].

a. <u>The role of type 2 immune cells in AT metabolism and beige adipogenesis</u>

In the last 5 years a substantial number of studies addressed the mechanisms, by which immune cells regulate adipocyte biology and function. So far, eosinophils, M2 macrophages and type 2 innate lymphoid cells (ILC2) have been identified to reside in the lean WAT and to regulate beige adipogenesis (reviewed in [68,74]).

Alternatively activated, M2-polarized macrophages are usually induced by helminth infection or during lung allergies. They display high expression of arginase 1, Found in inflammatory zone 1 (Fizz1), Chitinase like 3 (Chi3l3, Ym1), the mannose receptor (MRC1, CD206), CD301 (Clec10a) and Kruppel-like Factor 4 (Klf4) [46,49,75,83]. Their gene expression profile is very different from that of M1 macrophages; the latter express inducible nitric oxide synthase (iNOS), CD11c (Integrin, alpha X Itgax) and secrete proinflammatory cytokines, such as TNF, IL-1beta, IL-12 and IL-6 [46, 48,49,75]. In the lean state, M2 macrophages contribute to WAT homeostasis. They produce anti-inflammatory cytokines such as IL-10, which down-regulates MCP-1 production and inhibits TNF-mediated GLUT4-dependent glucose uptake [46]. However, IL-10 deletion in haematopoietic cells did not potentiate high-fat diet-induced inflammation or insulin resistance [76], rendering the role of IL-10 in the AT rather elusive. The major stimuli for M2 macrophage polarization are IL-4 and IL-13, which derive from eosinophils [77], M2 macrophages [78-80], invariant Natural Killer T (iNKT) cells [81], as well as adipocytes [82]. So far, eosinophils have been shown to be a major source of type 2 cytokines in the AT [77]. Mice lacking eosinophils, such as the ΔdblGATA mice carrying a mutated GATA1 promoter, or IL-5 deficient mice, exhibited increased obesity and insulin resistance, as compared to wild type mice, accompanied by attenuated presence of M2 macrophages [77]. Conversely, helminth-induced eosinophilia enhanced glucose tolerance [77].

Interestingly, a tight link between type 2 immunity and cold exposure-associated WAT and BAT thermogenesis has been recently revealed. Exposure to cold promotes M2 macrophage polarization in BAT and WAT [83]. Consistently, IL-4/IL-13 double knockout ($IL4^{-/-}IL13^{-/-}$) or STAT6 knockout ($STAT6^{-/-}$) mice were less cold resistant due to disrupted cold-induced thermogenic gene expression [40,83]. Furthermore, myeloid-specific depletion of the IL-4Ra resulted in reduced cold resistance [83]. On the contrary, IL-4 or IL-13 administration activated lipolysis and beige adipogenesis in the WAT, and increased oxygen consumption in mice [40,83]. This effect was blunted in mice with myeloid-specific deletion of IL-4Ra or following macrophage depletion, indicating the direct involvement of macrophages in this process [83]. The authors of this work also suggested that IL-4 triggers tyrosine hydroxylase activation and thus noradrenaline production in macrophages [83]. Additionally, mice with myeloid-specific depletion of tyrosine hydroxylase displayed reduced UCP-1 expression and disrupted body

temperature maintenance upon cold exposure [40]. The cold-induced beige adipogenesis was also abolished in ΔdblGATA mice, underlining the important role of eosinophils in these mechanisms [40]. In summary, the group of Chawla demonstrated that upon cold exposure eosinophils are recruited to the WAT and induce M2 macrophage polarization through production of IL-4. IL-4 in turn stimulates M2 macrophages to secrete noradrenalin, thus promoting thermogenesis and beige adipogenesis in the WAT [40,83]. The same group has added another important aspect to this mechanism by showing that IL-4 affects beige adipogenesis through a direct action on PDGFRa+Sca1+CD31-CD45- adipocyte progenitors [84]. Adipocyte progenitors, in contrast to mature adipocytes, express IL-4Ra and upon IL-4 stimulation they are biased towards the beige rather than the white adipocyte lineage, which is supported by the observation that IL-4 enhanced expression of beige adipocyte markers, such as Tmem26 and CD137 as well as UCP-1 expression [84]. Indeed IL-4 has been also demonstrated by others to inhibit white adipogenesis of pre-adipocytes by downregulating the expression of PPAR-gamma and CCAAT/enhancer-binding protein-alpha (C/EBP-alpha), and to promote lipolysis by activating hormone sensitive lipase (HSL) [85]. In agreement with the effect of IL-4 on beige adipogenesis and increased energy dissipation [40,83], IL-4 administration protected mice against HFD-induced obesity and insulin resistance [40,86,87].

So far, two hormones produced by the AT have been identified to regulate beige adipogenesis through modulation of M2 macrophage polarization. First, adiponectin interacts with T-cadherin on the surface of M2 macrophages and may promote M2 polarization through Akt signalling. M2 macrophage accumulation and beige adipogenesis induced by chronic cold exposure were inhibited in the subcutaneous AT of adiponectin-deficient mice [88]. Furthermore, meteorin-like (Metrnl), released by muscles and AT, induces WAT beige adipogenesis in an eosinophil-, IL-4-signaling and M2 macrophage–dependent manner [61].

Additionally, type 2 innate lymphoid cells (ILC2) residing in the subcutaneous AT of humans and mice, identified as $Lin^-CD25(IL\text{-}2Ra)^+CD127(IL\text{-}7Ra)^+GATA\text{-}3^+IL\text{-}33R^+$ cells [89], play an important role in beige adipogenesis [84,89]. The proliferation and maintenance of ILC2s in the WAT is dependent on IL-33 [84,89]. Consistently, IL-33-/- mice display increased body fat mass and reduced beige adipogenesis [89]. Intriguingly, IL-33 also drives the generation of Tregs in the visceral AT [90], whereas ILC2s regulate the presence of eosinophils and alternatively activated macrophages in the AT [91]. However, the role of ILC2s in beige adipogenesis is not necessarily dependent on the adaptive immune system, eosinophils or IL-4 signalling [89]. In fact, ILC2-produced methionine-enkephalin peptides mediate the action of ILC2s in beige adipogenesis, as they can induce UCP-1 expression in the WAT [89].

Furthermore, the inflammatory cytokines IL-6 and IL-15 have been implicated in the induction of beige adipogenesis. IL-6 secreted by skeletal muscles during exercise induces UCP-1 expression in the subcutaneous AT [92]. Along the same line, IL-6 gene delivery enhances expression of thermogenic genes [93]. Moreover, BAT transplantation of IL-6-proficient but not IL-6-deficient mice improved the metabolic profile and glucose tolerance in mice [36]. In conclusion, these studies point to a rather beneficial role of IL-6 for thermogenesis, which correlates with its protective role against inflammation and obesity [94]. IL-15 may also exert anti-obesity effects. It is produced in the AT by macrophages and fibroblasts [95]. In human plasma, IL-15 levels negatively correlate with visceral AT size independent of the existence of type 2 diabetes [96]. IL-15 deficient mice were more obese [97], while IL-15 administration reduced AT weight and enhanced UCP-1 expression in BAT [97,98].

b. <u>The role of immune cells in the brown adipose tissue</u>

Although the role of immune cells has been extensively described in WAT, less is known about their role in the BAT. A detailed characterization of immune cell populations in the BAT is missing, however, macrophages apparently reside in BAT [83,99,100]. During obesity, F4/80, a marker of macrophages, and the pro-inflammatory cytokine TNF increase in BAT [43,100], suggesting accumulation of pro-inflammatory macrophages. On the other hand, M2 macrophages are recruited to BAT upon cold exposure in an IL-4 dependent manner and induce BAT thermogenesis through catecholamine production [83]. Moreover, BAT was recently reported to possess a population of Tregs, which displays a unique gene expression profile [101]. Treg deficiency induced by diphtheria toxin application to Foxp3DTR mice, abrogated BAT thermogenesis, which was attributed to enhanced macrophage abundance and elevated BAT inflammation, suggesting that BAT activity requires the presence of Tregs [101].

c. Do pro-inflammatory cells inhibit beige or brown adipogenesis?

Although several studies have pointed to a role of type 2 immune cells (M2 macrophages, eosinophils, ILC2s) in the regulation of beige and brown AT, less information exists on a potential regulation of these processes by pro-inflammatory cells, such as M1 macrophages or T cells, such as CD4+ or CD8+ cells. High caloric intake stimulates adipocyte progenitor proliferation resulting in adipocyte hyperplasia [102], while existing adipocytes expand in size (hypertrophy) via lipid accumulation [103]. Features of the obese AT are hypoxia, reactive oxygen species (ROS) generation and endoplasmatic reticulum (ER) stress [104,105]. Under obese conditions, several inflammatory mechanisms mediate insulin resistance. Adipocytes secrete CCL2 (MCP-1), which attracts monocytes/macrophages to the AT [106,107]. M1 macrophages secrete pro-inflammatory cytokines, such as IL-1beta, TNF and IL-6 further promoting inflammation [2,46]. Saturated free fatty acids (FFA) are released by adipocytes and may activate Toll-like Receptor 4 (TLR4) promoting AT inflammation [108,109,110]. Fetuin-A has been suggested to mediate the interaction of FFA with TLR4; fetuin-A knockdown in mice attenuated TLR4-mediated inflammatory signalling in the AT [111]. TLR4 activation, oxidative stress and cell death trigger JNK phosphorylation in adipocytes [112,113], which may block insulin signalling by modification (e.g. Ser phosphorylation) of IRS proteins [114]. Moreover, TLR4 signalling and enhanced levels of inflammatory cytokines promote SOCS protein expression [115,116], which also interfere with insulin signalling, by inducing proteolytic degradation of IRS1/2 via interaction with the elongin BC ubiquitin-ligase and by inhibiting IRS1/2 Tyr phosphorylation [117-120]. Additionally, CD8+ cells have been shown to promote macrophage accumulation in the WAT and insulin resistance in obesity [48,72].

Scarce evidence exists on whether pro-inflammatory cells regulate beige or brown AT thermogenesis [45]. It was suggested that cytokines deriving from pro-inflammatory macrophages may directly down-regulate UCP-1 expression in adipocytes. For instance, IL-1beta and TNF were shown to suppress isoproterenol-induced UCP-1 mRNA expression in adipocytes in an Extracellular signal-Regulated Kinase (ERK)-dependent manner [121,122]. TNF was demonstrated to down-regulate endothelial NOS (eNOS) expression and mitochondrial biogenesis in white and brown adipocytes, while TNF deletion restored eNOS expression and mitochondrial biogenesis, which was in turn associated with decreased body weight gain in obese mice [123]. TNF could also repress beta-Klotho expression and thereby impaired adipocyte sensitivity to FGF21, in a JNK-dependent manner; JNK deletion restored β-Klotho expression and reversed the FGF21 responsiveness in adipocytes [124].

Future studies will be required to reveal if and how inflammatory cells and cellular signals regulate beige and brown adipogenesis through mechanisms other than pro-inflammatory cytokine secretion.

4. Outlook and perspectives

Several pharmacological strategies enhancing the activity of BAT in order to treat obesity are under investigation. The beta3 adrenergic agonist mirabegron resulted in increased BAT activity, as assessed by ^{18}F-fluoro-2-deoxy-D-glucose-PET-CT analysis [125]; further studies are needed to assess its efficacy in metabolic disease. The chemical uncoupler dinitrophenol causes rapid weight loss, however, several deaths have been associated with its use [126]. This toxicity may be bypassed by a controlled-release oral formulation of dinitrophenol, which improved insulin resistance and non-alcoholic fatty liver disease in rodents [127]. In addition to these approaches, targeting inflammation and immunity to modulate beige / brown AT thermogenesis, energy dissipation and insulin resistance may represent an intriguing perspective in the same context. Revealing the molecular mechanisms mediating the crosstalk between different immune cell populations and adipocyte progenitors or mature adipocytes will therefore provide indispensable knowledge for identifying such therapeutic targets.

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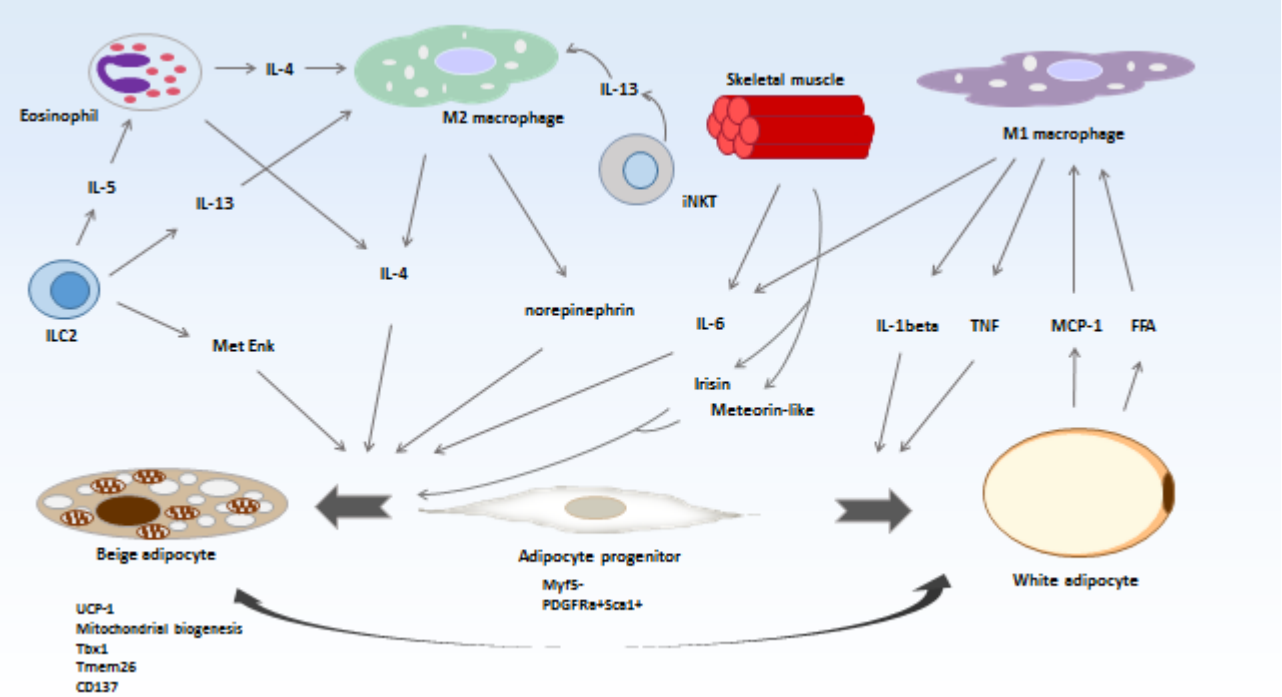

Figure legend

Inflammatory signals regulating beige and white adipogenesis

Signals from type 2 immunity promote differentiation of PDGFRa+Sca1+ adipocyte progenitors to UCP-1+ beige adipocytes [4,15,23,77,82-87,89-91]. M2 macrophages and eosinophils induce beige adipogenesis through norepinephrin and IL-4-dependent mechanisms [77,83,84], ILC2s promote beige adipogenesis through production of methionine-enkephalin peptides [89]. The exercised muscle produces IL-6 [92], irisin [60] and Meteorin-like [61], which can also stimulate beige adipogenesis [60,61,92]. On the other hand, M1 macrophages rather facilitate white adipogenesis through TNF and IL-1beta secretion [45,121-124]. IL-4, IL-13 and IL-5 cytokines retain M2 macrophages, eosinophils and ILC2 cells in the adipose tissue [77-81,83,84,87,89,91], while MCP-1 and FFA mediate the recruitment of pro-inflammatory M1 macrophages to the adipose tissue [2,46,106-111].

Abbreviations: CD137: Cluster of Differentiation 137; FFA: Free Fatty Acids; ILC2: type 2 innate lymphoid cells; IL: Interleukin; iNKT: Invariant natural killer T; MCP-1: Monocyte Chemoattractant Protein-1; Met Enk: methionine-enkephalin peptides; Myf5: Myogenic factor 5; PDGFRa: Platelet Derived Growth Factor Receptor a; Sca1: Stem cells antigen-1; Tbx1: T-box transcription factor; Tmem26: Transmembrane Protein 26; TNF: Tumor Necrosis Factor; UCP-1: Uncoupling Protein 1.