



Immune Cells in Thermogenic Adipose Depots: The Essential but Complex Relationship

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Brown adipose tissue (BAT) is a unique organ in mammals capable of dissipating energy in form of heat. Additionally, white adipose tissue (WAT) can undergo browning and perform thermogenesis. In recent years, the research community has aimed to harness thermogenic depot functions for new therapeutic strategies against obesity and the metabolic syndrome; hence a comprehensive understanding of the thermogenic fat microenvironment is essential. Akin to WAT, immune cells also infiltrate and reside within the thermogenic adipose tissues and perform vital functions. As highly plastic organs, adipose depots rely on crucial interplay with these tissue resident cells to conserve their healthy state. Evidence has accumulated to show that different immune cell populations contribute to thermogenic adipose tissue homeostasis and activation through complex communicative networks. Furthermore, new studies have identified -but still not fully characterized further- numerous immune cell populations present in these depots. Here, we review the current knowledge of this emerging field by describing the immune cells that sway the thermogenic adipose depots, and the complex array of communications that influence tissue performance.

Keywords: immune cells, batokines, crosstalk, thermogenesis, adipose tissue

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INTRODUCTION: OBESITY AND THE ADIPOSE TISSUE

Obesity and its underlying metabolic complications are a worldwide concern with significant medical and social implications (1–4). Adipose depots are the primary site of energy storage and also perform vital endocrine functions that regulate and maintain energy homeostasis (5). In mammals, two main types of adipose tissue exist, being different in origin, location, morphology and function (6–9). White adipocytes contain large unilocular lipid droplets that store large amounts of lipids, whereas brown adipocytes contain multilocular small lipid droplets as well as a high number of mitochondria and dissipate energy as heat. Additionally, beige adipocytes originate from a white adipocyte lineage but can undergo browning and acquire brown adipocyte-like features (10). Thus, both brown and beige fat tissues have thermogenic potential and will be referred to as thermogenic adipose tissues (TAT). After its re-discovery in adult humans (11–14), TAT gained considerable therapeutic interest for the treatment of metabolic disease (15, 16). A profound understanding of TAT functions and heterogeneity is required to properly harness its benefits, hence, great focus has been devoted on investigating key cells, such as immune cells, that are critical contributors of TAT health.

IMMUNE CELLS ARE RELEVANT BOTH IN WHITE AND THERMOGENIC ADIPOSE TISSUES

TAT not only harbor adipocytes, but stromal cells, nerves, pre-adipocytes and immune cells also reside within these tissues (17–19). Similarly to WAT, where immune cells reside and infiltrate the tissue for healthy expansion and homeostasis (20, 21) or contribute to chronic inflammation during obesity (22–25) immune cells in TAT may support tissue remodeling but might also contribute to alter thermogenic function. As of today, the knowledge about immunity and inflammation in the context of TAT is recent and more limited (26–31).

UNDERSTANDING THE ROLES OF IMMUNE CELLS IN THERMOGENIC ADIPOSE DEPOTS

The immune system is a complex family of molecules, cells and organs. Immune cells can be classified into myeloid or lymphoid lineages depending on the progenitor cell they arose from (32). Besides, the immune response can be rapid and unspecific (innate response) or slower but more sophisticated (adaptive response), which allows a simple classification of cells based on their origin and their ability to respond to a foreign threat. In absence of danger, immune cells contribute to tissue surveillance and homeostasis (33). In TAT, immune cells are essential not only to maintain tissue homeostasis, but also to help the tissue adapt to external stimuli, such as cold or pathogenic conditions. A summary of all immune cells described to perform important functions in TAT is presented in **Table 1**.

Macrophages: Patrollers With Wide Functions

Macrophages comprise the most well studied immune cell population in the AT. While the AT literature mostly classifies macrophages into the simple M1/M2 (pro/anti-inflammatory) subsets, macrophages are highly plastic, and many more subsets may be described according to a wide series of markers and functions (60, 61).

Macrophages within WAT and BAT present different profiles (62). BAT macrophages are generally profiled as the M2 subset (63) and have been proposed to support thermogenic functions (27). In addition to their role in BAT, M2 macrophages were also reported to facilitate browning by clearing out dead adipocytes and favoring the recruitment of PDGFR α ⁺ progenitor cells after β 3-adrenergic receptor activation (64). A later study showed that mice receiving adipose stem cell-derived exosomes induced M2 macrophage activation, favored WAT browning and improved metabolism (65). In another study, the suppression of M2 polarization affected BAT activity and WAT browning in obese mice (35). Conversely, other studies linked the M1 phenotype induction with loss of browning in WAT and impaired BAT thermogenic function (36, 37). Thus, M2 polarization, browning, and BAT functions are positively correlated (38, 39). However, a

recent study claimed a subset of M2 macrophages to partially hijack beige progenitor proliferation and browning (66). Overall, the precise link between macrophage alternative activation and thermogenesis still remains to be formally established, and it is important to highlight that a deep categorization of all macrophage populations was missing in these studies, raising the possibility that further distinct subpopulations of macrophages mediate different effects, potentially explaining some discrepancies.

M2 macrophages were initially reported to sustain adaptive thermogenesis through catecholamine production in response to cold (67, 68), bringing a new perspective in the study of TAT modulation through immune cells. However, recent studies disclaimed this fact, as no changes in energy expenditure were found between wild-type, *Ucp1*^{-/-} and *Il4ra*^{-/-} mice, nor were AT-resident macrophages (ATMs) expressing the catecholamine synthesizing enzyme, tyrosine hydroxylase (69). In fact, a subpopulation of macrophages, the so-called sympathetic neuron-associated macrophages (SAMs), has been suggested to metabolize catecholamines *via* the expression of the norepinephrine (NE) transporter solute carrier family 6 member 2 (SLC6A2) and the degradation enzyme monoamine oxidase A (MAOA) (40). Macrophages were also found to degrade NE *via* NLRP3 inflammasome activation (70). These conflicting results could rise from the fact that macrophages sustain sympathetic innervation (71, 72), and although not directly synthesizing it, they might contribute to the local titers of NE produced by sympathetic neurons present in TAT by directly communicating with them (73, 74). More recently, a study pointed out CX3CR1⁺ SAMs as a potential source of IL-27, which has been shown to contribute to thermogenesis and energy expenditure (75). Besides, a novel study proposed a subpopulation termed cholinergic adipose macrophages (ChAMs) to secrete acetylcholine and regulate thermogenic activation of beige fat (41), adding another layer of complexity to the global contribution of macrophages to sympathetic activation. The sufficiency of M2 macrophages in promoting browning independently of sympathetic neuron involvement was described in a *Fasn*^{-/-} mouse model (76). Furthermore, macrophages can also express uncoupling protein 1 (UCP1) and aid on beige AT remodeling after cold exposure (77).

Lineage tracing human studies suggested that WAT macrophages could dedifferentiate towards pre-adipocytes and vice versa (78). If applicable to the thermogenic depots, this could become a valuable approach to increase the portion of energy-burning cells within TAT. In other tissues such as the heart, macrophages have been proposed to be essential for mitochondria turnover leading to severe alterations in cardiac function and metabolism when ablated (79). This opens up a new horizon for alternative roles of macrophages in TAT and could lead to new therapeutic approaches.

Eosinophils and Type 2 Innate Lymphoid Cells: The Type 2 Immunity

Eosinophils and type 2 innate lymphoid cells (ILC2s) are usually present in the mucosas and act during helminthic infections and allergies (80, 81), although their functions are more diverse and

TABLE 1 | Overview of the general roles and specific functions of immune cells in thermogenic adipose depots.

| Cell | Lineage | Line of defense | Subsets | General functions | Functions in thermogenic adipose depots |
|---|----------|-------------------|--|--|--|
| Macrophage | Myeloid | Innate immunity | M1 | Pro-inflammatory. M1 cells exert anti-microbial and anti-tumoral activity. Involved in tissue damage (34). | Promote a pro-inflammatory state. Secretion of pro-inflammatory cytokines. Whitening of BAT and loss of thermogenic potential. Exacerbation of obese conditions (35–37). |
| | | | M2a, M2b, M2c, M2d | Anti-inflammatory. M2 cells regulate tissue homeostasis and repair. Phagocytic, angiogenic and immunomodulatory capacity (34). | Promote an anti-inflammatory state. Direct communication with eosinophils through secreted molecules to maintain thermogenic homeostasis. Contribute to browning of WAT possibly through catecholamine or acetylcholine production. A macrophage subset (SAM) impairs thermogenic activation through catecholamine degradation. Discrepancies may arise due to the wide heterogeneity of macrophage populations (38–42). |
| Eosinophil | Myeloid | Innate immunity | – | Involved in defense against parasites and helminths, and allergies (34). | Sustain adaptive thermogenesis by communicating with M2 and ILC2s. Involved in tissue browning and anti-inflammatory state promotion. Genetic loss of eosinophils negatively affects cold responses in TAT (42, 43). |
| T cell | Lymphoid | Adaptive immunity | CD4 ⁺ T helper (Th) | Th cells orchestrate and modulate adaptive immune responses (34). | Naïve Th cells in TAT differentiate towards Tregs upon cold stimuli. Altered tissue conditions may trigger skewing towards pro-inflammatory subsets (Th1) (44, 45). |
| | | | CD4 ⁺ T regulator (Treg) | Tregs express Foxp3 and are involved in immune suppression and homeostasis (34). | Support and regulate homeostasis in TAT by suppressing inflammatory signals. Treg loss affects cold responses and thermogenic identity. Their alteration through inflammatory signals affects metabolic syndrome (44–46). |
| | | | CD8 ⁺ T cytotoxic (Tc) | Tc cells kill virus infected and cancer cells (34). | Suppression of browning through IFN signaling (47). |
| B cell | Lymphoid | Adaptive immunity | Activated B cell Plasma cell | In charge of antibody production, antigen presentation and production of cytokines (34). | B cells comprise 20-30% of all leukocytes in TAT. Their number increases upon diet-induced obesity, and they negatively modulate IL-10 receptor in beige adipocytes (48, 49). |
| Innate lymphoid cell (ILC) | Lymphoid | Innate immunity | ILC1, ILC2, ILC3 | ILCs belong to the lymphoid family but do not express antigen-specific receptors. Thought to be the innate counterparts of Th1, Th2 and Th17 cells (34). | Induction of proliferation of PDGFR α progenitor cells and modulation of M2 macrophages and eosinophils to promote browning. ILC2 populations in TAT are altered during obesity (43, 50, 51). |
| $\gamma\delta$ T cell | Lymphoid | Adaptive immunity | V δ 1, V δ 2 | $\gamma\delta$ T cells express a unique T-cell receptor ($\gamma\delta$ TCR) different from conventional δ cells ($\alpha\beta$ TCR). They have cytotoxic and modulatory capacity (34). | Support Treg function and tissue innervation through IL-17 signaling (52, 53). |
| NKT cell | Lymphoid | Adaptive immunity | Type1, Type2, NKT-like | NKT cells express an invariant TCR α chain and share properties from both NK and T cells. They recognize lipid antigens presented by CD1d (34). | Modulation of Treg homeostasis and function through IL-2 secretion. Induction of FGF-21 production to promote browning (54, 55). |
| Monocyte | Myeloid | Innate immunity | Classical, Non-classical, Intermediate | Monocytes circulate in the blood and infiltrate inflamed tissues to differentiate into macrophages (34). | Support BAT homeostasis by promoting tissue expansion (56). |
| Mast cell | Myeloid | Innate immunity | – | Mast cells contain granules like histamine and play key roles in allergy and anaphylaxis (34). | Mast cells communicate directly with progenitor cells through molecules such as histamine or serotonin, albeit whether this supports or hampers TAT functions remains to be clarified (57–59). |

vary depending on their location in the body (82). In adipose depots, eosinophils express high levels of Siglec-F and produce IL-4 and IL-13 to induce M2 macrophage polarization (42). Genetic ablation of eosinophils or the IL4/13-IL4R α -STAT6 pathway has been linked to impaired cold-induced browning as a result of loss of macrophage M2 polarization (67). Therefore, the overall contribution of M2 macrophages to TAT functions and browning may be regulated upstream by the presence of

eosinophils and/or IL-4/13 signaling. Type 2 immune signaling could hence be a promising approach for the treatment of metabolic diseases. This strategy was tackled in a study which tried to counteract the HFD-induced eosinopenia by treating mice with helminth antigens (83). Despite increased eosinophils in WAT, the treatment neither did affect eosinophil numbers in BAT nor induced WAT activation or browning. Considering that immune cell profiles vary depending on their environment,

the immune response against helminths might have not been enough to induce the same eosinophil profile required for browning *in vivo*. However, advancements in understanding eosinophil plasticity could aid on harnessing type 2 immune responses against metabolic disorders.

Eosinophils infiltrate BAT in response to CCL-11 and IL-5 (43, 83, 84). ILC2s are the major source of IL-5 and their functions are negatively affected during obesity (43). ILC2s sustain adipose eosinophils and macrophages through IL-5 and IL-13 production (43) albeit it has been proposed that ILC2s alone could be sufficient to elicit browning and promote metabolic homeostasis independently from eosinophils (50). Upon activation by IL-33, ILC2s promote PDGFR α ⁺ adipocyte precursor proliferation and commitment to the beige lineage *via* IL-4R α , which overall culminates in increased beige fat mass and improved energy expenditure (51). A new study also revealed an intercoordinated mechanism between ILC2s and eosinophils to enhance sympathetic innervation in WAT (85). Detailed mechanisms by which ILC2s contribute to beige adipogenesis, and metabolism have been described elsewhere (86, 87). Overall, type 2 immune cells are able to directly and indirectly contribute to the positive functions of TAT in energy homeostasis. While the underlying mechanisms are emerging, further research is needed to decipher the complex array of communications between type 2 immune cells and adipocytes.

Regulatory T Cells and Unconventional T Cell Subsets

Regulatory T cells (Tregs) constitute a CD4⁺ T cell subset that highly expresses the forkhead box P3 (FOXP3) transcription factor and are crucial for the maintenance of self-tolerance and immune homeostasis. AT resident Tregs were only discovered by the end of the last decade (88), however, large-scale research allowed adipose Tregs to be one of the best characterized along all tissues. AT resident Tregs express PPAR- γ (89) as well as a distinct T cell-receptor (TCR) repertoire compared to other Tregs in the lymph node (88). Correspondingly to many other immune cells, Treg characterization and relevance have been more largely described in WAT (90), albeit it is predictable that these cells also play major roles in TAT.

BAT Tregs harbor a specific transcriptomic signature different from splenic Tregs or T conventional (T_{conv}) cells in all tissues, including T_{conv} cells in BAT (46). Interestingly, this signature is also different from WAT Tregs, which incites to question whether these cells perform different functions in WAT and TAT. Tregs have been proposed to maintain BAT identity and promote browning (46, 91), and a recent study showed that inflammatory signals mediated by the insulin receptor in visceral WAT and BAT Tregs give rise to detrimental outcomes in the regulation of diet- and age-induced metabolic syndrome (92). Other studies in mouse and humans also showed the presence of resident naïve CD4⁺ T cells that skew towards a regulatory phenotype under certain stimuli (i.e. cold), describing them as cold-inducible Tregs (44, 45). Cold-inducible Tregs mainly increase in BAT and beige AT and their depletion automatically affects the thermogenic identity of the tissue. Inversely, UCP1 ablation impairs Treg induction (44). Therefore, each cell type relies on one another to sustain adaptive

thermogenesis. Still, whether Treg-adipocyte communication happens directly upon cold exposure or through complex signaling events that lead to secretion of molecules needs to be investigated.

On the other hand, Tregs resemble the boring parents that shut down the party when it is time to go home. But how are these cells prevented to restrict too harshly? The AT harbors such a wide array of immune cells that it even allows to regulate the regulatory cells. This is the case for invariant natural killer T (iNKT) cells, a singular adipose resident immune cell subset, which tightly modulates the proliferation and suppressor function of adipose Tregs through the secretion of IL-2 (54). Besides, α -galactosylceramide-activated iNKT cells upregulate fibroblast growth factor 21 (FGF-21), which subsequently promotes adipocyte browning (55). Another subset of T cells, the so-called unconventional $\gamma\delta$ T cells, has also been shown to support Treg cell homeostasis and tissue innervation through IL-17 signaling (52, 53).

Other Immune Populations in Thermogenic Adipose Depots

Elucidating all the immune populations in TAT and their contribution to metabolism has become an attractive field of research. More immune populations have been recently described in TAT. Monocytes have been shown to support BAT homeostasis by promoting tissue expansion (56). B cells comprise 20 to 30% of leukocytes in BAT, and their number is further increased upon diet-induced obesity (48). Along with T cells, B cells have been suggested to negatively influence thermogenesis *via* adipocyte IL-10 signaling (49). CD8⁺ T cells have also been suggested to negatively influence beige adipogenesis through IFN- γ secretion in a lymphocyte deficient mouse model (47). Mast cells are also present in TAT and communicate with adipose cells through factors like histamine or serotonin, albeit whether they promote or hamper WAT browning remains to be clarified (57–59). Accordingly, further studies on these populations will be required to sustain the presented findings. More recent studies using single-cell or nuclei RNA sequencing approaches have shown still undescribed immune cell populations, such as neutrophils or dendritic cells, to be present in TAT of mice (56, 76, 93) and humans (93). It is therefore encouraging to expect that the roles of more immune cell populations in thermogenic depots will be unveiled in the coming future. Furthermore, it will be important to not only consider the ability of TAT immune cells to influence tissue identity and function, but also to modulate energy expenditure, following appropriate guidelines (94, 95).

THE COMPLEX AND RECIPROCAL INTERPLAY BETWEEN ADIPOCYTES AND IMMUNE CELLS: CYTOKINES, CHEMOKINES AND BATOKINES

The TAT environment is full of cells that continuously interact reciprocally to maintain tissue homeostasis and adapt to physiological conditions (**Figure 1**). Some of these intercellular crosstalks include autocrine communication between adipocytes,

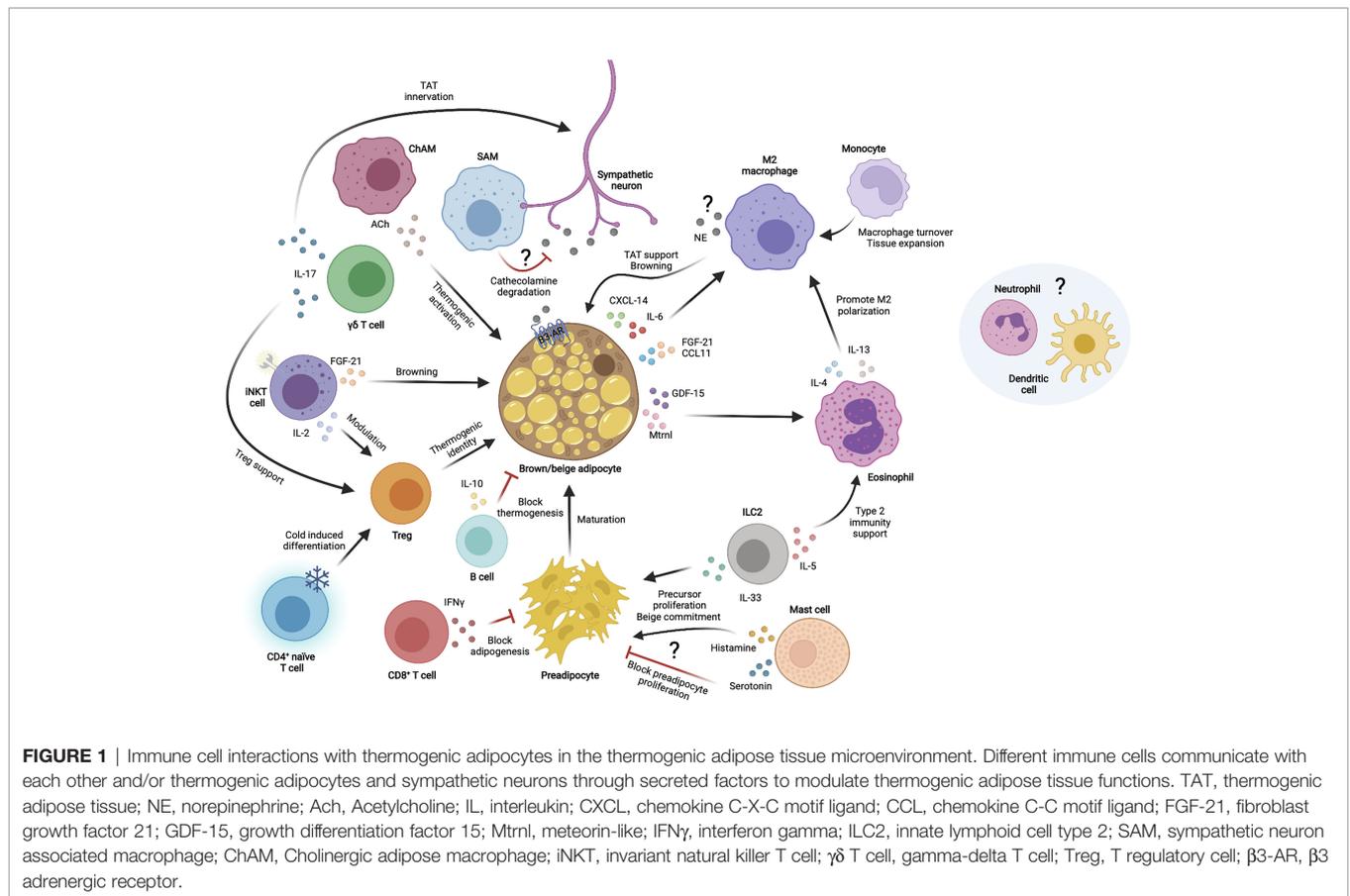


FIGURE 1 | Immune cell interactions with thermogenic adipocytes in the thermogenic adipose tissue microenvironment. Different immune cells communicate with each other and/or thermogenic adipocytes and sympathetic neurons through secreted factors to modulate thermogenic adipose tissue functions. TAT, thermogenic adipose tissue; NE, norepinephrine; Ach, Acetylcholine; IL, interleukin; CXCL, chemokine C-X-C motif ligand; CCL, chemokine C-C motif ligand; FGF-21, fibroblast growth factor 21; GDF-15, growth differentiation factor 15; Mtrnl, meteorin-like; IFN γ , interferon gamma; ILC2, innate lymphoid cell type 2; SAM, sympathetic neuron associated macrophage; ChAM, Cholinergic adipose macrophage; INKT, invariant natural killer T cell; $\gamma\delta$ T cell, gamma-delta T cell; Treg, T regulatory cell; β 3-AR, β 3 adrenergic receptor.

paracrine communication with immune cells, paracrine communication among different –or newly recruited– immune cells and communications among other cells within the tissue. We have previously outlined some of the cytokines and chemokines by which immune cells communicate among themselves to influence TAT homeostasis and function. Thermogenic adipocytes also secrete many of these factors (in this case called “BAT”okines) to directly communicate with immune cells.

IL-6 was one of the first interleukins found to be secreted by brown adipocytes upon noradrenergic stimulation (96) and was later implied in a direct effect on macrophage polarization and the decline of obesity-associated inflammation in WAT (97). FGF-21 is a circulating factor primarily originating from the liver that performs important metabolic functions, including increasing energy expenditure and browning (98). FGF-21 can be produced from other tissues to mediate local action, including BAT, which is an important source of FGF-21 following cold exposure (99, 100). FGF-21 was later shown to synergize with the chemokine CCL-11 to accumulate M2 macrophages and adipocyte precursor cells to enhance browning (101). Indeed, the type 2 immune response and browning is abolished in absence of FGF-21, whilst only CCL-11 treatment is sufficient to restore these processes, which brings in new key processes coupling immunity and thermogenic fat activation.

A different study reported the meteorin-like (Mtrnl) factor, produced by beige AT upon cold exposure, to communicate with

eosinophils to produce IL-4 and promote M2 macrophage skewing, thus enabling an anti-inflammatory environment in BAT and improving glucose tolerance and energy expenditure (102, 103). Another study revealed that CXCL14 is released by brown adipocytes in response to noradrenergic activation to directly induce macrophage recruitment and support thermogenesis in beige WAT (100). Additionally, *in vitro* studies by the same group revealed activated brown adipocytes to directly influence the anti-inflammatory state of macrophages through secreted GDF-15 (104).

The current knowledge on batokines and their targets has been detailedly described (105, 106). Proteomics studies have shown many more immune factors such as complement proteins, additional pro- and anti-inflammatory cytokines and chemokines to be part of the brown adipocyte secretome upon its stimulation (107, 108). Furthermore, alternative ways of communication also exist *via* lipid metabolites, extracellular vesicles and micro-RNAs (109–111). So far, the proper characterization of these novel batokines remains vague or inexistent. Some of the identified factors could conserve their chemotactic effects in TAT, as it has been described for CXCL14, and allow the infiltration of certain immune cell subsets to sustain TAT functions and health. Moreover, proteins like complement system factors are known to generally elicit inflammatory responses, making it quite intriguing to decipher whether this function is conserved in the physiological response to cold. Somehow, this would resemble the same first clues arisen around the anti-inflammatory roles of IL-6 in TAT compared to its

contrary effects in WAT (112); which endorses the key role of the environment in deciding the fate of immunological factors.

Overall, the mechanisms by which adipocytes communicate with the immune environment are just starting to be uncovered. Unraveling these complex interactive networks remains a challenge and still requires profound investigation.

IMMUNE CELL RECRUITMENT TO TAT: INFILTRATION IS NOT INFLAMMATION

It is now evident that TAT secretes factors upon activation that target immune cells. Based on this, one would think that the primary response to cold is to produce an inflammatory state in the tissue, which would affect TAT function. However, based on the immune cells that harbor and infiltrate TAT, one realizes that it is not the cells *per se* but their state that impacts tissue condition and performance. Most of the immune cells present in TAT show an anti-inflammatory phenotype, and the physiological response to cold seems to further impulse this state. The secretory profile of activated brown adipocytes converges with this idea, as immunosuppressor proteins such as IL-10 or the complement factor H are found in these data sets (107, 108). Furthermore, the shift towards pro-inflammatory states and signals are associated with the whitening of BAT, decreased energy expenditure and altered metabolism both in mouse and humans (35, 74, 113–115). Consequently, it is tempting to think that not only does TAT contribute to metabolic homeostasis by burning excess fat mass, but also by generating an overall anti-inflammatory environment that could even be spread in an endocrine manner to the white depots, thus helping to restrain obesity induced chronic inflammation (116).

CLOSING REMARKS AND FURTHER PERSPECTIVES

The improved metabolic profile of animals and patients upon TAT activation turns this energy burning depot into an

appealing alternative therapy ameliorating metabolic health. However, TAT is a heterogeneous tissue and many cells beyond brown adipocytes exert indispensable roles. Many immune cells contribute and tightly regulate metabolic processes that allow the normal function of the tissue. Akin, signal alterations consequence of the obese profile directly shift TAT immune cell behavior subsequently influencing thermogenic adipocyte responses. This tight link between immune cells and thermogenic adipocytes could be harnessed to boost thermogenic functions and improve the overall complications associated with obesity. Whether this could be approached through secreted molecules or by directly targeting specific cell populations will need deeper understanding. Despite being a rather novel field of research, promising animal studies that alter immune components in TAT provide reasonable hope that immune modulation of TAT may become an attractive therapeutic strategy to positively impact human metabolic health.

AUTHOR CONTRIBUTIONS

MA-O wrote the manuscript. BE contributed to manuscript structure, discussion of ideas, and revision. All authors contributed to the article and approved the submitted version.

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