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Review

The interplay between organized lymphoid structures and thermogenic adipose tissue

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Advances in the immunometabolism field have shown that infiltrated immune cells play a pivotal role in the development and function of thermogenic adipose tissue (TAT), including brown and beige fat. However, scarce research has focused on the role that organized lymphoid structures, like lymph nodes and lymphatics vessels, may exert on TAT. In this review we summarize the evidence suggesting that a significant link exists between the lymphoid tissues and adipose tissue, and we describe the most important *in vitro* and *in vivo* findings indicating that organized lymphoid tissues also play an important role in TAT biogenesis and function, raising relevant questions which are still unsolved in this emerging field.

Highlights

The presence of active thermogenic adipose tissue (TAT) has been related to better cardiometabolic health.

While immunity and metabolism were once considered distinct domains, emerging evidence highlights the critical role of infiltrated immune cells in orchestrating the development and activation of TAT. Despite this novel function of infiltrated immune cells, scarce research has focused on the role that organized lymphoid structures like lymph nodes (LNs) and lymphatics exert on TAT metabolism.

The presence of peripheral LNs relates to a higher browning and thermogenic capacity of the surrounding fat, at least in part, through the secretion of factors like IL-33 and CCL22, and the higher number of BST2-beige adipocyte progenitors compared to more distant fat.

The lymphatic vasculature also influences TAT function and adaptive thermogenesis through the secretion of neurotensin by the lymphatic endothelial cells.

Future research should elucidate whether exploiting the lymphoid tissue–TAT axis could constitute a potential therapeutic target to activate TAT.

Thermogenic adipose tissues at the crossroads between metabolism and immunity

Since the discovery of leptin [1], the understanding of adipose tissue as a passive tissue related to lipid storage, heat conservation, and as a 'building-block' in several organs, has changed and advanced. Indeed, we now know that white adipose tissue (WAT) has a major endocrine function secreting multiple hormones and adipokines, and that it works as a gateway connecting metabolism with immune function [2]. Further, it has been recognized that adipose tissue is very heterogeneous and plastic, and different types of adipose tissue – beyond WAT – have been identified and explored, including the thermogenic brown and beige adipose tissues, in humans [3,4].

Brown adipose tissue (BAT) is a specialized thermogenic tissue composed of brown adipocytes with the ability to dissipate chemical energy as heat due to mitochondrial **uncoupling protein 1** (**UCP1**) (see Glossary). Beige adipose tissue holds a similar function, but it comprises thermogenic (beige) adipocytes from a different cell lineage [5] that appear within WAT and can acquire a brown-like phenotype (a process known as browning) when stimulated. Of note, recent evidence suggests that brown and beige adipocytes are also able to dissipate energy as heat through UCP1-independent thermogenic processes, known as **futile cycles,** such as the calcium cycle, creatine cycle, and glyceride/fatty acid cycle [6]. Besides their thermogenic capacity, both tissues may have an important secretory role which could contribute to the systemic consequences of their activation [7]. The possibility that these thermogenic tissues may hold benefits for energy metabolism and cardiometabolic health has raised much interest on how to exploit them in humans [8,9]. Importantly, these thermogenic tissues have been shown to contain not only different adipocyte subtypes [10–12], but also a milieu of other cell types, such as B and T cells, macrophages, endothelial cells, fibroblasts, smooth muscle cells, pericytes, and **adipose progenitor cells** (**APCs**), which comprise regulatory networks. Importantly, numerous reports have demonstrated that infiltrated immune cells play a pivotal role in murine **thermogenic adipose tissue (TAT)** differentiation and physiology [13–15]. Therefore, targeting certain immune cell populations has become a potential strategy to improve TAT metabolism [16]. Given this

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close immunometabolic interplay, researchers have recently started to explore the relationship between TAT and other components of immune system, such as lymph nodes (LNs) and lymphatic vessels, a crosstalk which remains to be deciphered. Here we provide a comprehensive review of current evidence on this underexplored field. We summarize the clear connections between **organized lymphoid structures** and adipose tissue, present a concise and critical synthesis of key *in vitro* and *in vivo* evidence exploring the role of lymphoid tissues in TAT biology, and identify outstanding questions and key challenges to stimulate further research and advance understanding on this emerging field.

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The multifaceted lymphoid–adipose tissue interplay

LN–adipose tissue interactions

The lymphoid organs and lymphatic vessels are key components of the immune system serving a wide variety of different functions. Lymphoid organs are traditionally classified as primary (bone marrow and thymus) and secondary (e.g., spleen, LNs, tonsils). LNs are present in mammals and certain birds [17,18], where foreign antigens are presented to naïve lymphocytes initiating the adaptive immune response [19]. Thus far, much research has focused on investigating how targeting different immune cells or structural components of the LN can be utilized to therapeutically boost adaptive immune responses in cancer, infections and diseases [20,21]. However, the interaction of LNs with other organs/tissues (besides the tumoral environment) and their influence on metabolism has gained scarce attention.

Interestingly, LNs appear to have a close relationship with their surrounding adipose tissue [22]. Old work dating back to 1952 already postulated an intimate link to exist between the LNs and adipose tissue in mammals, including humans [23]. Nowadays, we know that most major LNs and many smaller ones are embedded in adipose tissue [24–26]. In addition, most peripheral adipose depots contain one or more LNs [22]. Reinforcing their link, rodent experiments have shown that adipocytes surrounding LNs (perinodal adipocytes) serve as energy reservoirs which power the immediate and effective immune response in LNs [27]. In fact, perinodal adipocytes respond to local immune challenge by increasing their lipolysis rate in comparison with adipocytes which are located further from the LN [28]. This response provides fatty acids and key lipid mediators which seem to be fundamental to ensure LNs' immune responses. Activation of the LNs also induces the release of adipose stromal cells from the encapsulating adipose tissue. Stromal cells travel through the lymph to the LNs where they are homed and may help to remodel the LN stroma, potentially helping to mount effective immune responses [29]. In addition, visceral hypertrophic adipocytes disrupt the structure and function of mesenteric and subcutaneous LNs [30,31]. For instance, they induce LN atrophy with a 50% decrease in immune cells and structural changes in the microarchitecture of LNs. Further, certain processes, such as ageing or cardiometabolic disease, are related to lipomatosis, a process by which the LN parenchyma gradually transforms into adipose tissue (LN fibroblasts differentiate into adipocytes), potentially contributing to decreased immune functions [32,33]. Altogether, it seems that the behavior of adipocytes is influenced by the proximity to LNs, and that LN structure and function are modulated by LN-resident and perinodal adipocytes.

Lymphatic vasculature–adipose tissue interactions

Evidence of crosstalk between the **lymphatic vasculature** and adipose tissue has begun to emerge in recent years, suggesting a potential link between lymphatic function and the development of metabolic disorders and obesity [34]. The clearest example linking lymphatics function and adipose tissue in humans comes from patients with secondary lymphoedema, a pathology in which lymphatic vascular injury by infection, surgery, or other trauma leads to interstitial fluid accumulation in the affected tissue, and consequently to abnormal adipose tissue accumulation (in

addition to inflammation and fibrosis) in the affected area [35]. Interestingly, being overweight or having obesity are important and independent risks factors for secondary lymphoedema [36,37]. In fact, the adipokine leptin – which directly relates to obesity – affects the function of **lymphatic endothelial cells** (**LECs**) and compromises the formation of lymphatic vessels [38], whereas adiponectin – which relates inversely to obesity – has opposing effects [39]. Fat deposition has also been described in the *Chy* mouse, a mouse model of lymphatic vascular dysfunction in which subcutaneous adipose tissue (scWAT) accumulates next to dysfunctional lymphatic vessels and in the tail skin [40]. Further, functional inactivation of a single allele of *Prox1* – a homeobox transcription factor crucial for the specification of the LEC fate and lymphatic development [28] – led to adult-onset obesity due to abnormal lymph leakage from malfunctional lymphatic vessels [41]. Providing some mechanistic evidence, studies have shown that certain components (lipids) of the murine mesenteric lymph (derived from chyle) [41] or lymph harvested from patients with lymphedematous limbs [42] promote adipogenesis *in vitro*, which could partially explain why lymph leakage/accumulation leads to fat deposition. Previous studies in mice also support the link between obesity and lymphatics, showing that obese mice have leaky capillary lymphatics and decreased collecting vessel pumping capacity, as well as decreased lymphatic migration of immune cells compared to lean mice [34,43,44]. Therefore, there seems to be a tight link between lymphatics, adipose tissue, and obesity, which is only beginning to be ascertained.

Following these findings, the desire to understand TAT heterogeneity and biogenesis better has led to the first observations linking the lymphoid tissues and TAT, which has opened a new field that we introduce and discuss in the following sections.

A newly discovered connection between lymph nodes and TAT

To our knowledge, the first indication of the LN–TAT interplay came from a study [45] investigating the 3D organization/heterogeneity of the inguinal fat pad in adult mice. It was revealed that the inguinal subcutaneous fat depot could be divided into two main regions: the core fat region located next to the inguinal LN (iLN), and the peripheral fat region. The most intriguing aspect was that the core fat region, in which the iLN was located, revealed smaller lipid droplets and an increased expression of the canonical *Ucp1* gene as well as other thermogenic and mitochondrial markers, such as *Cidea, Prdm16, Ppargc1a,* and *Mct1* – all characteristics of beige fat [45]. Further, cold exposure increased the expression of thermogenic markers exclusively in the core fat region, supporting the notion that browning was taking place. Moreover, other findings [46] from the same research group showed a higher sympathetic innervation and vascular density within the fat pad region close to the iLN, both of which are known to be essential characteristics of TAT [47] (Figure 1A, Key figure).

These findings were corroborated [48] by an independent study, which showed that UCP1 was mainly found in the core region of mice scWAT located next to the iLN, in opposition to the more remote areas. Indeed, they distinguished two regions within the scWAT, the inguinal and dorsolumbar regions, and found that when mice were exposed to cold browning took place mainly in the inguinal region surrounding the iLN. Interestingly, the areas where there was more UCP1 were also those areas in which there was higher tyrosine hydroxylase expression (indicative of sympathetic innervation). These observations suggest that the areas surrounding the iLN display the characteristics of beige fat and are more likely subject to browning when cold stimulated. Nevertheless, they do not provide causal evidence or show the mechanisms demonstrating that the iLN induce the appearance of beige fat.

A more recent study [49], however, elegantly showed one mechanism by which **fibroblastic reticular cells** (**FRCs**) of the iLN could induce browning of the scWAT in male mice. This

Glossary

Adaptive thermogenesis: a regulated process of heat production in response to environmental or physiological stimuli, such as cold exposure or food intake. It contributes to energy expenditure and is largely mediated by brown and beige adipose tissue in mice through both UCP1-dependent and -independent thermogenic mechanisms.
Adipose progenitor cells (APCs): multipotent cells residing within adipose tissue, capable of differentiating into various cell types, including adipocytes, and contributing to tissue regeneration, metabolic regulation, and immune modulation.
Anti-inflammatory macrophages: alternatively activated immune cells characterized by anti-inflammatory and tissue-repair functions, typically induced by cytokines such as IL-4 and IL-13, and associated with wound healing, immune regulation, and resolution of inflammation.
Fibroblastic reticular cells (FRCs): specialized stromal cells found in lymphoid organs that form a structural cable-like network and regulate immune cell trafficking, survival, and activation by producing chemokines, cytokines, and extracellular matrix components.
Futile cycles: metabolic pathways in which two opposing enzymatic reactions occur simultaneously, resulting in net energy loss without appreciable biochemical productivity. Notable examples include the calcium cycle, the creatine cycle, and the glyceride/fatty acid cycle.
Lymphatic endothelial cells (LECs): specialized cells lining the lymphatic vessels (and LN sinuses), responsible for facilitating lymph transport, regulating immune cell movement, and maintaining fluid balance through selective permeability and signaling functions.
Lymphatic vasculature: a network of lymphatic capillaries and collecting vessels that transport lymph – containing interstitial fluid, immune cells, antigens, and lipids – from peripheral tissues to draining LNs, playing a critical role in fluid balance and immune surveillance. Efferent lymphatic vessels and lymphatic trunks (e.g., the thoracic duct) convey the lymph to the systemic blood circulation.
Neurotensin (NTS): a neuropeptide that acts as both a neurotransmitter and a hormone, influencing dopaminergic pathways, gastrointestinal function, and

study firstly confirmed that the cold-induced browning capacity of scWAT was higher in the inguinal region, near the iLN, compared to more distant regions. Then, it proved that removal of the iLN impaired cold-induced thermogenesis and reduced expression of thermogenic markers in scWAT, without affecting other fat depots. Additionally, pharmacological ablation of peripheral LNs disrupted the development of cold-inducible beige fat in regions typically associated with TAT, like the inguinal scWAT and axillary WAT (Figure 2). Mechanistically, the authors proved that cold-enhanced sympathetic outflow to iLNs activates β1 and β2 adrenergic receptor signaling in FRCs to facilitate IL-33 release into iLN surrounding scWAT, where IL-33 activates the type 2 immune response – which controls the biogenesis of beige adipocytes [50] (Figure 1A). Of note, blocking this pathway impaired browning, while restoring IL-33 reversed the effect.

Another recent study provided an additional explanation by which iLNs could regulate the browning capacity of murine scWAT (Figure 1A) [51]. This study characterized a group of beige adipocyte precursors that could be classified/sorted by the high expression of the surface marker BST2. Differentiated adipocytes from BST2(high) precursors expressed more thermogenic markers *Ucp1* and *Dio2* compared to BST2(low) cell-derived adipocytes. In addition, these beige adipocyte precursors were increased by cold exposure, and diminished by a high-fat diet in scWAT, corroborating their importance for *in vivo* beige fat formation in inguinal adipose tissue. The most intriguing aspect was that the proportion of these beige adipocyte precursors was significantly higher in the peri-LN fat (near the iLN) compared to distal-LN fat (far from the iLN). Therefore, the authors hypothesized that the iLN might regulate the thermogenic features of scWAT through, at least in part, biogenesis of inguinal adipose tissue – specific BST2(high) beige adipocyte precursors. To test this, they dissected the iLN, finding that: (i) the expression of UCP1 was reduced in the scWAT surrounding the iLN, (ii) the proportion of BST2(high) precursors was also decreased in this area, and (iii) the induction of $UCP1^{+}$ beige adipocytes was dampened at room temperature, upon cold exposure and upon β3-adrenergic agonist treatment – confirming their hypothesis. However, it remains an open question whether these beige adipocyte progenitors, which highly express *Il33,* also regulate the thermogenic features of inguinal scWAT through the secretion of IL-33 in synergy with the FRCs [49].

A parallel mechanism [52] by which LNs could regulate the adipose browning process has also been proposed: iLN removal largely impairs cold-induced browning in the inguinal scWAT of mice [53,54] and is accompanied by a decrease in infiltrated **anti-inflammatory macrophages**, defined as $F4/80^{hi}$ $CD45^{+}$ $CD64^{+}$ $CD206^{+}$. These anti-inflammatory macrophages secrete the macrophage-derived C-C motif chemokine (CCL22), which facilitates the iLN mediated cold-induced browning of the surrounding fat (Figure 1A). Indeed, supplementation with CCL22 protein can rescue the cold-induced browning defects observed in the scWAT after iLN removal, whereas blocking CCL22 with antibodies prevents it. Mechanistically, CCL22 acts by binding to its receptor C-C chemokine receptor 4 on eosinophils, which then promotes interleukin-4 (IL-4) that regulates the p-STAT6 pathway through the IL-4 receptor α in specific APCs to induce beige adipocyte biogenesis. Of note, the authors of this study [52] did not explore the upstream regulators of this anti-inflammatory macrophage population. Therefore, it remains to be confirmed whether certain factors secreted by LN cells (e.g., FRCs secreting IL-33) could modulate anti-inflammatory macrophage activation, or rather whether it happens by some indirect mechanism.

Despite the relative immaturity of the field, the abovementioned findings strongly suggest that communication of the iLN with the surrounding fat is a key factor for the emergence of ($UCP1^{+}$) thermogenic adipocytes in mice. It is worthwhile noting that the iLN may also influence the thermoregulation through its interaction with specific G-protein-coupled receptors.

Organized lymphoid structures: regions of lymphoid tissue that facilitate immune cell development and activation. They include primary lymphoid organs (bone marrow and thymus) where lymphocytes develop, and secondary lymphoid organs such as LNs and spleen where immune responses begin. These tissues are integrated with lymphatic vessels to coordinate antigen transport and immune surveillance.

Thermogenic adipose tissue (TAT): a metabolically active form of adipose tissue specialized in energy expenditure through non-shivering thermogenesis. Comprising brown and beige adipocytes (among other cell types), TAT generates heat by oxidizing fatty acids, a process driven by mitochondrial uncoupling protein 1 (UCP1). In mice, it plays a key role in thermoregulation and energy homeostasis. UCP1-independent thermogenesis provides alternative heat-generating mechanisms, particularly relevant in obesity or adipose tissues with reduced UCP1 expression.

Uncoupling protein 1 (UCP1): a mitochondrial inner membrane protein found primarily in brown and beige adipocytes where it enables non-shivering thermogenesis by uncoupling oxidative phosphorylation from ATP production. This uncoupling dissipates the proton gradient as heat, supporting thermoregulation and increasing energy expenditure in response to cold or sympathetic activation.

Key figure

Role of lymph nodes and lymphatic vasculature on thermogenic adipose tissue (TAT) function and biogenesis

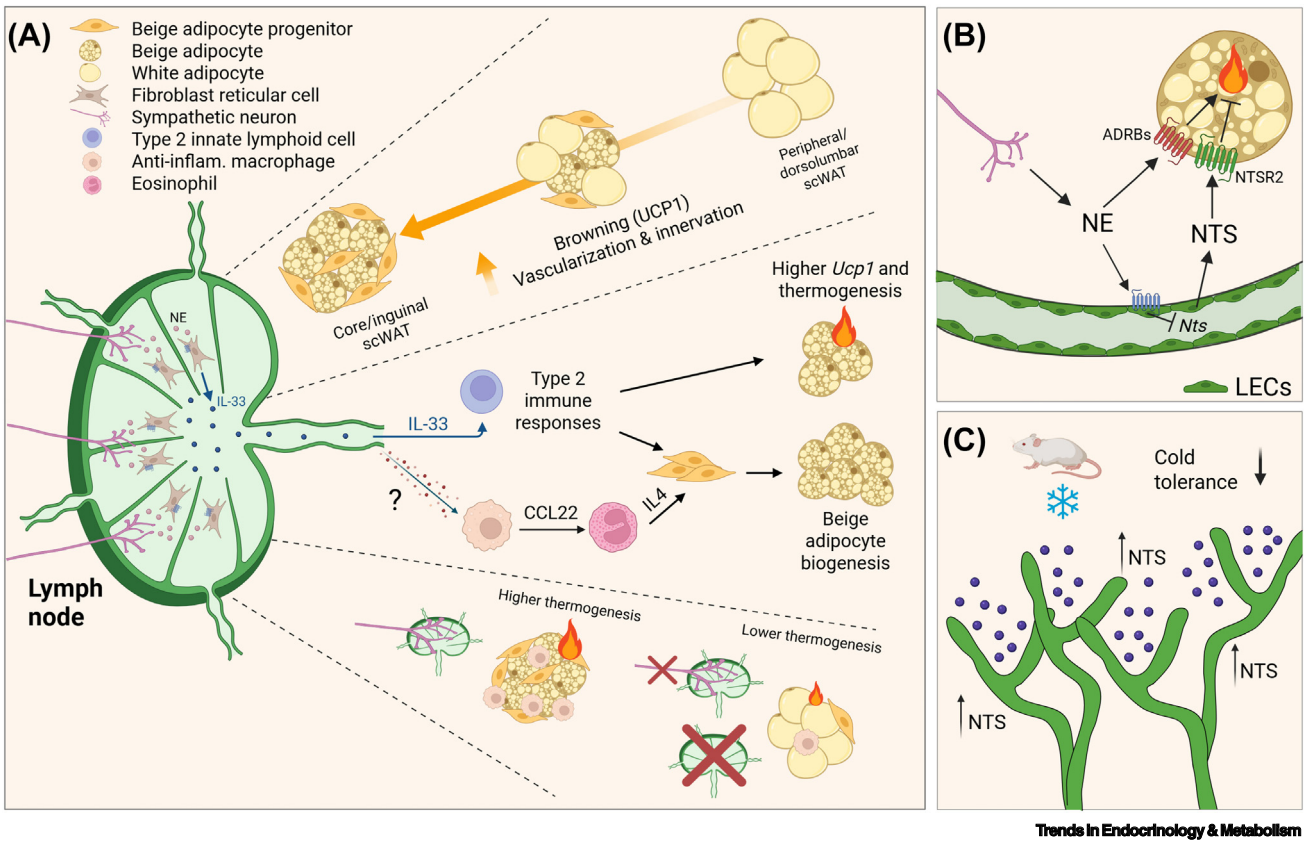

Figure 1. (A) (uppermost subpanel) The fat surrounding the inguinal lymph node (iLN) presents characteristics typical of beige fat in comparison to more distant fat (peripheral/dorsolumbar region), which has a whiter phenotype. These characteristics include the presence of adipocytes with smaller lipid droplets, higher expression of thermogenic markers, and a higher vascularization and innervation. One of the explanatory mechanisms is the greater presence of specific beige adipocyte progenitors next to the iLN. (A) (middle subpanel) Other mechanisms related to the increase of beige fat thermogenesis and/or biogenesis in inguinal fat are: (i) the release of interleukin (IL)-33 by the iLN fibroblastic reticular cells (FRCs); and (ii) the secretion of CCL22 by anti-inflammatory macrophages surrounding the iLN. (A) (bottom subpanel) Confirming the importance of lymph nodes (LNs) in beige fat thermogenesis/biogenesis, surgical removal of the iLN or pharmacological ablation of peripheral LNs, induces a lower expression of thermogenic markers, a decrease in the number of beige adipocyte progenitors, and/or impairment of cold-induced adaptive thermogenesis, in inguinal subcutaneous white adipose tissue (scWAT). (B) Peripheral lymphatic endothelial cells (LECs) highly express and secrete neurotensin (NTS), which has antithermogenic properties in interscapular brown adipose tissue (iBAT). (C) An increase in lymphatic density relates to an increase in the percentage of peripheral LECs and therefore of NTS release. This relates to impaired cold tolerance in mice exposed to acute cold exposure. ADRBs, beta-adrenergic receptors; NE, norepinephrine. Created in BioRender. Acosta Manzano, F. (2025) https://BioRender.com/bqsqxrg.

emergence of thermogenic adipocytes with low or absent UCP1 expression, which could significantly contribute to thermogenesis via noncanonical pathways, such as futile cycles like creatine cycling [55]. The mechanisms mediating LN–TAT communication remain to be fully elucidated. Proposed contributors include IL-33 secretion by iLN FRCs into the surrounding adipose tissue, and the presence of specific beige adipocyte progenitors near the iLN. However, other mechanisms, such as the local release of different pro-adipogenic/thermogenic factors by LN cells, the extravasation and stimulation of neighbor immune cells in proximal fat, and the high LN

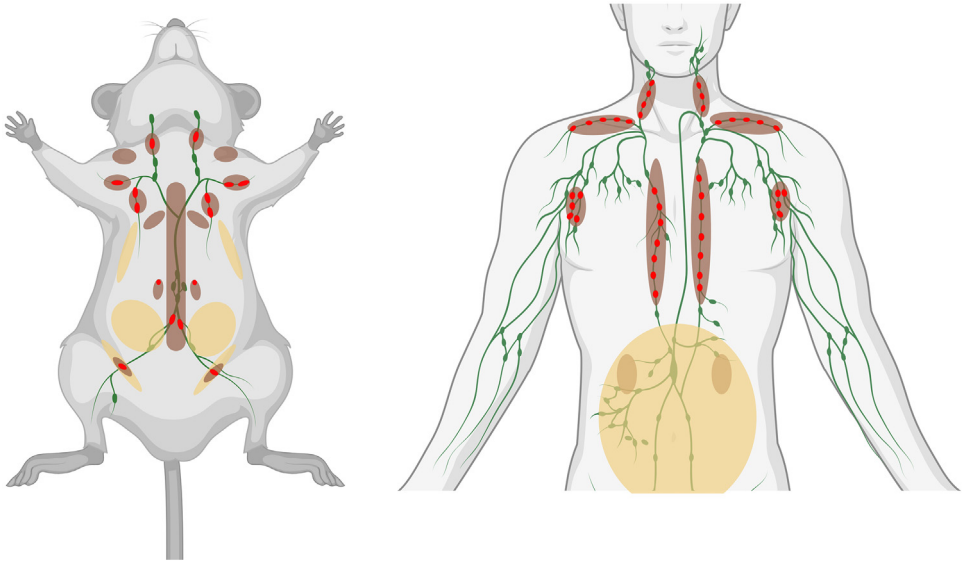

Figure 2. Lymph nodes overlap with thermogenic adipose tissue (TAT) in mice and humans. Representative illustration showing the presence of lymph nodes (red) in the areas where TAT is present in mice and adult humans. TAT is shown in brown, and white adipose tissue is shown in yellow. Created in BioRender. Acosta Manzano, F. (2025) https://BioRender.com/zqkv7rm.

sympathetic innervation needed to stimulate immune responses [49], could also be related to the appearance of TAT. Future research will ascertain some of these potential mechanisms, as well as whether this crosstalk extrapolates to other LNs (as was shown for the axillary LN) and fat regions besides the iLN-scWAT crosstalk – which likely has been investigated mainly due to the well-known browning capacity of this region and its easy access. Of note, the LN–TAT crosstalk may be particularly relevant in the context of some mammals' physiology, such as mice, since LNs and TAT largely colocalize to the same anatomical areas (Figure 2). For instance, murine LNs can be found in the axillary, cervical, perirenal, and paravertebral (lumbar) regions (where BAT is located) or in the inguinal fat (region susceptible to browning when stimulated) [56,57].

LN–TAT crosstalk may be bidirectional, with TAT also releasing specific proteins, metabolites, lipids or chemokines to the adjacent LN, 'feeding' or helping to stimulate the LN immune/stromal/vascular cells and therefore supporting effective immune responses. Indeed, in human BAT, the most expressed biological processes detected by transcriptomic analysis are immune-related pathways and host defense mechanisms (immune, defense, and inflammatory responses, and regulation of immune system processes) [58]. Besides the potential paracrine LN–TAT crosstalk, preclinical and *in vitro* experiments show that heat (i.e., high temperatures within the fever-range) empowers the adaptive immune responses [59]. For instance, it has been shown that fever-range thermal stress improves lymphocyte trafficking in peripheral LNs, increases lymphocyte proliferation in response to mitogens, and improves the differentiation of $CD8^+$ T cells into effector cells when activated by antigen-presenting cells [59,60]. Therefore, it could be speculated that the close spatial relationship between the LNs and TAT could be an evolutionarily preserved mechanism to boost effective adaptive immune responses (i.e., by TAT locally warming the surrounding LNs), especially in cold environments – or during infections [59,61]. This is particularly interesting, as TAT local temperature in humans has been reported to range from 37 to 42.6°C during cold exposure [62], although this remains unknown during infection states.

The role of lymphatic vasculature on TAT function

The lymphatic vasculature plays important physiological roles in the organs/tissues where it resides. Traditionally, adipose tissue was thought to be devoid of lymphatic vessels; however, this dogma has now changed, and although relatively sparse compared to other vascularized tissues, we know that lymphatic vessels are present in fat parenchyma, particularly in the mesenteric fat [34,53]. Similarly, in the context of TAT, the identification of LECs has confirmed the presence of lymphatic vessels, even in murine depots lacking LNs, such as the interscapular BAT (iBAT) [63]. However, whether lymphatic vessels in TAT play a role modulating tissue metabolic homeostasis is unknown.

Recently, it has been shown [63] that lymphatic vessel LECs from the iBAT highly express the gene encoding **neurotensin** (**NTS**) compared to other vascular cell types. Interestingly, the expression of *Nts* and NTS seemed to be downregulated by cold exposure and/or norepinephrine in an α-adrenergic-dependent manner [63]. This led the authors to suspect that NTS may have a role in **adaptive thermogenesis**, which was confirmed by showing that NTS released by peripheral LECs in iBAT has anti-thermogenic effects – which are mediated by NTSR2 receptor and ERK signaling. This ultimately led to a lower tolerance and energy expenditure upon acute cold exposure in mice. Further, inhibition of the NTSR2 receptor promoted higher energy expenditure and improved metabolic function in mice, at least in part by increasing iBAT thermogenesis. Altogether, this study elegantly established a mechanism by which lymphatics and TAT communicate (Figure 1B), and which could be targeted to prompt metabolic benefits.

Based on the previous arguments, one would assume that lymphangiogenesis (i.e., the formation of new lymphatic vessels from existing ones) would provide an additional source of NTS and therefore repress adaptive thermogenesis. Based on this hypothesis, other authors [64] used AdipoVD mice, which specifically show increased lymphatic vessel density in adipose tissue, including iBAT and inguinal WAT (iWAT). Interestingly, this increase was accompanied by an upregulation of *Nts* expression and NTS in both iBAT and iWAT compared to their control littermates. Moreover, AdipoVD mice which underwent acute cold exposure at 4°C demonstrated cold intolerance compared to control mice (Figure 1C). However, no changes were found in most iBAT thermogenic genes expression after this cold exposure. This is relevant, as in opposition to previous findings, the large increase in lymphatics density (and therefore in LECs presence and NTS levels) did not significantly decrease the expression of iBAT thermogenic genes. The authors also showed that NTS inhibition ablated cold intolerance in mice.

Altogether, the presence of lymphatic vessels seems to relate to lower cold tolerance. However, whether they relate to reduced adaptive thermogenesis mediated by a decrease in iBAT thermogenesis remains unclear, as previous studies show opposing findings [63,64]. Further, a recent study has shown that cold exposure (which increases iBAT thermogenesis) increases LECs density in murine iBAT [54]. These observations suggest a more nuanced or potentially complex role for lymphatic vessels in BAT function, which remains to be elucidated [54]. Of note, different LEC types with varied functions have been unveiled by single-cell RNA sequencing in LNs and lymphatic vessels [65,66]. Therefore, it is reasonable to assume that these contradictory findings could be explained because not all LECs necessarily release NTS or do it to the same extent. The summarized studies [54,63] analyzed a limited number of adipose tissues LECs, and did not investigate these LEC subpopulations, which warrants further research to clarify whether peripheral LECs can be subclassified and whether they vary in NTS secretion and function. In line with this, it is necessary to take into consideration that lymphatic vessels may be scarcely present in iBAT [64] and that the proportion of LECs has been reported to be very low in iBAT and iWAT [63] compared to other less thermogenic adipose depots like epididymal WAT [34,63,64].

More studies are needed to elucidate whether there are also different LECs types, or differences in the LEC–adipocyte crosstalk, across tissues which could explain differences in their thermogenic capacity.

Concluding remarks and future perspectives

This is an emerging field, and our understanding of the underpinnings of the lymphoid tissue–TAT axis and its health implications is still very limited, with many unanswered questions remaining (see Outstanding questions). It remains to be elucidated whether specific LNs can modulate TAT function/biogenesis in humans. Although this seems to be the case for mice, extrapolation to humans is challenging, especially considering the morphological and thermoregulatory differences across species. For instance, mice have a higher surface area to volume ratio, which translates into a higher heat loss and much higher basal metabolic rate relative to weight [67]. In addition, mice rely heavily on non-shivering thermogenesis during cold exposure; thus, high TAT thermogenic activity is essential for them [68], whereas humans rely more on shivering thermogenesis and behavioral adaptations, such as wearing more clothes. However, in both species most areas of the upper body – where LNs are located (i.e., cervical, supraclavicular, axillar, paravertebral, etc.) – are the main regions where TAT is present [4,58,69] (Figure 2)**.** One may speculate that there is some physiological purpose for this evolutionary adaptation. It remains to be ascertained whether lymphatic vessels, and more specifically, LECs, play a significant role on TAT metabolism. To our knowledge, there are no reports characterizing the lymphatic vessels in human TAT, and in our unpublished (and in others') previous work [11,12], few peripheral LECs have been found in the neck BAT of human volunteers. In addition, thus far most of the attention has been focused on the role of LNs, FRCs, and peripheral LECs on TAT function/biogenesis. However, we know that LNs and lymphatic vessels are composed of a complex mixture of cells and cell subtypes (i.e., leukocytes, stromal cells including blood and lymphatic endothelial cells, FRCs, and progenitors in LNs; and LECs and smooth muscle cells in lymphatics) [65,70], which may form part of this regulatory network too. Therefore, it is necessary to investigate whether other cell types and components of LN and lymphatic vessels (as well as of the surrounding adipose tissue) contribute to the modulation of TAT thermogenesis and biogenesis. Whether the lymphoid tissue–TAT axis contributes to other functions beyond adaptive thermogenesis and TAT biogenesis is an open question. Supporting this notion, we have discussed how TAT may help mounting more effective immune responses by locally warming LNs (heat improves adaptive immune responses, like leukocyte trafficking to LNs) [59] or by the secretion of specific molecules (TAT secretes numerous factors [71–73]) which may modulate the LN microenvironment. In addition, previous research has shown that the fat surrounding the iLN (potentially TAT) can communicate with the LN through a lymphatic vessel-independent route (collagen I^+ small conduits), a way by which antigens can be directly delivered from the periphery to the LN to facilitate an immune response [74]. Conversely, specific factors or antigens may also be delivered from the LN to the surrounding fat (e.g., TAT) through this channel. This is highly interesting, as WAT and TAT are now known to work as important immune and (bacterial, parasite, and virus) infection reservoirs, which can facilitate immune responses against pathogens [75]. The lymphoid tissue–TAT crosstalk in mice has been investigated in a very specific context (basal and cold stimulation conditions), in wild-type or genetically modified mice. How physiological conditions – such as aging or circadian rhythms, different pathologies like obesity, infections, and other inflammatory diseases, in addition to cancer or their treatments – alter this axis is another relevant question. Interestingly, obesity and aging are two of the main factors related to human BAT metabolic activity impairment [76–78], conditions in which LN morphology and function are also altered [31,79]. One plausible scenario is that the malfunction of LNs as weight and age increase would relate to the decrease in thermogenic activity of adjacent adipose tissue. Another hypothesis is that

Outstanding questions

Can LNs or lymphatics modulate TAT function and biogenesis in humans? Is TAT able to modulate local immune responses within these lymphoid tissues?

Is the location of TAT proximal to LNs in humans an evolutionary adaptation to favor their immunometabolic crosstalk?

Which cells and cell subtypes, and by which mechanisms (e.g., secretion of factors, thermogenesis, small conduits-antigen transport, etc.), mediate the interplay between lymphoid tissues and TAT?

How do physiological conditions – such as aging or circadian rhythms, pathologies like obesity, infections, and other inflammatory diseases, as well as cancer or its treatments – alter the lymphoid tissue–TAT axis?

Is the lymphoid tissue–TAT axis a clinically relevant target? Can the lymphoid tissue–TAT axis be targeted to enhance cardiometabolic health through the activation of TAT, or to stimulate immune responses in infections and other diseases?

Can other lymphoid structures and organs communicate with TAT?

malfunction of TAT lymphatics in these states could translate into leakage of lipid-containing lymph which would promote adipocyte hypertrophy or hyperplasia [34], leading to a 'whiter' TAT phenotype and reduced adaptive thermogenesis. Whether other lymphoid organs or structures, besides LNs and lymphatic vessels (our focus in this review), communicate with TAT, is also unknown. This may be the case for the thymus, which is particularly close to TAT depots in humans [80].

Future studies should aim to answer some of these questions to understand if (and how) lymphoid tissues can be selectively targeted to increase the amount of TAT in humans, as well as to improve its metabolic function. This may constitute a promising therapeutic tool as previous reports have shown individuals with more BAT have a lower prevalence of different cardiometabolic diseases [9,81].

Author contributions

F.A.M. and J.Ö. conceived the study; F.A.M. and J.Ö. wrote the manuscript; F.A.M., J.Ö., M.S. and K.A.V. contributed substantially to the discussion of the content; F.A.M., J.Ö., M.S., and K.A.V. reviewed the manuscript several times and edited it before submission.

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Declaration of interests

The authors declare no competing interests.

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