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REVIEW ARTICLE

Immune Cell-Mediated Inflammation in Obesity: Mechanisms, Links with Inflammaging, and Therapeutic Implications: A Review

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ABSTRACT

Chronic low-grade metabolic inflammation (metaflammation) is a hallmark of obesity and plays a role in adipose-tissue dysfunction, insulin resistance and metabolic comorbidities. Recruitment and activation of immune cells play a key role in this process, but their role is dependent on adipose tissue depot, disease stage and cellular phenotype. This review article focuses on the innate and adaptive immune cells such as macrophages, T cells, B cells, natural killer (NK) cells, natural killer T (NKT) cells, neutrophils, eosinophils and mast cells and their role in the inflammation associated with obesity. The evidence linking macrophage accumulation and activation, especially the interaction with T cells, to adipose metabolic dysfunction is more consistent, although evidence for other immune cells is more variable. Additionally, the link between metaflammation and inflammaging is also discussed. While they have common traits of immune dysregulation and inflammatory signaling, metaflammation is mostly triggered by nutrient excess and metabolic stress, and inflammaging by biological ageing and underlying cellular and molecular damage. There is a need for clinical translation of therapeutic targeting of inflammatory pathways, although this is not straightforward as these pathways are essential for host defense and tissue homeostasis. Human studies, understanding immune-cell heterogeneity and developing targeted approaches to inhibit pathological inflammation without affecting protective immune responses should be the focus of future research.

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1. INTRODUCTION

Obesity is a disease of global and public health affecting over one billion people worldwide (Mohajan & Mohajan, 2023). It is characterized by a state of low-grade chronic inflammation, which results in a range of metabolic dysfunctions, including insulin resistance (IR), dyslipidemia, hypertension, type 2 diabetes, cardiovascular disease, and even cancer (Hotamisligil, 2017). The global burden of overweight and obesity has increased substantially in recent decades. In 2022, approximately 2.5 billion adults aged 18 years and older were overweight worldwide, including 890 million who were living with obesity. This represented 43% of the global adult population being overweight and approximately 16% living with obesity (Mohajan & Mohajan, 2023; Smith & Smith, 2016). Since 1990, the prevalence of obesity among the adult population has more than doubled (Ng et al., 2025). During the same period, its prevalence among the adolescent population quadrupled (Ng et al., 2024, 2025).

Obesity is closely associated with increased infiltration and activation of immune cells within adipose tissue (Mohajan & Mohajan, 2023). White adipose tissue (WAT) is an important site of obesity-associated inflammation (Ghigliotti et al., 2014). Furthermore, accumulation of fat causes a low-grade increase in the expression of cytokines such as the tumor necrosis factor (TNF), IL-6, etc., and production and release of chemokines such as the monocyte chemoattractant protein 1 (MCP-1); and many immune cells such as T cells, macrophages (Khanna et al., 2022). In addition to storing lipids, adipocytes play a critical role in metabolism and inflammation via the release of cytokines and adipokines such as the proinflammatory and satiety hormones called leptin and the anti-inflammatory adiponectin (Balistreri et al., 2010). Adiponectin is known to downregulate pro-inflammatory cytokines such as TNF, IL-6, and MCP-1 (Balistreri et al., 2010). In obesity, the plasma concentration of leptin tends to increase while that of adiponectin tends to decrease, thus favoring a more inflammatory status (De Heredia et al., 2012). Hypertrophic visceral adipose tissue (VAT) is particularly susceptible to cellular stress and inflammation, with increased production of inflammatory mediators such as TNF and IL-6 that promote immune-cell recruitment and activation (Kolb, 2022). Activated immune cells in obesity are initially crucial for healthy tissue expansion and remodeling; however, when their activation is prolonged, they may result in fibrosis and hinder adipogenesis (De Heredia et al., 2012; Khanna et al., 2022). This process fuels a vicious cycle of lipotoxicity, systemic inflammation, adipocyte death, and metabolic dysregulation, which ultimately leads to metabolic disorder (Ghigliotti et al., 2014; Kolb, 2022).

Although previous reviews have examined adipose-tissue immune cells, immunometabolism, obesity-associated inflammation and inflammaging, these topics have often been considered in isolation or from the perspective of specific cell subsets (Medina-Urrutia et al., 2024; Nance et al., 2022). In this study, we review innate and adaptive immune responses in obesity-associated inflammation and inflammaging, with particular emphasis on human evidence. The review focuses on crosstalk between immune-cell populations, inflammatory mechanisms underlying metabolic dysfunction, and the relationship between obesity-associated metaflammation and inflammaging. Differences between human and rodent biology, therapeutic opportunities and limitations of targeting inflammation, and areas of uncertainty requiring further research are also considered.

2. LITERATURE SEARCH STRATEGY

This review was conducted as a narrative literature search focusing on immune-cell-mediated inflammation in obesity and its relationship with inflammaging. The literature search covered publications from 2002 to 2026 and was conducted using PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar. Search terms included combinations of obesity, obesity-associated inflammation, metaflammation, adipose tissue inflammation, immune cells, macrophages, T cells, B cells, natural killer T cells, neutrophils, eosinophils, mast cells, cytokines, chemokines, insulin resistance, inflammaging, ageing, cellular senescence, mitochondrial dysfunction, epigenetic changes, telomere shortening, NLRP3 inflammasome, CCR2 and CCL2. Boolean operators were used to combine the search terms. Studies were selected based on their relevance to the review objectives, with emphasis on research addressing immune-cell recruitment and activation in adipose tissue, inflammatory mediators, macrophage polarization, inflammasome activation, and the relationship between immune responses and metabolic dysfunction. Studies examining links between obesity-associated inflammation and ageing-related mechanisms, including cellular senescence, mitochondrial dysfunction, epigenetic modifications, telomere attrition and intercellular communication, were also considered where relevant to the review scope. Both human and animal studies were included. Human studies were used to assess the clinical relevance of immune and inflammatory mechanisms in obesity, whereas animal studies, particularly high-fat-diet-induced obesity models, were used to provide mechanistic insights into obesity-associated inflammation and its potential links with inflammaging. Where evidence was derived mainly from experimental models, its potential clinical relevance was considered. The literature was synthesized thematically, emphasizing consistent findings, areas of controversy, mechanistic evidence, interactions between immune-cell populations, and emerging links between obesity-associated inflammation and inflammaging. This was a narrative review rather than a systematic review or meta-analysis; therefore, no formal risk-of-bias assessment or quantitative synthesis was undertaken.

3. OBESITY AND INFLAMMATION: THE LINKING MECHANISM

Inflammation is a coordinated sequence of actions executed to preserve tissue and organ homeostasis (De Heredia et al., 2012; Hotamisligil, 2017). The release of inflammatory mediators and the expression of their receptors must be timely to effectively monitor and restore the tissues to their original state (Balistreri et al., 2010; Ghigliotti et al., 2014). The inflammation pathway is also activated as a protective mechanism in response to tissue injuries, thereby destroying or subduing the injurious agents and the injured tissues. The initial indication of obesity-induced inflammatory process is associated with increased tumor necrosis factor-alpha (TNF-α) in adipose tissue of obese individuals (Balistreri et al., 2010; De Heredia et al., 2012; Kolb, 2022). Since then, many researchers have reliably demonstrated elevated inflammation in adipose tissues in both human and animal subjects (Bradley et al., 2024). Two categories of inflammation exist: acute and chronic

inflammation. Acute inflammation occurs over a short duration and is marked by swelling and the recruitment of leukocytes to the target site. Chronic inflammation is identified by the recruitment of lymphocytes and macrophages to the target site and the activation of angiogenesis (Inflammation, 2009). Chronic inflammation persists for an extended period, which is a common feature of metabolic diseases that is associated with the release of inflammatory adipokines such as tumor necrosis factor-α (TNF-α), interleukin (IL-6), monocyte chemoattractant protein-1 (MCP-1), leptin, and resistin (Monteiro & Azevedo, 2010).

Obesity, being a common feature of metabolic disorders, is characterized by a chronic inflammatory state in patients following the secretion and release of several inflammatory mediators (Ghigliotti et al., 2014; Monteiro & Azevedo, 2010). Although inflammation may be activated in multiple tissues, most studies of obesity-induced inflammation implicated the adipose tissue-mediated inflammatory pathways. The focus of this review is to shed more light on the roles played by specific immune cells recruited into the adipose tissues of individuals with obesity, and their contribution to the inflammatory process that further worsens obesity.

4. IMMUNE CELL RECRUITMENT IN OBESE ADIPOSE TISSUES

Most of the mechanistic knowledge regarding the role of immune cells in obesity has been obtained from experimental models, including high-fat diet (HFD) fed mice, genetically engineered mice, and ex vivo and isolated cell studies (Ying et al., 2020). These models have offered valuable insights into possible causal links between immune-cell activation and inflammation of adipose tissue and metabolic dysfunction. Experimental models, however, cannot be blindly extrapolated to human obesity. Human studies, many of which are observational, can offer complementary information on immune-cell abundance, immune-cell phenotype, and association with metabolic outcomes but may not be able to determine causality. Therefore, the evidence in the subsequent sections is discussed in the context of the experimentation in which it was obtained and, wherever possible, material from animal experiments is separated from that of humans.

Research on obese mice and human subjects has demonstrated that the hypertrophic adipose tissue becomes significantly populated following the recruitment of various immune cells with a pro-inflammatory profile (Ghigliotti et al., 2014; Medina-Urrutia et al., 2024). This process is associated with the secretion of senescence-associated secretory phenotype (SASP) markers and reduced insulin sensitivity (Midha et al., 2021). Some anti-inflammatory molecules, including the innate lymphoid cells type 2, which generate substantial amounts of Th2 cytokines (IL-4, IL-5, and IL-13), and B1 B cells, which produce IL-10, as well as regulatory T cells (Tregs), have been identified in the obese AT, but in much smaller concentrations (Golebski et al., 2021; Wynn, 2015). In another study, inflammatory response started in the brain region of mice fed with high-fat diet before visceral fat tissue, suggesting a possible link between obesity-induced inflammatory response and neurodegeneration (Henry et al., 2024). Findings from the study also showed that prolonged high fat diet in mice upregulated inflammation in the brain and worsened with aging.

4.1 Obesity-induced Macrophage response

Macrophages are one of the most well-studied immune-cell populations in obese adipose tissue and have important roles in the development and maintenance of adipose-tissue inflammation (Castoldi et al., 2016). The early studies generally followed the classical M1/M2 paradigm with M1 macrophages being mostly pro-inflammatory and M2 mostly anti-inflammatory (Martinez & Gordon, 2014). While this model has proven to be useful for gleaning the general principles of macrophage activation, growing evidence shows that the phenotypes and functions of macrophages in adipose tissue are much more complex than the binary classification implies (Martinez & Gordon, 2014). Surface-marker expression, metabolic state, anatomical distribution, lipid-handling capacity and interactions with neighbouring adipocytes and other immune cells are dynamic and may differ between macrophage populations (Castoldi et al., 2016; Nance et al., 2022). Recent studies have presented adipose-tissue macrophages as a more complex functional population or state rather than solely as M1 or M2 (Chavakis et al., 2023; Nance et al., 2022; Ying et al., 2020). However, in obesity, macrophage abundance generally increases in adipose tissue and has been associated with adipocyte hypertrophy and local inflammatory activity (Martinez & Gordon, 2014; Nance et al., 2022; Weisberg et al., 2003). In obesity, macrophages form a crown-like structure (CLS) surrounding necrotic adipocytes (Chavakis et al., 2023; X. Li, Ren, et al., 2023; Weisberg et al., 2003).

In HFD-fed mice and other experimental models, $CD11c^{+}$ and metabolically activated macrophages have been associated with adipose-tissue inflammation and metabolic dysfunction (P. Li et al., 2010). More recent studies have identified heterogeneous macrophage populations, including TREM2-associated lipid-handling populations. However, correspondence between macrophage populations identified in mice and humans remains incomplete, highlighting the importance of interpreting experimental findings alongside human evidence (Jaitin et al., 2019; Reinisch et al., 2025).

In addition to macrophage hyperplasia in the adipose tissue, earlier experimental and human studies interpreted obesity-associated macrophage activation as a shift from M2-like toward M1-like inflammatory states, accompanied by increased expression of inflammatory mediators such as IL-6, TNF-α and IL-1β (Guria et al., 2023; Randall & Meza-Perez, 2024). The CD11c+ cells, including macrophages and dendritic cells in the adipose tissue of individuals with obesity, upregulate their expression of major histocompatibility complex II (MHC II), thereby promoting adipose tissue inflammation (Cho et al., 2016). CD11c+ macrophages, unlike the CD11c- cells in individuals with obesity, demonstrate increased expression of inflammatory molecules, contribute to obesity-mediated inflammation within the adipose tissue, and are typically regarded as M1 macrophages in the adipose tissue of obese mice(Castoldi et al., 2016). Studies in obese mice and humans have shown that adipose-tissue macrophages can adopt metabolically activated phenotypes characterised by increased expression of type 1 inflammatory markers alongside lipid metabolism-related markers, including ABCA1, CD36 and Plin2 (Hill et al., 2018; Jaitin et al., 2019).

Table 1: Major macrophage populations and functional states described in obese adipose tissue

Macrophage population /state	Markers	Characteristics	Change /Association with obesity	Evidence source	References
M1-like inflammatory state	CD11c and inflammatory mediators	Pro-inflammatory signaling and cytokine production	Associated with increased inflammatory activity in obesity	Experimental and human evidence	(Hill et al., 2018; Randall & Meza-Perez, 2024)
M2-like/regulatory state	CD206 and other type-2-associated markers	Tissue repair and regulatory functions	Altered during obesity; not necessarily equivalent to a discrete M2 population	Experimental and human evidence	(Cho et al., 2016; Guria et al., 2023; Randall & Meza-Perez, 2024)
$CD11c^+$ macrophages	CD11c	Inflammatory and metabolic activation	Increased/activated in obese adipose tissue	Mainly experimental, with human evidence	(Ghigliotti et al., 2014; Jaitin et al., 2019).
$CD11c^+CD206^+$ macrophages	CD11c, CD206	Mixed inflammatory and regulatory features	Reported in obese human adipose tissue	Human evidence	(Jaitin et al., 2019; Reinisch et al., 2025).
$CD9^+$ macrophages	CD9, CD63	Associated with lipid accumulation, inflammatory activity and CLS formation	Increased in obese adipose tissue	Mouse and human evidence	(De Heredia et al., 2012; P. Li et al., 2010).
$CD9^+TREM2^+$ macrophages	CD9, TREM2	Lipid handling and lysosomal/metabolic functions	Associated with lipid-rich obese adipose tissue	Experimental and emerging human evidence	(Jaitin, et al., 2019; P. Li et al., 2010).

A pattern recognition receptor, CD206, also frequently associated with M2 markers, is usually co-expressed with CD11c by CD11c+ macrophages found in the adipose tissue of obese humans, indicating a mixed phenotype rather than strictly M1 or M2 classifications for adipose tissue macrophages (Fujisaka et al., 2009). Interestingly, within the adipose tissue of obese humans, CD11c+CD206+ macrophages show high expression of type 1 cytokines, including IL-6, TNFα, and IL-1β, as well as the type 2 cytokine IL-10 (Castoldi et al., 2016; Fujisaka et al., 2009). The co-expression of CD11c and CD206, together with the production of both pro-inflammatory and regulatory cytokines, illustrates the limitations of assigning adipose-tissue macrophages to discrete M1 or M2 categories. Rather, these phenotypes appear to reflect overlapping functional programmes shaped by the local metabolic and inflammatory environment (Castoldi et al., 2016; Fujisaka et al., 2009).

Single-cell RNA sequencing has further revealed macrophage populations expressing CD9 and CD63 that are increased in visceral adipose tissue during obesity (De Heredia et al., 2012; P. Li et al., 2010). $CD9^+$ macrophages have been associated with crown-like structures, inflammatory cytokine production and lipid-handling functions, while TREM2 expression suggests involvement in lipid metabolism and lysosomal activity (Ghigliotti et al., 2014; Jaitin et al., 2019). However, the relationship between $CD9^+TREM2^+$ and $CD11c^+$ macrophages, and the extent to which populations identified in experimental models correspond to distinct human macrophage states, remain incompletely defined. Hypoxia and metabolic stress can alter macrophage metabolism and inflammatory signalling, while activation of pathways such as the NLRP3 inflammasome can promote production of IL-1β and other inflammatory mediators (Qiu et al., 2023). Increased inflammasome activity has been reported in macrophages from individuals with type 2 diabetes, providing a potential mechanistic link between macrophage inflammation and metabolic dysfunction (Bissonnette et al., 2023). These mechanisms provide a link between adipose-tissue metabolic dysfunction and macrophage-driven inflammation, although the relative contribution of individual pathways differs between experimental models and human disease.

Macrophage responses in obesity are heterogeneous and shaped by metabolic stress, lipid accumulation and inflammatory signalling (Chavakis et al., 2023; Midha et al., 2021). Although the M1/M2 framework remains useful for describing broad inflammatory and regulatory tendencies, evidence from human and experimental studies supports a continuum of macrophage states rather than a simple M2-to-M1 transition (Martinez & Gordon, 2014). Emerging populations such as $CD11c^+CD206^+$ and $CD9^+TREM2^+$ macrophages further highlight this complexity, although their functional relationships and correspondence between experimental models and human adipose tissue remain incompletely defined (Jaitin, et al., 2019; P. Li et al., 2010).

4.2 Obesity-induced T cell response

Experimental models indicate that T cells play a role in inflammation in the adipose tissue in obesity. In HFD fed mice, expansion and activation of CD8+ T cells have been linked with enhanced recruitment of macrophages and production of inflammatory cytokines, whilst experimental depletion or manipulation of T-cell populations have yielded evidence of their role in metabolic dysfunction (Kiran et al., 2021). There are also reports of changes in populations of T-cells in adipose-tissue of individuals with obesity, including changes in CD8+ T-cell and regulatory T-cell populations in human studies (Bradley et al., 2022). However, much of the mechanistic evidence is derived from experimental models, and the relative contribution of specific T-cell populations in human obesity remains incompletely defined.

T-cell accumulation in adipose tissue is increased during obesity, with a higher prevalence within visceral adipose tissue than subcutaneous adipose tissue in both obese mice and human subjects, and has been associated with systemic inflammation in humans at a level closely correlated with systemic inflammation in humans (Valentine & Nikolajczyk, 2024). Adipose tissue T cells include Th1 CD4+ and IFN-γ-producing CD8+ T cells (Q. Wang & Wu, 2018). These cells stimulate M1 macrophages to secrete pro-inflammatory cytokines, resulting in both local and systemic insulin resistance (Fujisaka et al., 2009; Martinez & Gordon, 2014). Th1 CD4+ T cells have a high expression of membrane glucose transporters and exhibit a strong glycolytic metabolism, a characteristic that supports inflammatory responses(Liu et al., 2023). The hallmark Th1 cytokine, interferon-γ, prompts macrophages and T cells to produce chemokines that attract immune cells to the inflamed adipose tissue(Bradley et al., 2022; Liu et al., 2023). Additionally, IFN-γ promotes the polarization of M2 macrophages to M1 macrophages and diminishes insulin receptor signaling by lowering the expression of insulin receptors and glucose transporters (Guria et al., 2023; X. Li, Ren, et al., 2023). T-bet regulates IFN-γ production, and T-bet deficiency in HFD-fed mice has been associated with improved insulin sensitivity and glucose tolerance, together with reduced adipose-tissue immune-cell accumulation and pro-inflammatory cytokine expression (Kiran et al., 2021; Stolarczyk et al., 2013).

Experimental studies in HFD-fed mice suggest that T-cell accumulation may precede substantial macrophage infiltration into adipose tissue (Stolarczyk et al., 2013). Early increases in $CD8^+$ T cells and findings from depletion experiments suggest that T cells may contribute to subsequent macrophage accumulation and inflammatory activation (Nishimura et al., 2009). However, this temporal relationship has not been established to the same extent in human obesity.

Regulatory T cells (Tregs), which are relatively enriched in lean adipose tissue, are reduced in visceral adipose tissue during obesity, suggesting loss of an important mechanism for limiting local inflammation (Bradley et al., 2022; Feuerer et al., 2009). Experimental manipulation of Tregs further supports a protective role in metabolic homeostasis, although the extent to which these findings translate to human obesity remains uncertain (G. Wang et al., 2024). Th2 cells have been associated with reduced systemic inflammation and improved insulin sensitivity, suggesting a potentially protective role in obesity (McLaughlin et al., 2014). On the other hand, Th17 and Th22 cells, which produce IL-17 and IL-22, have been reported to increase in adipose tissue of obese individuals, although their distribution differs between visceral and subcutaneous depots(McLaughlin et al., 2014; Nishimura et al., 2009).

T-cell involvement in obesity appears to reflect a shift in the balance between effector and regulatory responses rather than expansion of a single T-cell population (McLaughlin et al., 2014). $CD8^+$ and Th1 cells, particularly through IFN-γ signalling, may promote macrophage recruitment and inflammatory activation, whereas Tregs and, in some contexts, Th2 cells may exert protective effects (Feuerer et al., 2009; Nishimura et al., 2009). Th17 and Th22 cells may also contribute to obesity-associated inflammation, although their roles appear to vary between adipose-tissue depots (Valentine & Nikolajczyk, 2024). T cells interact with macrophages and adipocytes to influence the inflammatory environment and metabolic dysfunction, but the relative contribution of individual populations in human obesity remains incompletely established (Chavakis et al., 2023; Kolb, 2022). T cells interact with macrophages and adipocytes to influence the inflammatory environment and metabolic dysfunction, but the relative contribution of individual populations in human obesity remains incompletely established. These responses are also tissue-specific, as visceral and subcutaneous adipose depots exhibit different T-cell profiles.

4.3 Natural killer T (NKT) cells response

Natural killer T (NKT) cells have been implicated in obesity-associated adipose-tissue inflammation, although their precise role remains controversial. Evidence from experimental models indicates that NKT-cell activation can promote inflammatory responses in adipose tissue, whereas other studies, particularly those examining invariant NKT (iNKT) cells, suggest potential protective or immunoregulatory effects (Lynch et al., 2012; Satoh et al., 2012). This apparent discrepancy may reflect differences in NKT-cell subtype, adipose-tissue depot, dietary intervention and duration, animal model, stage of obesity, and cellular activation state. NKT cells constitute a heterogeneous population of T lymphocytes that express features of both conventional T cells and natural killer cells and can rapidly produce a range of cytokines, including Th1- and Th2-associated cytokines (Lynch et al., 2012; Satoh et al., 2012). They are broadly classified into type I NKT cells, which express a semi-invariant T-cell receptor (TCR), and type II NKT cells, which express a more diverse TCR repertoire (Jeong et al., 2023). This functional and phenotypic heterogeneity is important when interpreting their reported effects in obesity.

In mice fed with a high-fat diet (HFD), increased activation of NKT cells in visceral adipose tissue has been reported, while depletion or absence of NKT cells has been associated with reduced macrophage infiltration and adipose-tissue inflammation (Kiran et al., 2021; Kolb, 2022; Lynch et al., 2012). These findings suggest that NKT cells can contribute to obesity-associated inflammation. However, other studies have reported that invariant NKT (iNKT) cells are more abundant in lean adipose tissue than in obese adipose tissue and may exert protective effects through the production of anti-inflammatory or type 2-associated cytokines, including IL-4 and IL-10 (Lynch et al., 2012). These apparently conflicting findings indicate that the role of NKT cells in obesity is unlikely to be uniformly pro-inflammatory or anti-inflammatory.

Several factors may account for the divergent observations. First, NKT-cell subtype is an important consideration because type I (iNKT) and type II NKT cells differ in their antigen recognition, cytokine profiles and functional responses (Rossjohn et al., 2012). Findings attributed broadly to "NKT cells" may therefore reflect differences in the specific populations examined. Second, the adipose-tissue depot investigated may influence NKT-cell abundance and function, as visceral and subcutaneous adipose tissues have distinct immunological and metabolic characteristics(Dasgupta & Kumar, 2016; Lynch et al., 2012). Third, differences in dietary exposure and duration of HFD feeding may affect NKT-cell recruitment and activation, with their effects potentially changing during the progression from early metabolic dysfunction to established obesity. Similarly, differences in animal models, genetic background, age, sex and experimental conditions may contribute to variation between studies (Ji et al., 2012; Kondo et al., 2013). Finally, the activation state and cytokine profile of NKT cells may determine whether they promote inflammation or contribute to immune regulation (Dasgupta & Kumar, 2016; Satoh et al., 2012). Thus, NKT-cell responses in obesity should be interpreted in the context of NKT-cell subtype, adipose depot, disease stage and experimental model rather than as a single uniform response. Available evidence suggests that NKT cells have a context-dependent role in obesity-associated adipose inflammation (Guria et al., 2023). Their effects may vary according to NKT-cell subtype, metabolic environment and stage of obesity, which may partly explain the inconsistent findings across experimental studies. The predominance of experimental evidence also warrants caution when extrapolating these findings to human obesity.

4.4 Obesity-induced B-cell response

Examples of the mechanistic evidence that B cells contribute to obesity-associated inflammation come from mouse models. In HFD-fed mice, B-cell alterations and antibody responses have been associated with adipose-tissue inflammation and insulin resistance, while experimental B-cell depletion or manipulation provides evidence of their functional role (Winer et al., 2011). Changes in B-cell numbers and antibody profiles have also been reported in human obesity, although these findings do not necessarily establish causality (Kosaraju et al., 2017). Further studies are required to determine the extent to which these experimentally demonstrated mechanisms apply to human obesity.

Fat-associated lymphoid clusters (FALCs) have also been identified in the mesenteric adipose tissue of mice and humans (Moro et al., 2010). These structures can develop in response to inflammatory stimuli and provide a site for B-cell proliferation and differentiation, suggesting a potential role in regulating local antibody responses (Bénézech et al., 2015). B cells, especially B2 cells, are found in higher numbers in the visceral adipose tissue of mice fed with a high-fat diet (HFD) and are also present in crown-like structures in the subcutaneous adipose tissue of obese humans (Kosaraju et al., 2017; Winer et al., 2011). B cells isolated from obese mice display a type 1 inflammatory phenotype, with increased secretion of pathogenic IgG antibodies and type 1 cytokines like IL-6 (Kosaraju et al., 2017). Studies using obese mice have shown that a lack or reduction of B cells leads to decreased inflammation in adipose tissue, while the introduction of B2 cells results in increased inflammation (Ying et al., 2017). B cells, particularly the B2 subset, may play a role in promoting inflammation in adipose tissue by secreting pathogenic IgG antibodies, type 1 cytokines, activating macrophages and T cells, and by regulating Treg (T regulatory cells) (Ying et al., 2017). In contrast, B1 cells and regulatory B cells have been reported to be more abundant in lean adipose tissue and to decrease with obesity (Srikakulapu & McNamara, 2020). These populations may exert protective effects through the production of IgM and IL-10 and by limiting $CD8^+$ T-cell activation. The greater abundance of IL-10-producing B cells in subcutaneous compared with visceral adipose tissue in lean mice further suggests that B-cell responses may vary between adipose-tissue depots (Kosaraju et al., 2017; Srikakulapu & McNamara, 2020; Winer et al., 2011). The available evidence suggests that B-cell responses contribute to obesity-associated inflammation through changes in B-cell populations, antibody production and interactions with other immune cells. B2 cells and pathogenic IgG responses have been associated with inflammatory activity and metabolic dysfunction, particularly in experimental models, whereas B1 and regulatory B cells may have protective functions. However, much of the mechanistic evidence is derived from animal studies, and the extent to which these B-cell mechanisms contribute to human obesity remains incompletely established.

4.5 Other innate immune cells: neutrophils, eosinophils and mast cells

Neutrophils have been implicated in obesity-associated adipose-tissue inflammation. In high-fat diet-fed mice, prolonged neutrophil accumulation, particularly in visceral adipose tissue, has been associated with the release of pro-inflammatory mediators such as elastase, myeloperoxidase and IL-1β, as well as the recruitment of monocytes and macrophages (Talukdar et al., 2012). Experimental deficiency of neutrophil elastase or myeloperoxidase reduces adipose-tissue inflammation and macrophage accumulation. Increased numbers of activated neutrophils have also been reported in visceral and subcutaneous adipose tissue in obesity (Altamura et al., 2024), while their levels decrease following weight loss after bariatric surgery in humans (Talukdar et al., 2012). These findings support a potential role for neutrophils in obesity-associated inflammation, although much of the mechanistic evidence remains experimental.

Eosinophils have been proposed to exert a regulatory role in obesity-associated adipose-tissue inflammation. Their abundance is reported to decrease during obesity (Hu & Chakarov, 2023), while experimental studies have associated increased eosinophil levels with M2-like macrophages and type 2 cytokine responses, particularly through IL-4 and IL-13 (Lee et al., 2020). These findings suggest that eosinophils may contribute to the suppression of type 1 inflammation. However, this role remains controversial. For example, increasing eosinophil levels through recombinant IL-5 administration did not alter M2-like macrophage abundance or inflammatory markers in obese mice (Bolus et al., 2018). In addition, evidence from human studies is less consistent. Thus, the contribution of eosinophils to obesity-associated inflammation remains uncertain and may depend on the experimental model, adipose-tissue depot and stage of obesity.

Table 2: Comparative evidence for immune-cell involvement in obesity-associated adipose-tissue inflammation

Immune-cell population	Experimental evidence	Human evidence	interpretation	References
Macrophages	Strong mechanistic evidence for adipose-tissue accumulation, inflammatory activation and metabolic dysfunction	Increased accumulation and inflammatory signatures reported in obesity	Strong evidence for involvement, but mouse and human macrophage populations are not directly equivalent	(Castoldi et al., 2016; Fujisaka et al., 2009).
T cells	Experimental evidence links $CD8^+$ and Th1 responses with macrophage recruitment and metabolic dysfunction	Altered T-cell populations reported in obesity, but causal evidence is limited	Important contributor; relative roles of individual subsets remain uncertain	(Kiran et al., 2021; Bradley et al., 2022) .
NKT cells	Both pro-inflammatory and potentially protective effects reported depending on subtype and experimental context	Human evidence is limited	Context-dependent role; evidence remains heterogeneous	(Kiran et al., 2021; Kolb, 2022; Lynch et al., 2012).
B cells	Experimental evidence links B-cell responses and antibodies with adipose inflammation and insulin resistance	Altered B-cell populations and antibody responses reported	Mechanistic evidence is stronger in experimental models	(Winer et al., 2011; Kosaraju et al., 2017).
Neutrophils	Experimental evidence supports recruitment and inflammatory activation	Changes in neutrophil activity reported in obesity	Potential contributor; human mechanistic evidence remains limited	(Altamura et al., 2024; Talukdar et al., 2012).
Eosinophils	Some experimental evidence supports type-2 and regulatory effects	Human findings are less consistent	Potentially regulatory, but evidence remains conflicting	(Bolus et al., 2018; Lee et al., 2020).
Mast cells	Experimental studies suggest involvement in adipose inflammation	Human evidence is limited	Possible contributor, but role remains incompletely defined	activity (Ghigliotti et al., 2014; Sismanopoulos et al., 2012; Żelechowska et al., 2018)

Mast cells have also been implicated in obesity-associated adipose-tissue inflammation. Studies in obese animal models have reported increased mast-cell accumulation and activation in visceral and subcutaneous adipose tissue, together with increased inflammatory activity (Ghigliotti et al., 2014; Sismanopoulos et al., 2012; Żelechowska et al., 2018). On the contrary, experimental reduction or absence of mast cells has been associated with decreased adipose-tissue inflammation (Feyerabend et al., 2016). These findings suggest that mast cells may contribute to obesity-associated inflammation, although the available evidence is predominantly derived from animal studies. Neutrophils, eosinophils and mast cells appear to contribute differently to obesity-associated adipose-tissue inflammation (Bolus et al., 2018; Talukdar et al., 2012). Neutrophils and mast cells are generally associated with pro-inflammatory responses, whereas eosinophils have been linked to type 2 immune responses and potentially regulatory effects (Bolus et al., 2018; Henry et al., 2024; Lee et al., 2020). However, evidence for the role of eosinophils remains conflicting, and much of the mechanistic evidence for these cell populations is derived from experimental models. Further human studies are therefore needed to clarify their relative contributions to obesity-associated inflammation.

4.6 Integrated immune-cell interactions in obesity

Obesity-associated inflammation is not driven by individual immune-cell populations acting independently, but by interactions between innate and adaptive immune cells within adipose tissue (Khanna et al., 2022). Adipocyte hypertrophy and metabolic stress can promote the release of chemokines and cytokines that recruit and activate immune cells. In turn, macrophages, T cells, B cells, NKT cells and other innate immune cells interact with one another and with adipocytes, contributing to persistent inflammation and metabolic dysfunction (Trim & Lynch, 2022). However, the nature and relative contribution of these interactions vary according to adipose-tissue depot, disease stage and experimental model, and findings from animal studies cannot always be directly extrapolated to human obesity.

The evidence from both experimental and human studies supports an important role for immune cells in obesity-associated inflammation, although the strength of evidence varies among cell populations (Bradley et al., 2024). Experimental models provide stronger evidence for mechanisms and potential causality, whereas human studies more often demonstrate associations between immune-cell changes, adipose inflammation and metabolic dysfunction. In addition, immune-cell phenotypes identified in genetically modified or diet-induced mouse models do not necessarily have direct equivalents in human adipose tissue (Bradley et al., 2024). Greater use of human adipose-tissue studies, longitudinal investigations and high-resolution immune-cell profiling will therefore be important for determining which mechanisms identified experimentally are most relevant to human obesity (Guria et al., 2023; X. Li, Ren, et al., 2023).

5. INTERSECTION OF OBESITY-ASSOCIATED METAFLAMMATION AND INFLAMMAGING

Obesity-associated metaflammation and inflammaging are two closely related but clearly distinct phenomena (Qu et al., 2022). Whereas metaflammation is essentially a low-grade inflammatory response accompanying metabolic excess and dysfunctions (Hotamisligil, 2017), inflammaging is a syndrome characterized by chronic, low-grade inflammation associated with aging (Khanna et al., 2022). Both involve dysregulated immune responses, altered cellular metabolism, mitochondrial dysfunction, inflammatory signalling and changes in tissue homeostasis (Hotamisligil, 2017; Qu et al., 2022). Metaflammation primarily arises in response to sustained nutrient excess, adipose-tissue dysfunction and metabolic stress, whereas inflammaging develops in the context of biological ageing and the gradual accumulation of cellular, molecular and immune alterations (Schleh et al., 2023). Despite differences in their initiating stimuli, both processes involve dysregulated innate and adaptive immune responses, altered cellular metabolism, mitochondrial dysfunction, inflammatory signalling and changes in tissue homeostasis (Hotamisligil, 2017; Schleh et al., 2023). Obesity-associated metaflammation may therefore interact with age-related inflammatory processes and potentially amplify them, while ageing-related changes may in turn increase susceptibility to metabolic inflammation (Schleh et al., 2023). Understanding this intersection requires consideration of their shared and distinct cellular sources, inflammatory mediators, tissue changes and systemic metabolic consequences.

The relationship between metaflammation and inflammaging can be better understood by considering their initiating stimuli and downstream responses. First, the initiating stimuli differ: metaflammation is primarily associated with chronic nutrient excess, adipose-tissue expansion, lipid accumulation and metabolic stress, whereas inflammaging is associated with age-related cellular senescence, accumulation of damage-associated molecular patterns (DAMPs), impaired tissue maintenance, altered immune regulation and other age-related changes (Baechle et al., 2023; Schleh et al., 2023). Secondly, although both processes involve innate and adaptive immune cells, their relative contribution may differ according to tissue and disease context. Macrophages, neutrophils, T cells, B cells, NK cells and NKT cells have been implicated in obesity-associated adipose inflammation, while age-related alterations in T-cell, B-cell, NK-cell and innate immune function contribute substantially to inflammaging (Altamura et al., 2024; Kosaraju et al., 2017; Satoh et al., 2012). Third, the two processes share several inflammatory mediators, including IL-6, TNF-α and IL-1β, although their cellular sources, timing and regulatory mechanisms may differ (Ji et al., 2012). Fourth, adipose tissue represents an important point of convergence. In obesity, adipocyte hypertrophy, adipose-tissue hypoxia, altered adipokine secretion and immune-cell recruitment contribute directly to local and systemic inflammation (Bradley et al., 2024; Ghigliotti et al., 2014; Inflammation, 2009). With ageing, changes in body-fat distribution, particularly increased visceral and abdominal adiposity, may further contribute to metabolic and inflammatory dysregulation. Fifth, both processes can have systemic metabolic consequences, including impaired insulin sensitivity and increased risk of metabolic and cardiovascular disorders. However, these effects occur within different biological contexts: metaflammation is closely associated with metabolic excess and dysfunction, whereas inflammaging represents a broader age-associated inflammatory state that can affect multiple organ systems (Baechle et al., 2023; Inflammation, 2009; Schleh et al., 2023). Thus, obesity-associated metaflammation and inflammaging should not be regarded as interchangeable terms. Rather, they represent overlapping inflammatory processes with distinct initiating factors but several shared downstream pathways. Their interaction may create a reinforcing cycle in which metabolic dysfunction promotes inflammation and inflammation contributes further to metabolic impairment, while age-related immune and cellular changes may modify the intensity and persistence of this response.

In inflammaging, persistent low-grade inflammation develops progressively with advancing age and is associated with the accumulation of cellular and molecular stressors (Ghigliotti et al., 2014; Li, et al., 2023). The process of inflammaging is triggered by various factors, such as genetic variations in pro-inflammatory gene promoter regions, sustained viral (cytomegalovirus) activation of immune cells, the gut microbiome dysbiosis, and increased intestinal permeability (Inflammation, 2009; Qu et al., 2022). The chronic activation of innate receptors by endogenous signals, like damage-associated molecular patterns (DAMPs), during the ageing process fosters a chronic inflammatory environment that must be balanced by anti-inflammatory responses (X. Li, Li, et al., 2023). Cell senescence, along with the emergence of the senescence-associated secretory phenotype (SASP) in fibroblasts, endothelial, and immune cells, has also been identified as a key factor contributing to inflammaging (Wang et al., 2024). Cellular senescence can alter immune-cell function and promote the release of senescence-associated secretory factors, thereby contributing to a persistent pro-inflammatory environment (Giannoula et al., 2023). Insulin resistance, a common feature of aged individuals, plays a crucial role in metabolic disorders (Giannoula et al., 2023). Age-related redistribution of adipose tissue, particularly increased visceral and abdominal adiposity, is associated with impaired insulin sensitivity and may contribute to the metabolic and inflammatory changes observed during ageing (Zhao & Yue, 2024). Additionally, elevated levels of pro-inflammatory cytokines associated with ageing are known to disrupt insulin metabolism (Moro et al., 2010; Wynn, 2015). This suggests that shifts in age-related body fat distribution and metabolism are critical elements of a detrimental cycle that can hasten the ageing process and trigger age-associated anomalies.

A major point of overlap between inflammaging and obesity-associated metaflammation is dysregulation of both innate and adaptive immunity. The decline in the immune system's function with age has been established for decades, predisposing the older populations to infections and many chronic illnesses (Castelo-Branco & Soveral, 2014). As the immune function declines with age, both innate and adaptive immunity are severely impacted (Castelo-Branco & Soveral, 2014). A persistently pro-inflammatory status characterized by elevated levels of cytokines, such as interleukin 6 (IL-6) and tumor necrosis factor-α (TNF-α), just like in obesity, is a hallmark of ageing, as low-grade inflammation is typically prevalent in the elderly and during obesity (Inflammation, 2009; Monteiro & Azevedo, 2010; Qiu et al., 2023). The mechanisms responsible for maintaining these elevated proinflammatory biomarkers in the ageing process remain poorly understood. TNF-α and IL-6 have emerged as indicators of frailty among the aged human population. This state of chronic inflammation has been termed "inflammaging.

The convergence of obesity-associated metaflammation and inflammaging may have important consequences for metabolic health. Sustained low-grade inflammation can impair insulin signalling and promote insulin resistance, thereby contributing to the progression from metabolically healthy obesity to metabolic dysfunction (Baechle et al., 2023; Bénézech et al., 2015; Castelo-Branco & Soveral, 2014). In obesity, nutrient excess and adipose-tissue dysfunction are associated with elevated glucose, free fatty acids, lipids and reactive oxygen species (ROS), which can further activate inflammatory pathways (Castelo-Branco & Soveral, 2014; Hotamisligil, 2017). Both innate and adaptive immune cells, including macrophages, neutrophils, T cells, B cells, NK cells and NKT cells, can accumulate in metabolically active tissues such as visceral adipose tissue and contribute to inflammatory responses during obesity (Altamura et al., 2024; Chavakis et al., 2023; Golebski et al., 2021). Similarly, inflammaging is characterised by persistent elevations of inflammatory mediators, including IL-6, IFN-γ, TNF-α and IL-1β, as well as inflammatory chemokines and other mediators (Monteiro & Azevedo, 2010; Qu et al., 2022). The overlap in these inflammatory pathways provides a plausible biological basis through which ageing and obesity may interact to increase susceptibility to insulin resistance and other metabolic complications.

Adipose tissue represents an important site where obesity-associated metaflammation and inflammaging may intersect. In obesity, hypertrophic and metabolically stressed adipocytes interact with immune cells within the adipose tissue microenvironment, contributing to the production of inflammatory mediators such as TNF-α and IL-6 (Medina-Urrutia et al., 2024; G. Wang et al., 2024). However, the relationship between adipose-tissue mass, adipocyte size and inflammatory mediator production is not necessarily linear, and differences in adipose-tissue depot and cellular composition may contribute to variation between individuals (Medina-Urrutia et al., 2024; G. Wang et al., 2024). Age-related redistribution of fat mass, particularly increased visceral adiposity, may further alter adipokine secretion and insulin sensitivity and contribute to both local and systemic inflammation (Mancuso & Bouchard, 2019). Consequently, obesity and ageing may interact to create a persistent inflammatory and metabolically adverse environment, potentially increasing susceptibility to insulin resistance, cardiovascular disease and other age-associated disorders (Ghigliotti et al., 2014; Mancuso & Bouchard, 2019).

6. SHARED FEATURES BETWEEN OBESITY AND AGING

Although obesity and ageing are biologically distinct processes, they share several features that may contribute to persistent inflammation and metabolic dysfunction. This overlap has led to the concept of "adipaging," which describes the interaction between obesity-associated metabolic stress and age-related biological changes (Zhao & Yue, 2024). Chronic low-grade inflammation is a common feature of both conditions, although the initiating stimuli and relative contribution of individual pathways may differ (Schleh et al., 2023). Importantly, these shared biological features are relevant to the present review only insofar as they influence adipose-tissue immune-cell function, inflammatory signalling, or the progression of obesity-associated metabolic dysfunction.

Ageing is accompanied by changes in body composition, including increased visceral adipose tissue and reduced subcutaneous adipose tissue in many individuals (Baechle et al., 2023). These changes are important because visceral and subcutaneous adipose depots differ in their metabolic and immunological characteristics, with visceral adipose tissue generally exhibiting greater inflammatory activity (Schleh et al., 2023). Age-related changes in adipose tissue can therefore modify adipocyte function, adipokine secretion, immune-cell recruitment and local inflammatory signalling (Bradley et al., 2024). Accordingly, the following shared features are discussed in terms of how they may alter adipose-tissue immunity and contribute to obesity-associated inflammation.

Immune dysregulation: Immune dysregulation represents one of the most direct points of convergence between obesity and ageing. In obesity, metabolic stress, excess nutrient availability and adipose-tissue dysfunction can increase reactive oxygen species (ROS) production and activate inflammatory pathways such as nuclear factor-kappa B (NF-κB) (Chavakis et al., 2023). Ageing is similarly associated with increased oxidative stress, cellular senescence and altered immune-cell function (Goyani et al., 2024). These processes can promote the production of pro-inflammatory mediators and alter the recruitment and activation of macrophages, T cells, B cells, NK cells and other immune-cell populations within adipose tissue (Dasgupta & Kumar, 2016; Goyani et al., 2024; Inflammation, 2009). Thus, oxidative and metabolic stress may provide a mechanistic link through which age-related changes modify immune responses in adipose tissue and potentially intensify obesity-associated inflammation.

Mitochondrial dysfunction: Mitochondrial dysfunction provides another potential link between ageing and obesity-associated inflammation. In adipose tissue, mitochondrial stress can increase ROS production and cellular stress, which may activate inflammatory signaling and alter immune-cell function (Xu et al., 2025). Consistent with this relationship, Henry et al., (2024) reported that high-fat-diet-induced obesity was associated with increased inflammatory cytokines in the brains of mice, with inflammatory responses becoming more pronounced in aged animals. Although these findings extend beyond adipose tissue, they suggest that age-related

mitochondrial dysfunction may interact with obesity-induced metabolic stress to enhance inflammatory signaling. The relevance of this pathway to adipose immune-cell activation, however, requires further investigation.

Epigenetic modifications: Epigenetic alterations, including changes in DNA methylation, chromatin remodeling and histone modification, are associated with both obesity and biological ageing (Franzago et al., 2022). Accelerated epigenetic ageing has been associated with higher body mass index and obesity, whereas some studies suggest that weight loss may modify the rate of epigenetic ageing (Franzago et al., 2022; Tam et al., 2020). Importantly, epigenetic changes may also influence the expression of genes involved in immune-cell activation and inflammatory signaling (Franzago et al., 2022). Therefore, obesity- and age-associated epigenetic alterations could modify the phenotype and function of adipose-tissue immune cells, potentially affecting the production of inflammatory mediators and the persistence of adipose inflammation (Tam et al., 2020). This provides a plausible mechanism linking biological ageing with obesity-associated immune dysregulation, although the specific immune-cell pathways involved require further clarification.

Telomere shortening: Telomere shortening is a recognized feature of biological ageing and has also been associated with overweight and obesity (Gavia-García et al., 2021). Oxidative stress and chronic inflammation may contribute to accelerated telomere attrition, while shortened telomeres can promote cellular senescence and alter tissue homeostasis (Zhu et al., 2019). Of particular relevance to obesity, tissue-specific deletion of the telomerase reverse transcriptase gene in adipose tissue of mice has been associated with adipocyte hypertrophy, inflammation, premature ageing of adipose progenitor cells and systemic insulin resistance, with these effects being exacerbated by a high-fat diet (Gavia-García et al., 2021).

These findings suggest that impaired telomere maintenance may contribute to adipose-tissue dysfunction and create an inflammatory environment that favours immune-cell recruitment and metabolic impairment. Thus, telomere shortening may represent a potential link between biological ageing and obesity-associated adipose inflammation.

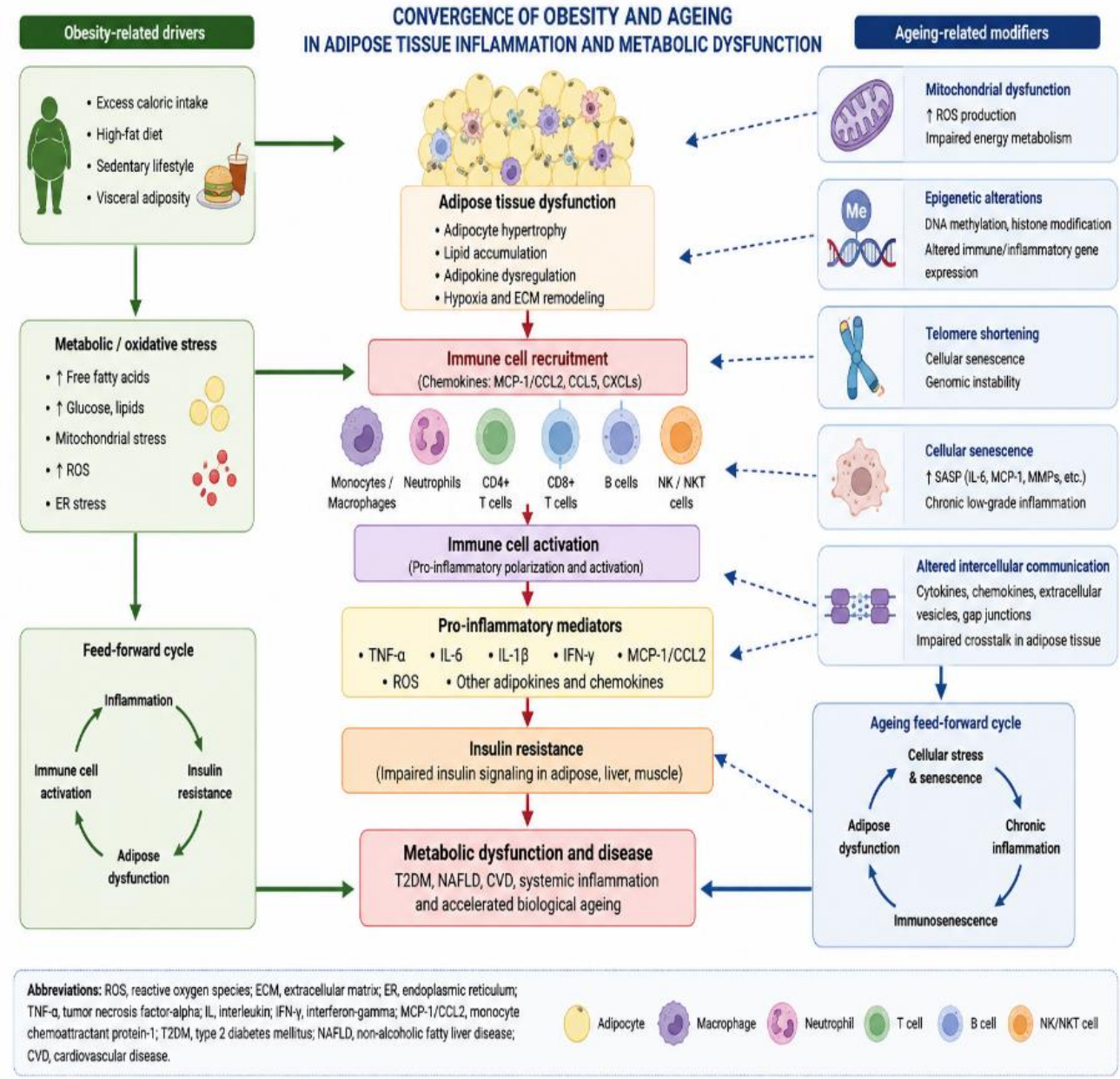

Fig.1. Convergence of obesity-associated adipose dysfunction, immune-cell activation and ageing

Cell-cycle inhibition: Studies have shown elevated expression of cell-cycle inhibitory molecules, including p16 and p53, in adipose-derived stem cells (ASCs) obtained from obese individuals (Conley et al., 2020). These proteins promote cell-cycle arrest and cellular senescence; a process strongly associated with biological ageing (Giannoula et al., 2023). Senescent ASCs can secrete pro-inflammatory molecules, including interleukin-6 (IL-6) and monocyte chemoattractant protein-1 (MCP-1), as components of the senescence-associated secretory phenotype (SASP) (Sahu & Satapathy, 2025). In addition, reduced expression of peroxisome proliferator-activated receptor gamma (PPARγ) in senescent ASCs may impair adipogenic differentiation (Palmer et al., 2019). Impaired adipose progenitor-cell function can contribute to abnormal adipose tissue remodeling and adipocyte hypertrophy, which are associated with inflammation, insulin resistance and metabolic dysfunction (Sahu & Satapathy, 2025). These findings suggest that cellular senescence in adipose progenitor and stromal cells may not only impair adipose tissue remodeling but also create a microenvironment that promotes immune-cell recruitment and sustains local inflammation.

Intercellular communication: Communication between adipocytes, stromal cells and immune cells is essential for maintaining adipose-tissue homeostasis, and its disruption may contribute to persistent inflammation in both obesity and ageing (Randall & Meza-Perez, 2024). Cytokines and chemokines provide important signaling mechanisms through which macrophages, T cells, B cells, NK cells and other immune populations interact within adipose tissue. Extracellular vesicles may additionally facilitate the transfer of proteins, lipids and nucleic acids between cells, thereby influencing inflammatory and metabolic pathways (Bradley et al., 2024). In obesity, endoplasmic-reticulum stress has been associated with altered connexin 43 (Cx43)-mediated cellular communication, while Cx43 silencing has been reported to improve insulin sensitivity and reduce hepatic fat accumulation (Gangarossa & Luquet, 2020). These observations suggest that altered intercellular communication may influence the recruitment, activation and functional state of adipose immune cells, thereby contributing to obesity-associated inflammation and metabolic dysfunction.

7. THERAPEUTIC IMPLICATIONS AND FUTURE PERSPECTIVES

The identification of immune-cell-driven inflammation as an important contributor to obesity-associated metabolic dysfunction provides a rationale for therapeutic strategies that target inflammatory pathways in addition to interventions aimed at reducing excess adiposity. However, therapeutic targeting of inflammation requires distinction between pathways that contribute to pathological chronic inflammation and those that are necessary for normal immune surveillance and tissue homeostasis (Kolb, 2022). The overlap between obesity-associated metaflammation and inflammaging raises the possibility that some inflammatory pathways may represent shared therapeutic targets; however, age-related immunosenescence and altered host responses may also influence the efficacy and safety of immune-directed interventions (Castelo-Branco & Soveral, 2014; Hotamisligil, 2017; Inflammation, 2009). Potential therapeutic strategies should therefore focus on specific pathways involved in immune-cell recruitment, activation and inflammatory signalling rather than indiscriminate suppression of the immune response. Candidate pathways include chemokine-mediated recruitment of monocytes/macrophages, Toll-like receptor signalling, NLRP3 inflammasome activation, NF-κB signalling and cytokine pathways involving TNF-α, IL-1β and IL-(X. Li, Ren, et al., 2023; Wen et al., 2012). Modulation of macrophage activation and other immune-cell phenotypes may also provide an approach to reducing pathological adipose inflammation while preserving essential immune functions (Chavakis et al., 2023; Qu et al., 2022).

Importantly, targeting obesity and targeting obesity-associated inflammation are not necessarily equivalent therapeutic strategies (Schleh et al., 2023). Weight-loss interventions primarily address the upstream metabolic drivers of adipose dysfunction, including excess energy storage, adipocyte hypertrophy and ectopic lipid accumulation (Yang et al., 2024). In contrast, immune-directed therapies aim to modify downstream inflammatory pathways that contribute to metabolic complications (Randall & Meza-Perez, 2024). Pharmacological or lifestyle interventions that reduce body weight may consequently improve inflammation indirectly, whereas selective anti-inflammatory approaches may reduce inflammatory signaling without necessarily correcting the underlying excess adiposity (Bulmer & Avenell, 2025; Soták et al., 2025). Combining interventions that address the metabolic cause of obesity with approaches that selectively modulate pathological inflammation may therefore provide greater therapeutic benefit than systemic suppression of immune responses alone.

Given the overlapping characteristics of obesity and the ageing process, with both primarily linked through inflammation, addressing the underlying immune cell-induced inflammation could offer a novel treatment approach for diseases associated with obesity as well as age-related conditions impacted by being overweight (Soták et al., 2025). Experimental studies have shown that selective modulation of inflammatory pathways can improve adipose inflammation, insulin sensitivity and other metabolic outcomes in some animal models of obesity (Soták et al., 2025). However, findings from experimental models cannot automatically be extrapolated to humans because immune responses, disease stage, adipose-tissue distribution and treatment duration may differ substantially. Clinical translation remains challenging.

Although several inflammatory pathways have been successfully targeted in other chronic inflammatory diseases, evidence that selective immune modulation can provide sustained improvements in obesity-related metabolic outcomes remains less established (Hotamisligil, 2017; Li, et al., 2023). Differences between experimental models and human obesity, heterogeneity in obesity phenotype, variation in adipose-tissue immune composition, disease duration and the complex redundancy of inflammatory pathways may partly explain this translational gap. Not all anti-inflammatory approaches have produced consistent metabolic benefits, highlighting the limitations of broadly suppressing inflammatory pathways. Interventions directed at a single cytokine or immune pathway may be insufficient because obesity-associated inflammation involves interconnected signaling networks and multiple

immune-cell populations. In addition, improvements in inflammatory biomarkers do not necessarily translate into clinically meaningful weight loss or reversal of metabolic disease.

These limitations suggest that future therapies may need to target specific pathological immune-cell functions or combinations of pathways rather than systemic inflammation as a whole. Safety is a major consideration when targeting immune-cell-induced inflammation. Inflammatory signaling is not exclusively pathological; many of the same pathways involved in obesity-associated inflammation are required for antimicrobial defense, tissue repair and immune surveillance (Randall & Meza-Perez, 2024; Soták et al., 2025). Prolonged systemic inhibition may therefore increase susceptibility to infection, impair tissue repair or produce other immune-related adverse effects (Yang et al., 2024). This concern is particularly relevant in older individuals, in whom immunosenescence may already compromise immune competence (Goyani et al., 2024). Therapeutic strategies should consequently aim for selective modulation of pathological adipose inflammation while preserving essential host-defense mechanisms. The development of anti-inflammatory targeted drugs for human obesity subjects remains elusive not only due to insufficient understanding of the specific pathways involved in immune cell-induced inflammation in humans, but also the complications that may result from suppressing immune cell inflammatory response, given its crucial role in maintaining tissue homeostasis. Future research should move beyond describing inflammatory associations and focus on identifying which immune-cell populations and signaling pathways are causally responsible for metabolic dysfunction in specific obesity phenotypes. Greater attention should also be given to differences according to age, sex, adipose-tissue depot, obesity duration and metabolic status. Single-cell and spatial approaches may help define the cellular interactions and inflammatory niches that distinguish metabolically harmful from potentially adaptive immune responses. Such approaches could support the development of more selective therapies that target pathological immune-cell activity while preserving protective immune functions

Ultimately, the therapeutic significance of immune-cell-induced inflammation in obesity lies not simply in suppressing inflammation, but in determining which inflammatory responses are pathological, which are protective and at what stage of disease intervention is most beneficial. Integrating weight-management strategies with selective modulation of adipose immune pathways may provide a more rational approach than treating inflammation in isolation. However, robust clinical trials are required to establish whether targeting specific immune pathways can produce durable improvements in metabolic health without compromising host immunity, particularly in older adults with coexisting age-related immune dysfunction.

8. CONCLUSION

Obesity-associated inflammation is a complex and dynamic process driven by interactions between adipocytes, metabolic stress and multiple immune-cell populations within adipose tissue and other metabolically active organs. The evidence reviewed indicates that macrophages, T cells, B cells, neutrophils, NK cells and NKT cells can contribute to the inflammatory environment associated with obesity, although their effects are context-dependent and may vary according to obesity stage, adipose-tissue depot, metabolic status and immune-cell phenotype. Rather than acting independently, these immune-cell populations interact through cytokines, chemokines and cell–cell signaling networks that can sustain chronic inflammation and contribute to insulin resistance and other metabolic complications. The evidence is strongest for several immune–adipose interactions demonstrated in experimental models, particularly the recruitment and activation of macrophages and the involvement of T-cell-mediated inflammatory responses in adipose-tissue dysfunction. However, evidence from human studies is more heterogeneous and remains comparatively limited for some immune-cell populations, including NKT cells and specific immune-cell subsets. Findings from animal models therefore provide important mechanistic insights but should not be directly extrapolated to human obesity without considering differences in immune-cell composition, adipose-tissue distribution, diet, disease duration and metabolic phenotype. Greater integration of human longitudinal and tissue-based studies is required to establish the clinical relevance of these mechanisms. The relationship between obesity-associated metaflammation and inflammaging is also more appropriately viewed as an interaction between overlapping but distinct processes rather than as a single inflammatory phenomenon. Metaflammation is primarily associated with chronic metabolic and nutrient excess, whereas inflammaging reflects persistent low-grade inflammation associated with biological ageing. Nevertheless, both processes share features including immune dysregulation, cellular senescence, mitochondrial dysfunction, altered inflammatory signaling and adipose-tissue remodeling. Obesity may therefore amplify age-associated inflammatory processes, while ageing-related changes in immune function and adipose tissue may increase susceptibility to obesity-associated metabolic dysfunction.

Important knowledge gaps remain. These include the need to clarify the causal contribution of individual immune-cell subsets, determine how immune-cell phenotypes change across the course of obesity, establish differences between visceral and subcutaneous adipose tissue, and better understand how ageing modifies these immune responses. The relative contribution of sex, obesity phenotype, metabolic health, diet, gut microbiota and genetic background also requires further investigation. Advanced approaches such as single-cell transcriptomics, spatial profiling and longitudinal human studies may help identify specific immune-cell populations and signaling pathways that drive pathological inflammation. From a translational perspective, the evidence supports therapeutic strategies that address both the metabolic drivers of obesity and selected inflammatory pathways rather than indiscriminate suppression of the immune system. Although experimental studies provide promising evidence for targeting inflammatory signaling, clinical translation remains challenging because many inflammatory pathways are also essential for host defense, tissue repair and immune surveillance. Future therapeutic approaches should therefore prioritize selective modulation of pathological immune-cell activity while preserving protective immune functions. A more precise understanding of the relationship between adipose immune responses, metaflammation and inflammaging may ultimately support personalized interventions for obesity-associated metabolic disease and age-related inflammatory disorders.

Table 3: Potential immune and inflammatory targets for the management of obesity-associated inflammation

Pathway	Proposed intervention	Mechanism	Preclinical evidence	Human evidence	Main limitation	References
CCR2/ CCL2 axis	Inhibition of CCR2/CCL2 signalling	Reduces recruitment of inflammatory monocytes/macrophages into adipose tissue	Reported reduction in adipose inflammation and/or metabolic dysfunction in experimental models	Limited /variable clinical evidence	Redundancy of chemokine pathways; effects on host immune surveillance	(Lee et al., 2020)
NLRP3 inflammasome	NLRP3 inhibition/modulation	Reduces activation of inflammasome-dependent IL-1β/IL-18 production	Evidence from experimental obesity models	Limited clinical translation	Long-term safety and effects on host defense	(X. Li, Ren, et al., 2023; Wen et al., 2012).
TNF-α signaling	TNF-α inhibition	Reduces a major pro-inflammatory pathway implicated in metabolic inflammation	Strong mechanistic/ preclinical evidence	Anti-TNF therapies are established for inflammatory diseases, but evidence for routine obesity treatment is limited	Infection risk; not established as an obesity treatment	(Guria et al., 2023; Randall & Meza-Perez, 2024)
IL-1β pathway	IL-1β/IL-1 receptor blockade	Reduces inflammatory signalling associated with metabolic dysfunction	Experimental and clinical metabolic studies	Human evidence exists but has not established routine use specifically for obesity-associated inflammation	Infection and other immune-related adverse effects	(X. Li, Ren, et al., 2023; Wen et al., 2012)
TLR4/NF-κB signalling	Pathway modulation	May reduce inflammatory responses to metabolic stress and nutrient-derived signals	Extensive experimental evidence	Limited evidence for targeted clinical application in obesity	Broad pathway involvement and potential off-target effects	(Chavakis et al., 2023; Qu et al., 2022).
Macrophage activation/ polarisation	Modulation of macrophage phenotype	Aims to reduce pro-inflammatory macrophage activity in adipose tissue	Strong experimental evidence	Limited direct clinical evidence	Macrophage phenotypes are dynamic; oversimplification of M1/M2 classification	
IL-6/JAK-STAT signalling	Targeted cytokine/signalling modulation	May reduce inflammatory and metabolic signalling	Experimental evidence	Clinical experience exists in other inflammatory diseases; obesity-specific evidence remains limited	Infection and immunosuppression concerns	(Bradley et al., 2024; Ghigliotti et al., 2014; Inflammation, 2009).

LIST OF ABBREVIATIONS

ABCA1: adenosine triphosphate (ATP)-binding cassette transporter A1
ASCs: adipose-derived stem cells
AT: adipose tissue
BMI: body mass index
CCL2: C-C motif chemokine ligand 2
CCR2: C-C motif chemokine receptor 2
CD11c: cluster of differentiation 11c
CD206: cluster of differentiation 206
CD4: cluster of differentiation 4
CD63: cluster of differentiation 63
CD69: cluster of differentiation 69
CD8: cluster of differentiation 8
CD9: cluster of differentiation 9
CLS: crown-like structure
Cx: connexin
Cx-43: connexin 43
DAMPs: damage-associated molecular patterns
FALCs: fat-associated lymphoid clusters
FFAs: free fatty acids
GJ: gap junction
HFD: high fat diet
HIF 1α: hypoxia inducible factor α
IFN-γ: interferon gamma
IgG: immunoglobulin G
IL-1 beta: interleukin-1β
IL-10: interleukin-10
IL-13: interleukin-13
IL-17: interleukin-17
IL-22: interleukin-22
IL-4: interleukin-4
IL-5: interleukin-5
IL-6: interleukin-6
IR: insulin resistance
MCP1: monocyte chemoattractant protein 1
MHC II: major histocompatibility complex II
NF-kB: nuclear factor kappa B
NK: natural killer
NKT: natural killer T cell
NLRP3: nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3
Plin2: perilipin 2
PPARγ: peroxisome proliferator-activated receptor gamma
SASP: senescence-associated secretory phenotype
T2D: type 2 diabetes
Th1: T helper 1
Th17: T helper 17
Th22: T helper 22
TNF: tumor necrosis factor
TNF-α: tumor necrosis factor-alpha
Tregs: regulatory T cells
Trem2: triggering receptor-expressed on myeloid cells 2
VAT: visceral adipose tissue
WAT: white adipose tissue

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CONFLICT OF INTERETS

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