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The gut microbiota as a versatile immunomodulator in obesity and associated metabolic disorders

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Obesity has reached epidemic proportions and is associated with chronic-low-grade inflammation and metabolic morbidities. Energy-dense diets and a sedentary lifestyle are determinants of obesity. The gut microbiome is a novel biological factor involved in obesity via interactions with the host and the diet. The gut microbiome act as a synergistic force protecting or aggravating the effects of the diet on the metabolic phenotype. The role of the microbiome in the regulation of intestinal and systemic immunity is one of the mechanisms by which it contributes to the host's response to the diet and to the pathophysiology of diet-induced obesity. Here, we review the mechanisms whereby “obesogenic” diets and the microbiome impact immunity, locally and systemically, focusing on the consequences in the gut–adipose tissue axis. We also review the structural and microbial metabolites that influence immunity and how advances in this field could help design

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microbiome-informed strategies to tackle obesity-related disorders more effectively.

Introduction

Obesity remains a significant public health challenge due to its high prevalence and associated conditions, including insulin resistance, type 2 diabetes (T2D) and cardiovascular disease. Obesity results from the interaction between genetic predisposition and an obesogenic environment. Genome-wide association studies for body mass index, waist-to-hip ratio, and other adiposity traits have identified more than 300 single-nucleotide polymorphisms associated with obesity [1]. However, the variation in obesity explained by genetic factors is relatively low (heritability) and, in clinical practice, not useful alone for early management of the obesity course in the majority of cases [2]. Instead, modifiable environmental factors are major contributors to excessive body-weight gain, making obesity largely preventable. These include high caloric intake together with other lifestyle factors, like low physical activity, stress, or sleep alterations.

The gut microbiome is a peculiar biological factor that mediates neuroendocrine and immune functions involved in body weight regulation and metabolic disease, such as T2D [3,4]. The microbiome structure and function partly depend on the host, but are also modifiable by the environment, particularly the diet, which could act in concert to favour a healthy or disease metabolic phenotype. Many observational studies support that gut microbiota alterations are associated with excessive body weight gain and obesity [5,6], T2D [7], and prediabetes [8,9]. The microbiome of individuals with metabolic disease is often characterized by low microbial diversity or richness, decreased butyrate production, and other enhanced functions, such as hydrogen sulphide and mucus degradation, compared with that of lean individuals [7]. Recent evidence also shows that long-term instability of the intestinal microbiome is associated with metabolic disease, such as T2D [9]. Furthermore, jejunal biopsies from obese individuals show increased immune cell density and enhanced mucosal inflammation, reducing the insulin sensitivity of enterocytes [10]. In contrast, adherence to a diet to induce weight loss not only improves metabolic outcomes but also restores the bacterial richness in the faeces [11] and immune populations in intestinal biopsies [12]. Moreover, transference of the faecal microbiota and replication of the metabolic phenotype of the donor in the recipient host has shown causation [13]. These and other studies show that microbial changes, partly driven by energy-dense diets, may influence adiposity, insulin resistance, and other hallmarks of obesity and metabolic syndrome [14]. Furthermore, specific microbiota signatures (like bacterial species) are consistently associated with a healthy metabolic phenotype in different population studies [15,16] and may help to predict metabolic outcomes [17]. In addition, the benefits of specific commensal bacteria in preclinical obesity models support causality, surpassing evidence provided by associative studies and predictive models [16]. Nonetheless, multiple mechanisms could be activated by microbe–diet interactions and contribute to defining the host metabolic phenotype.

Of special interest is the role the gut microbiome plays in regulating intestinal immunity and, thereby, local and systemic inflammation associated with energy-dense diets and obesity-complications, such as T2D. Although inflammation in the visceral adipose tissue was originally identified as a major cause of obesity-associated insulin resistance [18], we now know that the inflammatory state of obese individuals is elevated in many other organs and tissues, such as the liver, brain, and gut, and also contributes to insulin resistance and metabolic disease [19–21]. In fact, loss of intestinal immune homeostasis is considered an early step preceding the development of systemic low-grade inflammation associated with obesity and metabolic complications [22]. The intestine is both the largest immune organ of the body and the first site exposed to the effects of the diet and trillions of bacteria. Obesogenic diets (also known as energy-dense diets or Western diets) are known to exert a Pro-inflammatory effect that increases the risk of developing metabolic disease [23], which is

partly mediated by the dietary-induced microbiome changes [21]. Transference of the gut microbiota, resulting from the exposure to obesogenic diets, to a new recipient replicates the inflammatory tone of the donor along with the metabolic phenotype, highlighting its role as mediator of immune alterations in obesity [23,24]. Likewise, the gut microbiota resulting from the intake of healthy diets can change the host response to an obesogenic diet and protect from inflammation and adiposity [23].

In this review, we first present the current knowledge of the effects of obesogenic diets and the gut microbiota on intestinal immunity, emphasizing the role of innate immunity and innate lymphoid cells (ILCs) in driving obesity-associated inflammation. Second, we review the role of immune cells infiltrated in the adipose tissue in metabolic dysfunction and its connection with the microbiota via the gut–peripheral organ crosstalk. Finally, we provide an update on the understanding of how structural bacterial components and metabolites modulate the inflammatory immune dysregulation in obesity and the implications for tackling metabolic morbidities more effectively in the future.

How obesogenic diets and gut microbiota affect intestinal immunity

The intestinal immune system is governed by immunocompetent cells located along the intestinal epithelial surface and lamina propria which work in cooperation with epithelial cells. Its function is to maintain the delicate balance between the ability to mount a rapid defensive immune response against invading microbial pathogens and tolerance toward commensals. This equilibrium is maintained by tight regulation of the different branches of innate and adaptive immunity. In obesity, this harmonic cellular dialog is disrupted and compromises the immune function, as illustrated by chronic low-grade inflammation associated with obesity and a greater susceptibility to viral and bacterial infection and mortality in obese individuals [25,26].

The above observations are partly explained by the effect of obesogenic diets on both the intestinal immune system and the microbiota, which also interact. Obesogenic diets are rich in saturated fatty acids, which can trigger an inflammatory response in the gut and beyond [27]. Saturated fatty acids can be recognized by the CD14–TLR4 complex and trigger inflammatory pathways similar to the lipopolysaccharides (LPS) of Gram-negative bacteria [27]. Also, dietary fat *per se* affects the microbiota as mice fed isocaloric diets differing only in fat composition (either lard or fish oil, which are rich in saturated and polyunsaturated lipids, respectively) present dramatic changes in the microbial ecology [23]. Saturated fatty acids also lead to oxidative stress, thereby producing atherogenic lipids triggering an inflammatory response [27]. Simultaneously, high-caloric diets are low in fibre and deprive commensal bacteria of their main energy source and diminish the production of bacterial metabolites, such as propionate and butyrate. The latter is well-known to strengthen the gut barrier and stimulate the differentiation of regulatory T lymphocytes (Tregs) necessary for maintaining immune homeostasis [28]. An imbalanced diet and microbiota also weaken the intestinal barrier function, which eases the translocation of bacterial products triggering “metabolic endotoxemia” and systemic inflammation [29]. The effects on the physical gut barrier integrity have been widely reviewed and will not be discussed here [30,31]; instead, we describe the immune mechanisms activated in response to obesogenic diets that impact adiposity and insulin sensitivity (Fig. 1).

Intestinal innate immunity in obesity

The intestinal innate immune defences comprise secretions such as mucus and antimicrobial peptides, intestinal epithelial cells, ILCs, and myeloid cells. The release of mucus and antimicrobial peptides (AMPs) produced by goblet and paneth cells are one of the primary mechanisms of protection [32]. In animal models, exposure to an obesogenic diet causes the impairment of both defence systems. Everard et al. demonstrated that a high-fat diet blunts the expression of the AMPs (Reg3g and PLA2g2) in the intestine [33], and Schroeder et al. later showed that an obesogenic diet affected the penetrability of the colonic mucus layer [34]. In these two studies, the detrimental effects of the high-energy diets occur parallel to shifts in the microbial community, which could have secondary effects contributing to aggravation of the immune and metabolic phenotype in obesity. In fact, high-fat diet reduced the abundance of *Akkermansia* spp. while the administration a strain of *Akkermansia*

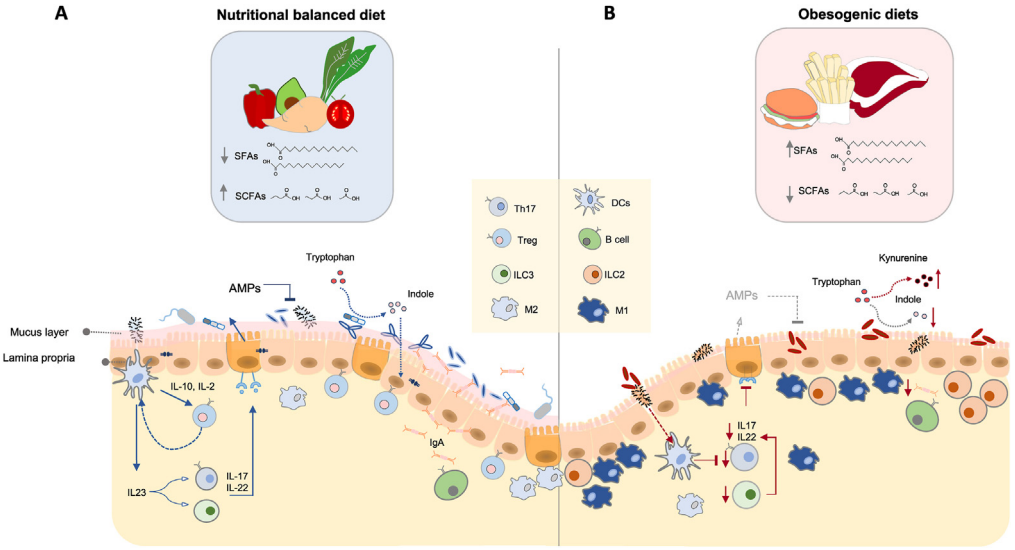

Fig. 1. **(A)** A well-balanced diet is rich in fruit and vegetables that prompt colonization by a highly diversified microbiota and provide fermentable substrates that the gut microbiota transforms into SCFAs. Epithelial cells control gut microbiota through the release of AMPs and secretory IgA by B cells. The immune system associated with the gut induces tolerogenic responses via DCs that induce Treg differentiation by releasing cytokines, such as IL-10 and IL-2, and stimulating ILC3s and Th17 responses by the release of IL-23. **(B)** In obesity, the gut microbiota is altered, and the species diversity reduced. A diet rich in saturated fat induces Pro-inflammatory responses directly by dietary components and mediated by a dysbiotic microbiota. There is also impaired production of AMPs and secretion of IgA. The gut microbiota sends signals that impair the functionality of DCs that hamper the Th17 response and Treg generation. Rupture of the intestinal homeostasis eases the recruitment of immune cells and interacts, aggravating the Pro-inflammatory milieu, which may precede systemic inflammation that worsens the metabolic disease. AMPs, antimicrobial peptides; DCs, dendritic cells; IgA, immunoglobulin A; ILCs, innate lymphoid cells; SCFAs, short-chain fatty acids; SFAs, saturated fatty acids; Tregs, T regulatory cells.

muciniphila restored the diet-induced downregulation of AMPs in obesity models, showing the direct involvement of specific commensal bacteria is the regulation of this defensive mechanism [33].

At the cellular level, the intestinal immune activation is initiated by pattern recognition receptors, such as Toll-like receptors (TLRs) or NOD-like receptors (NLPs), which sense microbe-associated molecular patterns (MAMPs), such as LPS, flagellin, and peptidoglycan (e.g., meso-diaminopimelic acid). Animal models genetically engineered to suppress the expression of TLRs have allowed links between the microbiota and the inflammatory immune dysregulation that occurs in obesity to be established. One of the first demonstration of this was achieved using TLR4 knockout (KO) mice and confirmed that TLR4 depletion protects against adipose tissue inflammation and insulin resistance [35]. Along the same line, TLR2 depletion prevents the effects of an obesogenic diet as it improves glucose tolerance, insulin sensitivity, and adipose tissue inflammation [36]. In contrast, TLR9 KO mice gained more weight under a high-fat diet and exhibited more severe glucose intolerance and insulin resistance, an effect associated with increases in M1 macrophages and Th1 cells in the adipose tissue [37]. NLP signalling is important to reduce diet-induced obesity and maintain the commensal microbiota. For example, NLRP12 depletion is associated with intestinal dysbiosis and increased obesity [38]. Furthermore, NOD1-deficient mice fed a high-fat diet present exacerbated systemic inflammation, changes in the microbiota, and worse metabolic phenotype [39].

Myeloid cells

Myeloid cells, and particularly those that play a role as antigen-presenting cells (APCs), such as dendritic cells (DCs) and macrophages, are part of the intestinal immune environment and prime adaptive immune cell responses [40]. In the steady-state, tolerogenic DCs can induce Treg

differentiation via cell–cell contact-dependent signalling and via cytokines such as IL-10 or IL-2 [41]. Tregs, in turn, also induce tolerogenic DCs [41]. Other DCs-derived cytokines (e.g., IL-23) regulate IL-17 and IL-22 production by Th17 cells and ILCs, promoting intestinal barrier function, and limiting microbial translocation [42]. In obesity, the protective effect of DCs on a high-fat diet challenge has been recently demonstrated using CD11c-hBcl2 mice (a model with increase lifespan and immunogenicity of DCs) [43]. The enhanced DC lifespan is translated into a phenotypic resistance to a high-caloric diet and the associated metabolic alterations, which is a protective effect mediated by the gut microbiota [43]. Specifically, under fat-enriched diet conditions, the microbiota of CD11c-hBcl2 mice behaves differently in terms of bacterial composition (lower amount of LPS and flagellin) and functions (increased butyrate), leading to lower immunogenicity and sustained immune tolerance [43]. Another study in wild type mice showed that feeding an obesogenic diet induced changes in the gut microbiota that caused the impairment of the APCs function, which in turn hampered the Th17 response [44]. The role of Th17 cells was demonstrated by increasing IL17-expressing cells in the intestine using dextran sodium sulphate (DSS) [44]. Interestingly, pretreatment with DSS prevented high-fat diet-induced glucose intolerance and insulinopenia [44]. Nevertheless, the role of Th17 cells in obesity remains controversial as other authors have reported conflicting conclusions [45]. Finally, Christ et al. went further and deciphered that a high-fat diet causes transcriptomic and epigenomic reprogramming of myeloid progenitor cells, which were long-lasting effects, as they remained after mice had returned to the control diet [46]. However, the potential relationship with the intestinal microbiota was not investigated.

The role of macrophages in adipose tissue is well established, and will be discussed below. However, the role of these APCs in the intestine has been less well studied, despite the gut comprising the largest macrophage reservoir in the body. Although some authors found no changes in the abundance of the

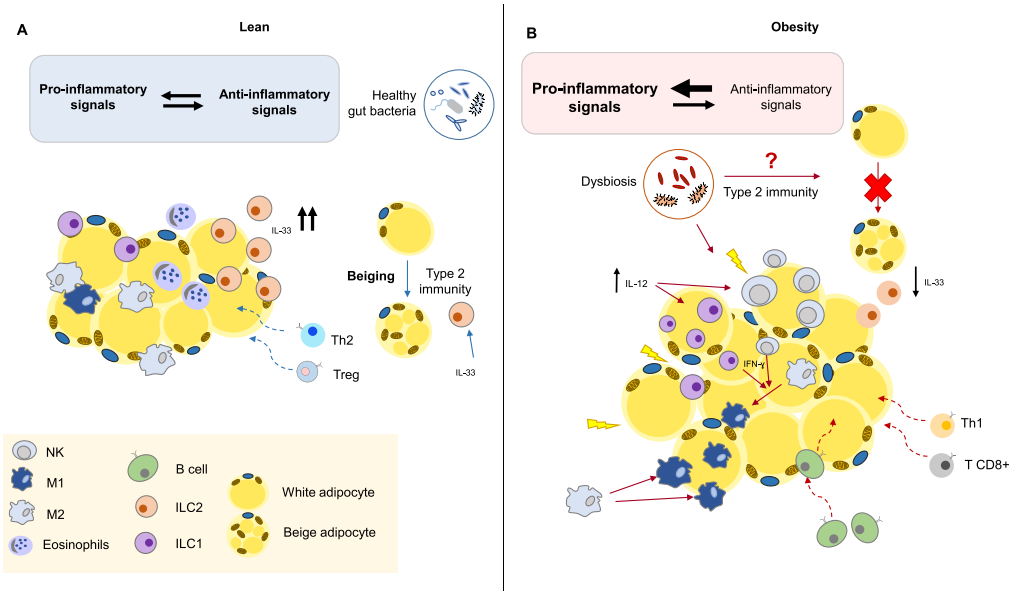

Fig. 2. **(A)** In the lean state, energy balance is tightly regulated by the crosstalk between adipocytes and immune cells. ILC2 acts via the release of IL-33 in the fat depots to play a protective role inducing a Th2-like response that eases beiging and improves metabolic health. **(B)** In obesity, expansion of the adipose tissue activates an inflammatory cascade. There is an increase of Pro-inflammatory signals (IFN-g, IL-12) and number of M1 macrophages, driven by increases in NK cells and ILC1s. There is also a decrease in ILC2, Treg, eosinophils, and Th2-type mediators. Overall, breakdown of the immune homeostasis reduces the thermogenic capacity of adipose tissue and worsens downstream obesity-related insulin resistance. ILCs, innate lymphoid cells; NK, natural killer; Tregs, T regulatory cells.

intestinal macrophages as a result of an obesogenic diet [44], our group recently reported an increase in the macrophages in the lamina propria that was restored by the administration of the combination of *Bacteroides uniformis* CECT 7771 with fibre [47]. These changes in macrophage numbers might impact metabolic health as different doses of an inhibitor to deplete macrophages correlates with improvements in glucose homeostasis in a dose-dependent manner, and the inhibition of colonic macrophage recruitment prevents insulin resistance [48].

Intestinal ILCs

ILCs are newly discovered tissue-resident cells described as the innate counterparts of T lymphocytes due to the lack of rearranged antigen receptors despite their lymphoid morphology. The nomenclature recently revised establishes five subsets: NK cells, ILC1s, ILC2s, ILC3s, and LTi [49]. Some evidence pinpoints a role for ILCs in obesity due to their presence in the adipose tissue, as discussed in the coming sections. However, ILCs are mainly localized in mucosal surfaces, such as the intestine, conferring high responsiveness to the gut microbiota and the diet [49].

At the intestinal level, attention has mainly focused on two subsets, ILC3s and ILC2s. Mice fed an obesogenic diet present reduced intestinal IL-22-producing ILC3s compared with control mice [50]. Despite representing less than 5% of intestinal lymphocytes, ILC3s are among the major source of IL-22, which is a cytokine with attributed protective effects on the gut barrier function and inflammation [50]. Accordingly, mice deficient in IL-22 receptor and fed a high-fat diet are prone to developing metabolic disorders [50]. Interestingly, another study showed that prebiotic supplementation restores the detrimental effects caused by an obesogenic diet via a microbial-dependent induction of IL-22 [51], and more recently, similar results have been reported following the administration of a symbiotic [47]. The potential of the microbiota to activate IL-22 production by ILC3s was also confirmed in vitro using a culture of human lamina propria mononuclear cells [52]. With regard to ILC2, Sasaki et al. confirmed the importance of ILCs in obesity and explicitly linked this effect with ILC2. To that end, the authors observed that *Il2rg*$^{-/-}$*Rag2*$^{-/-}$ mice (lacking all type of lymphocytes, including ILCs) presented resistance to obesity, and that the adoptive transfer of bone marrow cells from *Rag2*$^{-/-}$ mice (lacking T and B lymphocytes) to *Il2rg*$^{-/-}$*Rag2*$^{-/-}$ mice reversed this resistance [53]. The most interesting finding was to attribute to intestinal ILC2s, but not to adipose tissue ILC2s the induction of obesity. However, in this case, no clear association was found with changes in the intestinal microbiota [53].

Intestinal adaptive immunity in obesity

The adaptive immunity is also involved in the effects of the obesogenic diet. Among the best-studied cells are Th17 cells, which accumulate in the gut and secrete IL-17 and IL-22. These two cytokines are known for inducing the production of AMPs and tight junction proteins and, thereby, protect gut barrier integrity [54]. As stated above, animal models have shown that obesity development is followed by a reduction in Th17 cells that has been shown to exacerbate the metabolic response to the diet [44]. This detrimental effect was reproduced when axenic lean mice underwent a faecal transplant from obese mice, supporting this causal role of the microbiota in the induction of these immune changes [44]. Hong et al. reported that injections of *in vitro*-differentiated gut-tropic Th17 cells into obese *Rag1*$^{-/-}$ mice led to improved metabolism [55]. Together, these findings confirm that intestinal Th17 cells are shaped by intestinal microbiota and contribute to the maintenance of metabolic homeostasis, although controversial results have also been published. Another link between obesity and the adaptive immune system is the production of immunoglobulin A (IgA) by B cells, which is affected in obesity. As a key example, Luck et al. observed that diet-induced obesity led to a failure in the host defence due to reductions in IgA + cell producers and IgA + levels, which led to dysfunctional glucose metabolism [56]. Petersen et al. also related obesity with impairments in the IgA targeting gut bacteria [57]. In this case, this effect was responsible for an increase in *Desulfovibrio* and the reduction in *Clostridium*. Interestingly, *Clostridia*-colonized germ-free mice tempered the expression of CD36 (a receptor mediator of fat uptake) with beneficial metabolic effects, thus demonstrating a link between immune-mediated changes, gut microbiota, and obesity [57].

How obesogenic diets and gut microbiota affect the immune milieu in adipose tissue

Under normal energy balance conditions, adipocytes and immune cells work co-ordinately to regulate the storage or mobilization of energy according to the organism's needs. In obesity, expansion of the adipose tissue breaks this balance and activates an inflammatory response [58]. The primary events that occur in the adipose tissue during obesity are described below and are summarised in Fig. 2. The connections between intestinal and adipose tissue immune dysregulation and the role played by the microbiota are also discussed below.

Classic innate and adaptive immunity in obese adipose tissue

Both adaptive and innate immune systems participate in the chain of events that drive the metabolic damage linked to obesity. For instance, mice lacking adaptive immunity and fed a high-fat diet gained more weight than wild type mice [59]. Caesar et al. later reported that mice lacking innate immune components, such as MyD88, are protected against high-fat diet-induced inflammation and metabolic perturbations [23]. They also established a pivotal role for the gut microbiota in promoting adipose tissue inflammation via CCL2/MCP1, which ultimately leads to macrophages accumulation [23]. In general, infiltration of Th1, CD8+ T cells, and B cells has been related to the progression of inflammation in the adipose tissue and insulin resistance, an effect ligated to the release of pro-inflammatory signals and the accumulation of M1 macrophages [58,60,61]. In contrast, Treg cells and Th2 lymphocytes produce anti-inflammatory cytokines and improve insulin sensitivity and, overall, promote well-balanced adipose tissue homeostasis [62,63]. Interestingly, microbiome-based strategies, such as those based on the consumption of probiotic bacteria, have proven the potential to revert the immune alterations associated with a high-fat diet in the adipose tissue through regulatory effects initiated in the gut via the so-called gut–adipose tissue axis. Specifically, *A. muciniphila* reduces adipose tissue inflammation and glucose tolerance by increasing Treg cells [64], *Bifidobacterium pseudocatenulatum* CECT 7765 prevents M1 polarization and B cells infiltration in fat [61], and *B. uniformis* CECT 7771 reverses the immune-metabolic dysfunction by increasing Treg cells and reducing B cells and the M1/M2 macrophage ratio [65] in experimental models.

The role of ILCs in obese adipose tissue

Recent evidence suggests a role for some of the subtypes of ILCs in metabolic health, particularly ILC2s, ILC1s, and NK cells. In the case of ILC1s and NKs, human and animal studies have described that obesogenic diets increase their number and activation in the adipose tissue [66]. These changes are followed by the accumulation of Pro-inflammatory M1 macrophages in the adipose tissue, a well-documented event involved in developing metabolic disease [67–69]. Conversely, the depletion of both NKs and ILC1s using genetic tools or neutralizing antibodies improved obesity-induced insulin resistance and decreased adipose tissue M1 macrophage numbers [67–69]. Regarding the origin of the reported increases in NK cells and ILC1s in obesity, O'Sullivan et al. attributed this process to the cytokine IL-12 in an IL-12R and STAT4-dependent manner [69]. However, the mechanism that potentiates IL-12 expression in adipose depots during obesity remains unknown. Taken together, the evidence accumulated so far demonstrates that adipose NK cells and ILC1s act via modulation of macrophage polarization to control metabolic homeostasis. The potential role of the gut microbiota in this process remains unknown.

On the other hand, the immune response mediated by ILC2s promotes insulin sensitivity and glucose tolerance, which was attributed to increased eosinophil accumulation and macrophage polarization to M2-type macrophages [70]. One explanation is that the connection between ILC2s and their stimulatory cytokine IL-33 (namely ILC2/IL-33 axis) can promote beiging of white adipose tissue, limiting the development obesity [71,72]. Besides, the ILC2s/IL-33 axis is also involved in insulin

secretion at pancreatic islets [73]. A recent study described the molecular basis of the impairment in IL-33 signalling that occurs in obesity [74]. Specifically, overproduction of the soluble isoform of the ST2L receptor (called sST2) by adipocytes prevents IL-33 binding to its receptor [74]. In addition to the evidence from animal studies, human studies have shown that obesity and consumption of a high-fat diet are linked to decreased ILC2 in the adipose tissue [66]. These observations suggest a protective role of ILC2 in fat depots, in contrast to the detrimental effect of ILC2 in the small intestine [53]. Although no studies have clearly established an association between ILC2s and the gut microbiota, preliminary evidence suggests a possible link between the microbiota and beiging with type 2 immune response (a similar response as that induced by ILC2) [75]. Specifically, Suarez-Zamorano et al. observed that germ-free mice present increased beiging in the white adipose tissue, which was reverted by the intestinal recolonization with the commensal microbiota as well as by suppression of type 2 immune response signalling [75].

Structural and metabolic bacterial mediators of immune effects in obesity

Structural bacterial mediators of immune effects

One of the mechanisms by which the intestinal microbiota influences immunity in obesity is governed by bacterial structural components recognised by epithelial cells and innate immune cell receptors. First, the involvement of LPS from Gram-negative bacteria in obesity-associated inflammation was demonstrated by intraperitoneal infusion of LPS to the same blood levels as those observed in high-fat diet-fed mice, which recapitulated the obese phenotype induced by diet alone [29]. Observations in the opposite direction have been reported in the case of flagellin [76]. In particular, flagellin-immunised mice gained less weight and exhibited less adiposity than non-immunised animals, demonstrating that flagellin ameliorates diet-induced obesity [76]. Similarly, muramyl dipeptide (MDP; peptide derived from the bacterial peptidoglycan) limits metabolic inflammation and reduces insulin resistance via NOD2 signalling, and MDP injections reduce adipose inflammation in obese mice [77]. As LPS, flagellin, and MDP are present in the cell wall of many bacteria, the specificity of the reported effects can be questioned. However, it has been shown that the effects of LPS may largely vary depending on the origin (bacterial species and strains), and the consequences of these specificities remain to be elucidated. Mazmanian et al. made some progress in determining the role of some cellular structural components like the polysaccharide A (PSA) from the capsule of the species *Bacteroides fragilis*, which prevented intestinal inflammation by inducing IL-10 production in T cells [78]. Mechanistically, the PSA from *B. fragilis* activates TLR2 on CD4+ T cells to suppress the immune reaction. More recently, TLR2 signalling has also been identified as the molecular pathway through which a protein of the membrane *A. muciniphila* exerts anti-obesity effects [79]. Indeed, the administration of the membrane protein partially recapitulates the effects of *A. muciniphila* against obesity and insulin resistance in mice [79].

Bacterially produced metabolic mediators of immune effects

Deep shotgun sequencing has revealed the potential role of microbial gene functions and metabolites in determining the metabolic phenotype. Some studies have shown differences in the metagenome of obese individuals compare with lean individuals that are associated with metabolic outcomes [80,81]. Most of the information on the role of microbially produced metabolites in obesity has focused on short-chain fatty acids (SCFAs) generated from dietary fibre. Indeed, a proof-of-concept experiment in obese animals showed a reduction in obesity and insulin resistance after dietary supplementation with butyrate [82]. However, in contrast to animal studies, orally administered butyrate had no effect on both insulin sensitivity and energy expenditure in humans with metabolic syndrome

[83], but did in lean individuals [84]. The reported beneficial effect of butyrate involves the induction of a Treg response via the induction of tolerogenic DCs, a phenomenon mediated by the inhibition of histone deacetylation [85]. Similarly, propionate, another SCFAs, is also an inhibitor of histone deacetylation and induces Treg differentiation [86]. This control of intestinal inflammation may help to maintain immune homeostasis and integrity of the gut barrier. Indeed, SCFAs may also protect metabolic health by reinforcing the epithelial junctions and the production of AMPs [87].

Koh et al. investigated the detrimental effect of a gut microbiota-derived metabolite produced from histidine [88]. Specifically, this metabolite, called imidazole-propionate, can contribute to insulin resistance and, eventually, T2D [88]. The authors concluded that the shift in the gut environment resulting from dietary changes or altered immune response could contribute to the expansion of imidazole-propionate-producing bacteria [88]. On the other hand, accumulating evidence suggests that microbial metabolites produced from tryptophan are essential contributors to immune homeostasis. In particular, catabolites, namely indoles, play a key role as ligands of aryl hydrocarbon receptor (AhR, a transcription factor widely expressed by immune cells), providing new insights into how the microbiota can affect the immune system in obesity [89]. In this sense, the gut microbiota of subjects with metabolic syndrome presents a reduced capacity to metabolize tryptophan into derivatives that activate the AhR [90]. In agreement, an animal model of obesity also shows reduced production of AhR agonists, which was found to contribute to the pathogenesis of the disease through the reduction of IL-22 production [90]. In parallel, another study in obese or T2D individuals described a shift in tryptophan metabolism significantly correlated with deleterious metabolic and clinical consequences [75]. Microbial tryptophan metabolism deviates from the production of indole derivatives and IL-22 towards its degradation via the kynurenine pathway due to increased expression of indoleamine 2,3-dioxygenase in the intestine in obese individuals, which is involved in insulin sensitivity and chronic inflammation [91].

Summary

The intestine is emerging as an early contributor to systemic inflammation associated with obesity complications. The triggers for this inflammatory state have not been fully identified, but recent evidence unequivocally points to a role of gut microbiota and derived immune signalling molecules (bacterial structural components and metabolites) found to be altered in obese individuals. Studies in models are also contributing to demonstrate the causal role of specific microbiota changes, bacterial species and strains and bacterially-produced metabolites in regulating inflammatory immune dysfunction in obesity. In the light of these findings, the future use of microbiota modulation strategies together with healthier dietary habits, hold promise for the prevention and mitigation of obesity-associated complications.

Practice points

- Obesity and its metabolic comorbidities are associated with an inflammatory immune dysregulation initiated in the intestine, which represents a therapeutic target.
- Diet-induced microbiota changes cooperate with the diet to protect or aggravate the metabolic phenotype in obesity via immune-mediated mechanisms.
- Commensal bacteria could ameliorate the adverse effects of obesogenic diets on immunity and reduce the disease risk in study models, which holds promise for tackling obesity more effectively.

Research agenda

- Establishing the significance of early immune events that occur in the intestine and the window of opportunity for intervention to prevent or intercept metabolic complications.
- Deciphering the role of recently discovered immune components, such as the innate lymphoid cells, in obesity and the interactions with the microbiota.
- Defining the precise mechanisms of action of bacterial components or metabolites to accelerate their use in nutritional and clinical practice.

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