Review

Omega-3-derived mediators counteract obesity-induced adipose tissue inflammation

Esther Titos a, b, *, Joan Claria a, b, c

a Department of Biochemistry and Molecular Genetics, Hospital Clinic, Centre Esther Koplowitz (CEK), IDIBAPS, Barcelona 08036, Spain
b CIBERehd, Barcelona 08036, Spain
c Department of Physiological Sciences I, University of Barcelona, Barcelona 08036, Spain

ABSTRACT

Chronic low-grade inflammation in adipose tissue has been recognized as a key step in the development of obesity-associated complications. In obesity, the accumulation of infiltrating macrophages in adipose tissue and their phenotypic switch to M1-type dysregulate inflammatory adipokine production leading to obesity-linked insulin resistance. Resolvin are potent anti-inflammatory and pro-resolving mediators endogenously generated from omega-3 fatty acids that act as “stop-signal” of the inflammatory response promoting the resolution of inflammation. Recently, a deficit in the production of these endogenous anti-inflammatory signals has been demonstrated in obese adipose tissue. The restoration of their levels by either exogenous administration of these mediators or feeding omega-3-enriched diets, improves the inflammatory status of adipose tissue and ameliorates metabolic dysfunction. Here, we review the current knowledge on the role of these endogenous autacoids in the resolution of adipose tissue inflammation with special emphasis on their functional actions on macrophages.

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Contents

1. Lipid mediators in inflammation and resolution .................................................. 00
2. Obesity as a metabolic inflammatory disorder ................................................... 00
3. SPM and resolution of adipose tissue inflammation ........................................... 00
4. Immune cells in adipose tissue inflammation .................................................... 00
   4.1. Macrophages ............................................................................................... 00
   4.2. Neutrophils ............................................................................................... 00
   4.3. Lymphocytes .............................................................................................. 00
   4.4. Eosinophils ............................................................................................... 00
   4.5. Mast cells .................................................................................................. 00
5. Mechanisms of resolution in adipose tissue inflammation ................................. 00
6. Conclusions ......................................................................................................... 00
Acknowledgements ................................................................................................. 00
References ................................................................................................................ 00

1. Lipid mediators in inflammation and resolution

Inflammation is an adaptive response to infection or tissue injury. Its purpose is to localize and eliminate the injurious agent and remove damage tissue components in attempt to restore homeostasis. The onset of the inflammatory response is a well known process that involves a complex interplay of soluble and cellular components and it is primarily characterized by changes in blood flow, an increase in permeability of blood vessels, and migration of fluid, proteins and white blood cells from the circulation to the site of damage [1,2]. The termination of the inflammatory response, also known as resolution, is less characterized but recent studies indicate that it is not a passive process but rather it is a highly orchestrated program coordinated by a complex regulatory network of cells and mediators that switch inflammation off in a specific time-limited manner [3]. Consequently, current scientific
Efforts are aimed at identifying the exact molecular pathways and cellular components of this resolution and tissue-repair phase. Their characterization may help combat pathological conditions derived from unresolved acute and chronic inflammatory processes leading to tissue damage and loss of function.

Several lipid mediators derived from the metabolism of essential polyunsaturated fatty acids have been postulated as molecules facilitating the resolution of inflammation. In this regard, lipoxins (LX), generated from the omega-6-polyunsaturated fatty acid (PUFA) arachidonic acid, and resolvins and protectins, endogenously generated from omega-3-PUFAs, are paradigmatic examples of this genus of anti-inflammatory and pro-resolving (Fig. 1). These endogenous anti-inflammatory and pro-resolving mediators, collectively termed specialized pro-resolving mediators (SPM), counteract the effects of pro-inflammatory signaling systems and act as ‘braking signals’ of the persistent vicious cycle leading to unremitting inflammation [4]. In fact, the formation of these mediators follows a temporal order of events and a precise molecular program which is conserved for the effective resolution of the inflammatory response. Initially, tissue injury, microbes and surgical trauma all activate the local formation of vasoactive amines, lipid mediators, cytokines and chemokines which coordinate the initial events of acute inflammation. Of special interest in this process is the biosynthesis of cyclooxygenase (COX) and 5-lipoxygenase (5-LO)-derived eicosanoids such as prostaglandins (PGs) and leukotrienes (LTs) [4] (Fig. 1). These eicosanoids modify vascular permeability, blood flow and vascular dilation needed for the recruitment of inflammatory cells (i.e. leukocytes) from the peripheral circulation to the inflammatory site via adhesion to the endothelial cells and diapedesis. These changes are permissive for the initial increase in protein exudation and PMN accumulation in the inflamed tissue, which efficiently destroy the injurious insult. However, the same factors that initially trigger the inflammatory response also signal the termination of inflammation by stimulating the biosynthesis of pro-resolving lipid mediators [5]. For instance, both PGE2 and PGD2 transcriptionally activate the expression of 15-LO in human PMN, switching the mediator profile of these cells from the pro-inflammatory LTB4 to the anti-inflammatory LX4, which was the first identified omega-6-PUFA-derived lipid mediator with consolidated immunomodulatory and anti-inflammatory properties [3].

The biosynthesis of LXs from endogenous sources of arachidonic acid has been previously described elsewhere [6,7]. Briefly, LXs are trihydroxy-eicosatetraenoic acids generated by transcellular routes from endogenous sources of the omega-6-PUFA-arachidonic acid [6]. A major route of transcellular LX biosynthesis is initiated by 15-lipoxygenase (15-LO) forming 15S-hydroxyeicosatetraenoic acid (15S-HETE), which is rapidly converted to LX4 by 5-LO [8] (Fig. 1). Another major route of transcellular biosynthesis produces LXs of different stereochemistry, the 15-epi-LXs, generated either by COX-2 in an aspirin (ASA)-dependent manner or by cytochrome P450 enzyme in the absence of ASA. In the first identified circuit, biosynthesis of 15-epi-LXs also called “aspirin-triggered” LXs, is initiated by ASA-acetylated COX-2 [9] (Fig. 1). Briefly, when ASA inhibits PG formation in cells bearing a cytokine-induced COX-2, the resulting ASA-acetylated COX-2 converts arachidonic acid into 15R-HETE, rather than the 15S-enantiomer. Alternatively, and in the absence of ASA, cytochrome P450 significantly contributes to the formation of 15R-HETE from arachidonic acid [10]. Subsequently, 15R-HETE is transformed by 5-LO of activated neutrophils into 15-epi-LXs, which carry the carbon-15 alcohol in the R configuration, instead of the S as in the native LXs [9]. These SPM act as “stop-signals” for inflammation and inhibit leukocyte chemotaxis, adhesion to and transmigration across endothelial monolayers in
response to LTB_{4} [5]. LX stable analogs inhibit in vivo LTB_{4}-induced leukocyte rolling, adherence, margination and extravasation and when applied topically to mouse ears they dramatically inhibit leukocyte infiltration and vascular permeability [5].

Another example of this class switch is the displacement of pro-inflammatory lipid mediators derived from omega-6-PUFAs by anti-inflammatory mediators (i.e. resolvins and protectins) derived from omega-3-PUFAs [11] (Fig. 1). These anti-inflammatory and pro-resolving mediators exert a strict control of the resolution process and not only stop PMN and eosinophil functions but also pave the way for monocyte migration and their differentiation to phagocytosing macrophages, which remove dead cells and then terminate the inflammatory response [4,12]. Resolvins are endogenously generated from the omega-3-PUFAs docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). Resolvins are classified as either resolin E-series if they are generated from EPA, or resolin D-series if the biosynthesis is initiated from DHA [11,13] (Fig. 1). DHA is transformed by the sequential enzymatic actions of 15-LO and 5-LO or by an acetylated COX-2 to D-series resolvins [11,13] (Fig. 1). Alternatively, DHA can also be metabolized through an enzymatic epoxidation mechanism to form protectin D1 (PD1) (Fig. 1) [11,13,14]. Similarly, sequential enzymatic actions of cytochrome P450 and 5-LO or ASA-treated COX-2 are responsible for the generation of E-series resolvins from EPA (Fig. 1) [11,13,15]. Resolvins and protectins are biologically more potent than their DHA and EPA precursors exerting significant anti-inflammatory and pro-resolving effects through their binding to G-protein coupled receptors [16,17]. Resolvins have been shown to exert anti-inflammatory and protective actions in vivo in several experimental disease models of acute inflammation by decreasing and limiting PMN infiltration and T cell migration, promoting macrophage phagocytosis of apoptotic PMN and macrophage eflux into lymphatics, and reducing the production of inflammatory cytokines such as TNFα and IFNγ [14–23]. More information on the actions of resolvins can be found in Rius et al. [7].

2. Obesity as a metabolic inflammatory disorder

The rise in worldwide obesity has triggered a dramatic increase of obesity-related health problems, including insulin resistance, type 2 diabetes, dyslipidemia, cardiovascular disease and non-alcoholic fatty liver disease [24]. Given the increasing prevalence of obesity among young children [25], obesity is currently considered the major healthcare concern for developed countries.

A considerable effort has been made during the last two decades to elucidate the molecular factors responsible for obesity-associated co-morbidities, and as a result, it is now well established that the key pathogenic mechanism is the presence of a “low-grade” state of inflammation in the white adipose tissue [26,27]. This “low-grade” inflammation, also known as “metabolic-triggered inflammation” or “metainflammation”, can be described as a long-term inflammatory response triggered by nutrients and metabolic surplus [27]. It involves a similar set of molecules/signaling pathways to those involved in classical inflammation, but in obesity-induced inflammation these molecules/signaling pathways have a dual role as inflammatory mediators as well as regulators of energy storage and metabolism. In fact, a rise in pro-inflammatory cytokines and adipokines such as TNFα, IL-6, IL-1β, monocyte chemoattractant protein-1 (MCP-1), leptin and resistin accompanied by a reduction in the anti-inflammatory and insulin-sensitizing adipokine, adiponectin has been reported to signal the onset of metabolic dysfunction [28]. One of the most important sequelae of adipose tissue inflammation is insulin resistance. In general, several casual factors present in this inflammatory milieu converge on a series of stress-activated kinases that target intermediates in the insulin signaling pathway. In fact, stress sensors activate both the c-Jun-N-terminal kinase (JNK) and inhibitor of κ kinase (IKK) pathways through classical receptor-mediated mechanisms [29]. JNK and IKK activation induce insulin resistance by disrupting serine phosphorylation of IRS-1, a protein that connects the insulin receptor to the PI(3)K signaling cascade. In parallel to the activation of these kinases and their downstream signaling cascades, there is an increased production of pro-inflammatory adipokines (i.e. TNFα, IL-6, and MCP-1) in obese subjects, whose levels directly correlate with the degree of glucose intolerance and insulin resistance [30].

The presence of a chronic state of unresolved inflammation in obesity appears to be also driven by a deregulated balance between the activation of pro-inflammatory arachidonate-derived lipid mediators and the impaired biosynthesis of SPM in adipose tissue. Indeed, over-expression of Five-LO-Activating Protein (FLAP) is a common finding in adipose tissue of patients and animals with obesity and insulin resistance [31,32]. Moreover, linkage studies have identified 5-LO as a gene with pleiotropic actions on adipose fat accumulation and pancreatic function [33]. The ability of adipose tissue to generate 5-LO-derived products has recently been challenged by Horrillo and collaborators [32]. These authors have demonstrated the presence of all enzymes necessary for the formation of 5-LO products (5-LO, FLAP, LTA₄ hydrolase, and LTC₄ synthase) as well as all receptors involved in LT signaling (BLT1, BLT2, CysLT1, and CysLT2) in adipose tissue of both lean and obese mice [32]. Importantly, adipose tissue samples from obese mice showed increased formation of 5-LO products, mainly LTB₄ [32]. Similar findings have been reported in visceral adipose tissue from obese Zucker rats [34]. An important observation of the study by Horrillo et al. was that LTB₄ unequivocally triggered an inflammatory response in adipose tissue by inducing the nuclear translocation of p50 and p65 subunits of NF-κB [32]. Secondary to LTB₄-induced NF-κB activation, there was an enhanced release of MCP-1 and IL-6, which directly connect adipose tissue inflammation with insulin resistance and hepatic steatosis [32]. The physiological consequences of these changes in adipose tissue function were corroborated in vivo by observing that either pharmacological inhibition of the 5-LO pathway or genetic deletion of Alox5, the gene coding for 5-LO, alleviated insulin resistance and hepatic steatosis in obese animals [32,35].

In addition to increased activity of inflammatory eicosanoid-generating pathways, obesity is associated with a deficit in the production of SPM. In particular, and although a large heterogeneity in the fatty acid composition and fundamental differences among fat depots [36–38], a deficit in the production of omega-3-derived SPM is a common feature for inflamed subcutaneous and visceral adipose tissue [38–40]. Specifically, a deficit in the production of RvD1 and PD1 and the metabolic precursors 14-HDHA, 17-HDHA and 18–HEPE has been recently demonstrated in inflamed visceral and subcutaneous obese adipose tissue [39,40]. This deficit in pro-resolving mediators has also been observed in non-obese patients with peripheral vascular disease in whom the inflammatory status of subcutaneous adipose tissue is remarkably enhanced [38–41]. This finding suggests that both inflammatory processes share similar mechanisms for the impaired production of SPM. Interestingly, a major difference exists in the SPM profile in adipose tissue surrounding systemic vessels. In fact, perivascular fat from patients with perivascular disease display an enhanced capacity of SPM biosynthesis as compared to subcutaneous fat suggesting the activation of resolution circuits in this anatomic depot [38].

Whether these differences in the SPM profile between the three major fat depots (i.e. visceral, subcutaneous and perivascular) are also present in obese individuals and whether impaired SPM formation in visceral adipose tissue also implies a deficit in the response to these mediators are questions that need to be addressed. However, and taking into account that visceral
adipose tissue inflammation is the pivotal pathogenic link between abdominal obesity and the metabolic complications, impaired SPM production in the visceral compartment represents a major player in the development of chronic low grade inflammation in obesity.

3. SPM and resolution of adipose tissue inflammation

Nutrition is considered an environmental factor of major importance in health and disease. In fact, nutritional and evolutionary studies indicate that ratio between omega-6 and omega-3 fatty acids in the Western diet has transitioned in parallel with our sociocultural evolution from a balanced situation during the pre-industrialized period to an increased intake of omega-6 and saturated fats in our industrialized societies favoring the formation of proinflammatory eicosanoids [42]. This is relevant in terms of pathophysiology because it has appeared at the same time as the so-called diseases of civilization, namely inflammatory, immune and metabolic diseases.

Based on these observations, enhancement of natural host defenses and formation of anti-inflammatory and pro-resolution mediators represent an emerging strategy to combat inflammation. Such therapeutic approaches might be based on the use of dietary supplements enriched in omega-3 PUFAs that boost the formation of endogenous anti-inflammatory signals, such as resolvins and protectins, or by the exogenous administration of these bioactive lipid autacoids together with the use of stable LX analogs that may expedite resolution of inflammation in the obese adipose tissue.

The beneficial actions of omega-3 fatty acids in inflammation were initially described in 1989 by Endres et al. [43]. Since then, supplementation of omega-3 fatty acids has proven to exert overall benefits in obesity and metabolic syndrome both in human and rodent studies [44]. In humans, a number of pre-clinical and clinical studies have demonstrated that regular consumption of modest amounts of omega-3 PUFAs (<3 g/day) improves serum lipid profiles, exerts cardiovascular protective actions, and may reduce the risk of conversion from impaired glucose tolerance to type 2 diabetes [45]. In animal studies, omega-3 PUFAs are protective against adipose tissue inflammation and obesity-related complications including insulin resistance, dyslipidemia, cardiovascular disease and NAFLD induced by a high-fat diet [46–49]. In a very comprehensive study, González-Périz et al. have demonstrated that administration of an omega-3-enriched diet to ob/ob mice, an experimental model of obesity and fatty liver disease, resulted in increased adiponectin levels and reduced insulin resistance and hepatic steatosis [46]. These changes occurred in parallel with augmented formation of omega-3-derived SPM (mainly RvD1 and PD1) in adipose tissue, while formation of the omega-6-derived products PGE2, 5-HEPE and LTB4 was significantly inhibited [46]. Similar findings were recently reported by Neuhofer et al. [40] in leptin receptor-deficient (db/db) obese/diabetic mice. In this study, a dietary omega-3-PUFA treatment decreased adipose tissue inflammation and improved insulin sensitivity in parallel with a dramatic increase in 17-HDHA, PD1 and 18-HEPE levels [40].

Consistent with these findings, mice with transgenic expression of the worm Caenorhabditis elegans fatty acyl desaturase (fat-1), which endogenously converts omega-6 into omega-3 PUFAs, display reduced body weight and improved glucose tolerance [50] and are protected from obesity-linked inflammation and insulin resistance upon high-fat feeding [51,52].

SPM have been shown to reproduce the anti-inflammatory and pro-resolution actions of omega-3 PUFAs. Indeed, intraperitoneal injection of nanogram doses of RvE1 elicited significant insulin-sensitizing effects by inducing adiponectin, GLUT-4 and IRS-1 expression in adipose tissue and conferred significant protection against hepatic steatosis [46]. Furthermore, PD1 increased adiponectin expression in adipose tissue explants from ob/ob mice to a similar extent as that of the insulin-sensitizing agent rosiglitazone [46]. Moreover, RvD1, RvD2 and 17R-RvD1 induce adiponectin secretion while reducing leptin in adipose tissue explants from obese mice [39]. In addition, these SPM reduce IL-1β, TNFα and IL-12 secretion in adipose tissue [39]. Importantly, RvD1 is a potent inducer of macrophage phagocytosis and enhances the phagocytic activity of macrophages from the adipose tissue stromal vascular cell fraction [53]. Similarly, in db/db obese/diabetic mice, nanogram doses of RvD1 improved glucose tolerance, decreased fasting blood glucose, and increased insulin-stimulated Akt phosphorylation while reducing the formation of crown-like structures rich in inflammatory macrophages in adipose tissue [54]. Intraperitoneal injection of nanogram doses of 17-HDHA (the precursor of RvD1) to obese mice has been shown to improve glucose tolerance and insulin sensitivity by increasing PPARγ, PPARα, GLUT-4 and adiponectin. Moreover, 17-HDHA elicited anti-inflammatory effects in these mice by reducing the expression of pro-inflammatory cytokines MCP-1, TNFα, IL-6 and osteopontin in adipose tissue [40]. Recent findings also have demonstrated that local application of RvD1 accelerates wound healing in db/db mice [55]. Similar beneficial actions in adipose tissue have been described for LXA4 in an experimental model of age-associated adipose inflammation [56].

4. Immune cells in adipose tissue inflammation

Immune cells from innate and adaptive immunity (i.e. macrophages, eosinophils, mast cells and regulatory T cells (Treg)) that reside in lean adipose tissue contribute to normal insulin signaling through mechanisms that maintain normal tissue homeostasis [57,58]. Upon an inflammatory response, these resident adipose tissue immune cell populations shift in phenotype and numbers in a coordinated way that differs somewhat between an acute and a chronic process. For instance, in an acute inflammatory response neutrophils are the first immune cells to respond to inflammation followed by recruitment of monocytes and adaptive cells to promote cell clearance and prepare tissue for the resolution. In a chronic inflammatory disease, the injury stimulus persists (bacteria or injury signals), and the plethora of the inflammatory cascade is mainly driven by monocytes and long-lived macrophages. In fact, in obesity-induced sterile inflammation, adipose tissue macrophages are considered the primary cells responsible for chronic low-grade inflammation and derived insulin resistance [59,60]. The role of other immune cells in insulin resistance is less characterized but it seems likely that these cells exert their main effects by modulating the polarization or activation state of adipose tissue macrophages [61].

4.1. Macrophages

The presence of an increased number of adipose tissue-infiltrating macrophages is a pathological hallmark of obesity. Macrophages encircle and phagocytose necrotic adipocytes forming the so-called “crown-like structures” which perpetuate a vicious cycle of macrophage recruitment and exacerbated production of pro-inflammatory mediators [62–65]. Consistent with this view, the disruption of central pro-inflammatory pathways within macrophages by creating myeloid cell-specific knockouts of IKK-beta, JNK-1 or Toll-like receptor 4 (Tlr4), the upstream component of these signaling pathways, protects mice from diet-induced insulin resistance [66–68]. Importantly, obesity induces a phenotypic switch in macrophages toward a classically activated M1-like phenotype [69] (Fig. 2). These inflammatory tissue macrophages selectively secrete high amounts of TNFα, IL-1β and IL-6 and express the

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cell surface markers F4/80, CD11b and the dendritic cell marker CD11c [70,71] (Fig. 2). In our laboratory, we have recently gathered data indicating the presence of a specific subset of macrophages with high expression of the surface glycoprotein F4/80 (F4/80hi) in adipose tissue from obese mice [53]. This finding is consistent with that reported by Bassaganya-Riera et al. [72] who identified two functionally distinct subsets of macrophages in adipose tissue based on their surface expression of F4/80 (F4/80lo) macrophages predominately in adipose tissue of lean mice, obesity causes accumulation of both F4/80lo and F4/80hi. Importantly, lean adipose tissue macrophages are M2-like, display F4/80 and CD11b but are negative for CD11c and do not exhibit activation of the inflammatory pathways (Fig. 2). In a series of elegant studies, Lumeng et al. [70] and Nguyen et al. [71] have demonstrated that adipose tissue macrophages undergo a phenotypic switch from the M2 polarization state to a more M1-like, CD11c+ polarization state upon high-fat feeding. Moreover, Patsouris et al. [73] have reported that selective depletion of CD11c+ macrophages in adipose tissue reverses insulin resistance in high-fat diet-induced obese mice. Recently, Li et al. [74] have reported that the M1-like, CD11c+ macrophage subset can exhibit phenotypic plasticity between inflammatory and non-inflammatory states, depending on the presence or absence of insulin resistance.

4.2. Neutrophils

The role of these cells in adipose tissue inflammation is poorly understood. However, despite being considered temporary infiltrating cells, with a short life-span, they exert an important immune modulatory role at early stages of the disease. Recent findings by Talukdar et al. [75] have demonstrated the presence of a sustained neutrophil infiltration after 3 days of acute high-fat feeding in mouse adipose tissue. Importantly, secreted elastase from neutrophils seems to be a key effector of inflammation-derived insulin resistance by activating signaling pathways which triggers pathogen-eating macrophages to secrete proinflammatory cytokines [75]. In addition, an imbalance between the neutrophil elastase and its inhibitor, α-1 antitrypsin, causes inflammation, obesity, insulin resistance and fatty liver in mice and humans providing a new unexpected role for neutrophils in metabolic disease [76].

4.3. Lymphocytes

Intensive studies in rodents and humans suggest that sub-sets of infiltrating adaptive immune cells may represent a primary event in the initiation of adipose tissue inflammation and development of insulin resistance probably by stimulating preadipocytes to induce MCP-1-induced recruitment of macrophages [77]. Diet induced obesity leads to an orchestrated trafficking initially of B cells, T helper 1 polarized T (Th1) cells, which express the surface marker CD4+, and effector T cells, which express the surface marker CD8. At later stages of adipose tissue expansion, accumulation of inflammatory macrophages and natural killer cells occurs in parallel to the appearance of insulin resistance [78,79]. However this temporal pattern of T cell recruitment during obesity development is under discussion because Strissel et al. [80] found that Th1 cells did not increase until 20 weeks of high-fat feeding, several weeks after the appearance of infiltrated macrophages and insulin resistance in adipose tissue [80]. In addition there is considerable controversy over the precise subset of T cells that is important in the progression of adipose tissue inflammation with some studies suggesting a role for CD8+ T [81] while others postulating a role for CD4+ Th1 cells [82].

B cells can also accumulate in mouse visceral adipose tissue earlier than T cells or macrophages and prior to the appearance of
insulin resistance [78]. Moreover, infiltrated B cells can promote the activation of T cells that potentiate M1-like macrophage polarization and development of insulin resistance [83].

Special attention has been given to tissue Treg. This is a sub-set of immune suppressive CD4+ T<sub>H</sub> cells, which express forkhead-winged-helix transcription factor (Foxp3) and play a critical role in modulating tissue inflammation via interactions with several components of the immune system [84]. Different studies have reported that lean adipose tissue contain high numbers of these cells whereas a dramatic decrease is observed in obese fat [82, 85, 86]. Importantly, adoptive transfer of Treg or their targeted activation and proliferation improve adipose tissue inflammation and ameliorate insulin resistance in ob/ob mice [87, 88]. This is controversial because a recent observation in obese patients does not support the existence of an obesity-associated loss of Treg in human visceral adipose tissue as would have been expected from animal studies. By contrast, a functional failure in the augmented T<sub>8</sub>2 and Treg subsets could explain the correlation between the increase in these populations and obesity-induced inflammation in humans [89].

4.4. Eosinophils

Eosinophils are innate immune cells typically associated with allergy and worm infection and more recently also linked to metabolic homeostasis. This new concept arose from data published by Wu et al. [90] showing that eosinophils were significantly reduced in adipose tissue from obese mice. In this study eosinophils helped controlling adipose tissue inflammation and insulin sensitivity by promoting the polarization of adipose tissue macrophages toward an M2-like phenotype. Eosinophils are the main cells expressing M2-inducing cytokines such as IL-4 and IL-13 in adipose tissue, and, in their absence, the number of M2-like macrophages is greatly reduced and animals become more obese and glucose resistant. In addition, increasing eosinophil counts in helminfected mice on a high-fat diet program has been shown to improve insulin sensitivity and glucose tolerance and to decrease the total number of adipose tissue macrophages [90].

4.5. Mast cells

Mast cells are well known for their role in allergy and anaphylaxis, but, similar to eosinophils, they also seem to play a role in obesity. Liu et al. [91] have reported an increase in mast cells in visceral fat from obese mice. Moreover, genetic depletion or pharmacological stabilization of mast cells appear to reduce body weight gain, to attenuate inflammatory responses and to improve glucose homeostasis and energy expenditure [91].

5. Mechanisms of resolution in adipose tissue inflammation

Cellular processes involved in resolution of inflammation include macrophage engulfment of apoptotic neutrophils (effrocytosis), macrophage efflux into lymphatics, phenotypic switching of macrophages to a pro-resolving phenotype and recruitment of Treg. Many of these cellular processes are facilitated by SPM during the initial resolution phase to effectively repair and restore tissue architecture and function.

In this regard, SPM are able to induce changes in the status of macrophage polarization toward a pro-resolution phenotype. A recent study from our laboratory has demonstrated that RvD1 consistently induces M2 polarization of adipose tissue macrophages [53]. The first observation of this study was that DHA did not modify the total number of macrophages in obese adipose tissue, but markedly reduced the percentage of CD11b<sup>high</sup>F4/80<sup>high</sup> expressing cells in parallel with the emergence of low-expressing CD11b/F4/80 macrophages, suggesting a phenotypic switch in macrophage polarization. Indeed, we further demonstrated that DHA and RvD1 up-regulate a complete panel of M2 markers including IL-10, CD206, RELM-<i>α</i> and Yam1, and remarkably stimulated arginase 1 expression while promoting nonphlogistic macrophage phagocytosis and attenuating IFNγ/LPS-induced T<sub>1</sub> cytokine secretion [53] (Fig. 2). These results were in agreement with those reported by Helleman et al. [54], who showed the ability of RvD1 to improve insulin resistance in obese-diabetic mice, by reducing macrophage F4/80<sup>CD11c<sup> expression and increasing the percentage of positive F4/80 cells expressing the M2 marker Mgl-1 in adipose tissue. More recently, obese mice treated with 17-HDHA showed a reduced ratio CD11c<sup>+</sup> to CD206<sup>+</sup> adipose tissue macrophages [40] supporting the notion that SPM target tissue macrophages. The ability of resolvins to modify macrophage plasticity has also been demonstrated by Schif-Zuck et al. [22], who reported that administration of RvD1 and RvE1 to peritonitis-affecte mice enhances the appearance of pro-resolving CD11b<sup>low</sup> macrophages by enhancing their immune –silencing and satiation that is, by reducing the number of engulfment-related events required for macrophage deactivation and by reducing the ability of peritoneal macrophages to produce pro-inflammatory cytokines upon LPS stimulation. As the majority of macrophages that accumulate in obese adipose tissue are M1 inflammatory type, these findings are a strong argument in favor of the pro-resolution actions of omega-3-derived mediators in obese adipose tissue.

The interaction of SPM with adaptive immune cells in the resolution of adipose tissue inflammation is still an unknown research field. Based on other inflammatory processes as allergic asthma, one could speculate that RvE1 would promote the resolution of the inflammatory response by down-regulating T<sub>17</sub> – inflammatory responses by directly suppressing the release of IL-23 by dendritic cells [19]. In fact, a recent study from Bertola et al. [92] have suggested a dendritic cell–depending induction of T<sub>17</sub> responses in obese adipose tissue from mice and humans. In addition, and taking into account that eosinophils and Treg cells could be acting as potent cellular mediators of resolution it would be very interesting to study SPM generation and their effects on these cells during the course of the disease.

6. Conclusions

The prevalence of obesity-related metabolic disorders such as type 2 diabetes, dyslipidemia, cardiovascular disease and fatty liver disease, is tightly associated with the appearance of a chronic “low-grade” inflammatory state in the adipose tissue, which severely disrupts the endocrine function of this organ. Indeed, a number of studies have appreciated that changes in the size of adipocytes during the expansion of adipose tissue during weight gain are associated with the reprogramming of adipose tissue endocrine function toward an inflammatory phenotype and with the recruitment of inflammatory cells, mainly macrophages, in the adipose tissue. Therefore, targeting inflammation in the adipose tissue would be a useful strategy to prevent systemic complications associated with obesity. Although, there are many anti-inflammatory drugs that could in theory control adipose tissue inflammation, actually none of them is faithfully effective because of their potential side effects. A very provocative strategy to manipulate inflammation is by replacing drugs that inhibit the formation of pro-inflammatory mediators by endogenously generated autacoids that boost the resolution of inflammation. Indeed, obesity-induced adipose tissue inflammation appears to be the perfect scenario for testing the novel omega-3-derived anti-inflammatory and pro-resolving lipid mediators. Notably, these inflammation-resolving factors can induce a proper skew of macrophages toward a
unique pro-resolving phenotype, thus ameliorating the incidence of obesity-related metabolic disorders.

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