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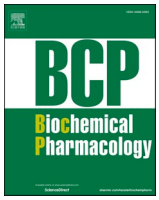

Review

Interrelation of adipose tissue macrophages and fibrosis in obesity

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ABSTRACT

Obesity is characterized by adipose tissue expansion, extracellular matrix remodelling and unresolved inflammation that contribute to insulin resistance and fibrosis. Adipose tissue macrophages represent the most abundant class of immune cells in adipose tissue inflammation and could be key mediators of adipocyte dysfunction and fibrosis in obesity. Although macrophage activation states are classically defined by the M1/M2 polarization nomenclature, novel studies have revealed a more complex range of macrophage phenotypes in response to external condition or the surrounding microenvironment. Here, we discuss the plasticity of adipose tissue macrophages (ATMs) in response to their microenvironment in obesity, with special focus on macrophage infiltration and polarization, and their contribution to adipose tissue fibrosis. A better understanding of the role of ATMs as regulators of adipose tissue remodelling may provide novel therapeutic strategies against obesity and associated metabolic diseases.

1. Obesity and white adipose tissue expansion

Obesity is described by World Health Organization (WHO) as abnormal or excessive fat accumulation that may impair health. In the last years, obesity and overweight have reached epidemic proportions where the number of individuals with obesity has almost tripled since 1975. In the latest data released by WHO in 2022, it was revealed that more than 1 billion people worldwide are living with obesity of whom around 65 % are adults, 34 % adolescents and less than 1 % children. Moreover, obesity is related to co-morbidities such as type 2 diabetes mellitus (T2DM), Metabolic dysfunction-associated fatty liver disease (MAFLD)", cardiovascular diseases (CVDs) and cancer which are associated with premature disabilities and lowered life expectancy [1,2].

White adipose tissue (WAT) is one of the key organs involved in energy homeostasis control and could respond to caloric excess through a healthy or unhealthy expansion. It has been well established that the capacity of WAT to adapt to the energy surplus and sustain it through expansion and alterations in metabolic pathways determines the

Abbreviations: 11β-HSD1, 11β-hydroxysteroid dehydrogenase type 1; A2R, A2 adenosine receptor; ADSC, Adipose-derived stem cell; ATM, Adipose tissue macrophages; BAT, Brown adipose tissue; CCL2 C, C motif chemokine 2; CLS, crown-like structure; CVD, Cardiovascular disease; DAMP, Damage-associated molecular pattern; ECM, Extracellular matrix; eWAT, Epididymal white adipose tissue; FABP4, Fatty Acid-Binding Protein 4; FFA, Free fatty acid; FGF-2, Basic fibroblast growth factor; Gpnmb, Glycoprotein (transmembrane) nmb; HFD, High fat diet; HGF, Hepatocyte growth factor; HMGB1, High mobility group box 1 protein; IFN-γ, Interferon-gamma; IGF-1, Insulin-like growth factor; IL-6, Interleukin 6; ILC, innate lymphoid cell; iNOS, Inducible nitric oxide synthase; IR, Insulin resistance; LPS, Lipopolysaccharides; MAFLD, Metabolic dysfunction-associated fatty liver disease; MFe, Iron-rich macrophages; Mfge8 Milk, fat globule epidermal growth factor 8; Mincle, Macrophage-inducible C-type lectin; MMe, Metabolically activated macrophage; MMP, Matrix metalloproteins; MMT, Macrophage-to-myofibroblast transition; Mox, Oxidized macrophages; Mrc1, Mannose receptor C-type 1; MSC, Mesenchymal stem cell; NO, Nitric oxide; NOX2, NADPH oxidase 2; OXPHOS, Oxidative phosphorylation; PAMP, Pathogen-associated molecular pattern; PDGF, Platelet-derived growth factor; PPAR, Peroxisome proliferator-activated receptor; PVM, perivascular macrophage; ROS, Reactive oxygen species; sEV, Small extracellular vesicles; sWAT, Subcutaneous white adipose tissue; T2DM, Type 2 diabetes mellitus; TAM, tumor-associated macrophage; TGFα, Transforming growth factor alpha; TGF-β1, Transforming growth factor beta-1; Th1, T helper 1; Th2, T helper 2; TIMP, Tissue inhibitor of metalloproteinase; TLR-4, Toll-like receptor 4; TNF-α Tumor, necrosis factor; VEGF, Vascular endothelial growth factor; VEGF, vascular endothelial growth factor; VLDL, Very-low density lipoproteins; vWAT, Visceral white adipose tissue; WAT, White adipose tissue; WD, Weight-discordant; WHO, World Health Organization.

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metabolic health of individuals with obesity [2–4]. Adipocytes, the main WAT cells, have a high degree of plasticity, expanding cell size and number to compensate the need for increased lipid storage, and also secrete adipokines to regulate energy metabolism. However, prolonged WAT expansion is associated with a loss of plasticity, adipocyte dysfunction and unhealthy WAT expansion.

Under healthy conditions, WAT expansion includes an effective recruitment of adipocyte precursors, appropriate angiogenic response, extracellular matrix (ECM) remodelling and minimal inflammation. In contrast, under obese conditions, WAT expansion is related to adipocyte enlargement (hypertrophy), reduced angiogenesis, ECM deposition and fibrosis, and high degree of immune cell infiltration (mainly activated macrophages) and inflammatory responses [2,5–7]. Moreover, adipokines (leptin, Fatty Acid-Binding Protein 4-FABP4 …) secreted by adipocytes and damage-associated molecular patterns (DAMPs) including high mobility group box 1 protein (HMGB1) released by apoptotic/necroptotic/pyroptotic adipocytes also contribute to local inflammation [7], metabolic complication [5] and unhealthy WAT expansion [6].

Although most of these changes are carried out by adipocytes, the contribution of other adipose tissue cell types, including adipose-derived stem cell (ADSCs) and immune cells has been highly relevant in the last years.

A special importance is attributed nowadays to stem cells and stem cells of WAT are known as adipose-derived stem cell (ADSCs) and they are part of the family of mesenchymal stem cells (MSCs). One of the 3 criteria that classifies ADSCs as MSCs is their ability to differentiate into adipocytes, osteocytes or chondrocytes based on their microenvironment. Thus, when ADSC commit to the adipogenic pathway they become recognized as adipocyte progenitors or precursors, and they contribute to the expansion of WAT via adipogenesis mainly. However, ADSCs has been found to promote angiogenesis and cell proliferation and to alter immune responses [8–10]. ADSCs secrete a range of growth factors and chemokines such as transforming growth factor alpha (TGFα), insulin-like growth factor (IGF-1), hepatocyte growth factor (HGF), and basic fibroblast growth factor (FGF-2) activating cell proliferation. These stem cells also produce and secrete other signaling molecules like vascular endothelial growth factor (VEGF), IGF-1, and angiopoietin-1 to recruit endothelial lineage cells and stimulate vascularization [10] contributing to adipose tissue expansion. However, several studies documented changes in ADSCs under pathophysiological conditions. Juntunen *et al.* aiming at eliminating the genetic factor by using weight-discordant (WD) monozygotic twin pairs, documented decreased angiogenic potential of heavier WD twins compared with leaner cotwins. Results from the same investigation revealed an increase in adipogenic differentiation capacity in the obese twin compared to the lean [11]. Serena *et al.*, demonstrated that ADSCs derived from obese and T2D subjects exhibited a reduction in typical immunosuppressive activities attributed to stem cells. Accordingly, obese and T2D-ADSCs were less effective in suppressing lymphocyte proliferation, activating the M2 macrophage phenotype, and in increasing transforming growth factor beta-1 (TGF-β1) secretion, than lean-derived ADSCs [12]. Interestingly, VendrelÍs group demonstrated differences in cell surface marker of ADSCs from people with obesity compared with lean donors, are related to changes in proliferation, migration, and differentiation capacity of ADSCs [13]. These data could evidence the possible presence of ADSCs subtypes, with different functions depending on the surrounding microenvironment.

Besides the ADSCs, immune cells have a special interest. Among them, the relevance of adipose tissue macrophages (ATM) is highlighted since, like adipocytes and ADSCs, ATMs have high degree of plasticity and are regulated by the surrounding microenvironment, affecting adipose tissue expansion. Although classically, macrophage phenotypes are described as “M1” or activated macrophage and “M2” or resident macrophages, the characterization of these cell types are not entirely appropriate because macrophage phenotype spans a continuum *in vivo* and additional “novel” macrophage subtypes could be identified based on external conditions [14]. Thus, obesogenic conditions (i.e high insulin, glucose, free fatty acids,..) give rise to a population of “other” activated macrophages such as metabolic activated (MMe) or oxidized (Mox) macrophages associated to an insulin-resistant state [15,16]. Other obesogenic stimulus including ECM remodeling and fibrosis has been previously explored on macrophage phenotype [17]. Springer *et al.*, observed that at obesity-associated interstitial fibrosis promotes macrophage phenotype similar to tumor-associated macrophage. However only classically M1/M2 adipose tissue macrophage polarization were evaluated [17], but the possible contribution of “novel” fibrotic macrophage phenotype in adipose tissue fibrosis could be discussed. Since ECM can be remodeled to accommodate adipocyte, changes in ECM remodelling could contribute to stiffness microenvironment affecting adipose tissue expansion. The characterization of novel ATM phenotype could be essential to avoid adipose tissue dysfunction and design future strategies and therapeutic targets for obesity.

2. Role of macrophages in white adipose tissue (dys)function

Obesity has been widely linked to a low-grade chronic inflammatory state. Both the innate and the adaptative immune systems have been identified in WAT and represent a heterogeneous population of immune cells including macrophages, dendritic cells, granulocytes, innate lymphoid cells and T and B cells. It has been widely established that human omental adipose tissue (epididymal eWAT, or visceral vWAT in mice) is more prone to inflammation than subcutaneous adipose tissue (sWAT) and is closely related to metabolic complication such as insulin resistance (IR) [4,7,18] Recent bioinformatic studies based on gene expression markers evidence differences in immune cell proportion between different fat depots that could explain these metabolic complications. Thus, the proportion of immune cells differ between WAT fat depots. eWAT presents a higher proportion of immune cell population than sWAT, revealed as 10 % of cell population in eWAT versus 7 % in sWAT. Among immune cell population proportion, monocytes/macrophages are the major abundant immune cell population in both fat depots. eWAT could present a higher monocyte proportion compared to sWAT (4.3 % vs 1.5 % proportion) [4]. However, no differences in macrophage proportion were observed between adipose tissue depots [4,18]. Interestingly, these bioinformatic analyses showed differences in macrophage population between depots [4]. Different macrophage subpopulations were detected in both depots including M1/M2-like, lipid associated and metabolic associate macrophage (MMe), while only a redox-regulatory metabolic were detected in sWAT [21]. However, these results will need to be further explored and validated but could be key to understand metabolic differences observed between fat depots and decipher novel therapeutic target.

In obesity, adipose tissue macrophages account for 50 % of WAT immune cells, representing the most abundant immune cell type in adipose tissue and deemed crucial in the low-grade chronic inflammation in WAT during obesity [17,19–22]. Moreover, similar to monocyte proportion, it has been shown eWAT having higher levels of chemokines that attract macrophages than sWAT [23]. Specifically, interleukin 6 (IL-6), a potent regulator of energy expenditure and obesity, appears to be produced in vWAT and correlates with the chemokine C-C motif chemokine 2 (CCL2), a superfamily of secreted proteins involved in immunoregulatory and inflammatory processes, with specific chemotactic activity for monocytes. In contrast, these correlations were not observed in sWAT. Data could be related to differences in monocyte/macrophage proportion between fat depots, that could promote difference in cytokine secretory profile [23] increasing pro-inflammatory cytokine production [22] and other metabolic complications including IR [24] promoting the pathogenesis of obesity-driven inflammation.

Moreover, it has been demonstrated that macrophages have an essential role in adipose tissue angiogenesis since ATMs are the main producers of angiogenic factor PDGF (platelet-derived growth factor) in this tissue [25]. In fact, the chemical deletion of macrophages in adipose

tissue using clodronate liposomes significantly reduced capillary density in adipose tissue [26]. In a most recent study, the macrophage phenotype was evaluated including specific markers to M1 and M2 type and PDGF production in diet-induced obesity mice. Data demonstrate that both phenotypes produce the angiogenic factor, however, due to the elevated proportion M1/M2 in obese adipose tissue, M1 phenotype was the major contributor to PDFG production in adipose tissue in obesity [27]. Additional studies including obesity-associated hyperglycemia and chronic inflammation, evidenced altered PDFG production from macrophage that could contribute to unpaired angiogenesis. Thus, the *in vitro* treatment of high glucose and higher glucose with lipopolysaccharides (LPS) conditions, increased PDGF production in macrophages RAW264.7 affecting adipose tissue vascular remodelling [28].

Adipose tissue inflammation [29–33] is not the sole culprit associating with the comorbidities of obesity. Recently, other adipose tissue complications such as fibrosis, have been correlated with major risk of IR and metabolic complications [34,35]. Fibrosis is defined as the excess or dysregulation in deposition of ECM components, especially collagens, leading to severe organ dysfunction associated to a variety of disorders. Increased collagen deposition and fibrosis during obesity-driven chronic low-grade inflammation in WATs has been reported [34,35]. However, the obesity-inflammation-fibrosis link has not been fully explored. Although there is evidence that elements of the innate and adaptive immune response participate in the differentiation and activation of fibroblasts into ECM-producing myofibroblasts, however, the contribution of ATMs on ECM remodelling and adipose tissue fibrosis are not well elucidated yet.

Thus, macrophage population plays a critical role in inflammation, angiogenesis and ECM remodelling, which are essential contributors to WAT dysfunction and key component of healthy/unhealthy WAT expansion [34]. In this context, this revision focuses on the ECM remodelling-adipose tissue macrophage phenotype cross-link and the possible role of adipose tissue macrophages in the prevention or promotion of adipose tissue fibrosis.

3. Adipose tissue macrophages (ATMs) origins

The tissue-resident macrophages originate from the early developing embryonic stages as yolk sac-derived myeloid progenitors and fetal monocytes [36–39]. To track the origins of resident macrophages in mice, it has been shown that at embryonic age – specifically day 8 – primitive ectoderm from the yolk sac develops into macrophages that are different from those with a monocytic progenitor. Hematopoiesis follows in the fetal liver which is considered the generator of circulating monocytes during embryogenesis. As the formation of bone takes place postnatally, hematopoiesis in the liver is replaced gradually by bone marrow hematopoiesis [40–42]. This latter and definitive hematopoiesis is the source of circulating monocytes; thus, the source for all resident macrophages in tissues [41,42]. Hence, tissue-resident macrophages are a mixture of embryonic-derived (yolk sac and fetal liver) and adult bone marrow-generated macrophages [43–45]. However, some studies argue about the real origin of ATMs. Thus, in healthy/lean WAT of humans and mice, the resident macrophages are recognized as adipose-resident perivascular macrophages (PVMs) by some references [44,46–48] and by others, resident macrophages were considered alternatively activated M2 phenotype with surface markers F4/80 and CD206 [49–51]. Even though the nomenclature differs, the resident macrophages were described as self-renewing cells by proliferation under homeostatic conditions [52,53] localizing in a proximity to adipocyte progenitor cells [54] forming crown-like structures (CLS) to envelope and ingest adipocyte debris at the site of adipocyte death.

The accumulation of ATMs preferentially in vWAT in humans [55–57] and mice [58,59] has been considered a hallmark of obesity-associated chronic inflammation leading to IR [39,60–62]. These accumulating ATMs under obesogenic conditions – stimulated by high-fat diets – are subpopulations of ATMs distinctive from resident ATMs and usually less abundant under steady state conditions [39,49,63,64]. While resident ATMs (also recognized as M2 macrophages) reportedly proliferate locally via the activation of Thelper2 (T_H2) and the release of IL-4, accumulating ATMs under obesogenic conditions (categorized as M1 macrophages) are mostly newly recruited CCR2 + blood monocytes maturing into macrophages [61,65]. The bone marrow-derived ATMs recruited in obesity-associated inflammation display pro-inflammatory markers such as CD11c, CD9 and Trem2 [49–51,63] and are usually lipid-laden cells directed towards the crown-like structures of the adipose tissue – where damaged, dead and/or hypertrophic adipocytes are found [63,66,67]. This phenomenon of ATMs recruitment has been shown to be a positive feedback where ATMs of a chronically inflamed vWAT release cytokines promoting hematopoietic progenitor cells to proliferate in the bone marrow, increasing the production and release of myeloid cells thus, allowing more monocytes to be recruited to the adipose tissue and maturing into pro-inflammatory macrophages hence, aggravating the inflammation [61]. The actors of this positive loop have been suggested to be Toll-like receptor 4 (TLR4) ligands which bind to TLR4 found on the surfaces of macrophages in the CLS, activating MyD88 and the NLRP3-inflammasome and consequently the expression of IL-1β which bind to IL-1R in the bone marrow stimulating the proliferation of hematopoietic progenitor cells [61,68–70]. Besides the recruitment of monocytes from the bloodstream, under obesogenic conditions, ATMs number increases through mechanisms inducing local proliferation within the CLS, impairment in macrophage egress and increased cell longevity [20,71–74].

However, the accumulation of macrophage in adipose tissue is also related to tissue injury and repair. Both pro-inflammatory and anti-inflammatory macrophages phenotypes are most frequently investigated in studies of wound repair, fibrosis and tissue regeneration. In fact, it has been described that macrophage could exhibit different functions including pro-wound healing, pro-fibrotic, anti-fibrotic, pro-resolving, and tissue regeneration, under specific macrophage phenotype activation [75]. There is sufficient evidence to suggest that these macrophage activation states are not always mutually exclusive, and it is still to be described if some functional subsets of macrophages represent distinct phenotypes or whether they are specific subsets of pro-inflammatory and anti-inflammatory macrophages and pro-fibrotic or anti-fibrotic macrophages. However, uncontrolled production of inflammatory mediators and growth factors, deficient generation of anti-inflammatory macrophages, or failed communication between macrophages and tissue progenitor cells could contribute to a state of persistent injury, and this could lead to the development of pathological fibrosis [75]. For that, it is essential to expand our knowledge in macrophage population characteristics and activation attending the external environment that surrounds ATM, especially during tissue injury and expansion of adipose tissue in obesity.

The classification of macrophages is determined by their functions and roles in WAT. ATMs are major contributors to WAT inflammation and fibrosis, thus their classification can either be based on their inflammatory function or their fibrotic function (Table 1). These two functions might sometimes be inline but other times not necessarily, which is the reason behind this review focusing, in the first part, on ATMs as inflammatory modulators and, in the second, on ATMs as fibrotic agents.

4. Inflammation, macrophages and adipose tissue dysfunction

4.1. Atms subtypes based on inflammatory function

The major classes of macrophages are still considered to be the **pro-inflammatory M1** (M1-like) or classically activated macrophages and the **anti-inflammatory M2** (M2-like) or alternatively activated macrophages [19,20]. In a healthy state, the predominant ATM population is M2-like macrophages that express genes like interleukin-10 (IL-10), mannose receptor C type 2 (Mrc2), arginase 1 (Arg1) and chitinase 3-

Table 1
Properties of white adipose tissue macrophage subtypes.

Subtype	Markers	Induced by	Secreted factors	Functions	References
M2a	CD206, IL-1r, CCL17	IL-4, IL-13	TFGb, fibronectin	Resolution of inflammation and wound healing	[17,18,76]
M2b	CD86, IL-10, CCL1	TLR and IL-1R agonist	IL12	Immunoregulation	[17,18,76]
M2c	CD206, CD163	IL-10	TFGb	Tissue remodelling, phagocytosis	[17,18,76]
Profibrotic macrophages	Not identified	Aberrant ECM remodelling	IL10, TFGb, ECM components	Promotion of ECM overproduction and deposition	[19]
Antifibrotic macrophages	Not identified	Appropriate ECM remodelling	MMPs, Mrcs	Promotion of ECM degradation and phagocytosis	[19]
M1	CD80, TNFa	LPS, TLR4	TNFa, Il1b, IL6	Pro-inflammatory signaling	[17,18,76]
Metabolic (Mme)	ABCA1, CD36, PLIN2	Saturated FFAs	Not identified	Lysosomal activity and lipid buffering for dead adipocytes	[18,76,79]
Oxidative (Mox)	HO-1, GST, Txnrd1	ROS, Oxidized lipids, Nrf2	Not identified	Oxidative stress buffering	[18,76,79]

like-3 (Chi3l3, Ym1) and are characterized by surface markers CD206 (mainly in mice) and CD163 (in humans). M2-like macrophages recognized for driving immune regulation and tissue remodelling can be further divided into different subtypes (M2a, M2b, M2c…) based on specialized surface markers and functions [76].

M2a macrophages are known as wound-healing macrophages, and they are induced by IL-4 and IL-13 that are produced by eosinophils. They contribute to tissue repair by releasing pro-fibrotic factors like TGF-β, fibronectin and insulin-like growth factor (IGF). Main M2a macrophages markers include high levels of mannose receptor (CD206), CC motif chemokine ligand 17 (CCL17), Arginase 1 (ARG1), YM1 and decoy IL-1 receptor.

Subtype **M2b** is a regulatory macrophage stimulated by exposure to immune complexes and Toll-like receptor (TLR) agonists or by IL-1R agonists. IL-10 is the primary marker for M2b and highly secreted by it. M2b are also recognized for a low level of secretion of IL-12; thus, high IL-10/IL-12 ratio is accepted as the major characteristic marker for M2b. Among the other marker for M2b are CCL1, CD86 and IL-6.

M2c macrophages are induced by the activation of signal transducer and activator of transcription 3 (STAT3) via the binding of IL-10 to its receptor. These cells display strong anti-inflammatory and pro-fibrotic activities through the secretion of large amounts of IL-10 and TGF-β, respectively. M2c macrophages are highly involved in the phagocytosis of apoptotic cells and thus they express several scavenger receptors as special markers.

M2d macrophages are known as tumor-associated macrophages and are stimulated by the binding of TLR ligands to A2 adenosine receptor (A2R) agonists or by IL-6. M2d cells are mainly characterized by high IL-10, TGF-β, and vascular endothelial growth factor (VEGF), and by low IL-12, tumor necrosis factor alpha (TNF-α) and IL-1β production [76,77].

On the other hand, in obesity, the balance is tilted towards M1 macrophages which express genes like TNF-α, IL-1b, IL-6, inducible nitric oxide synthase (iNOS) and are characterized by surface markers such as CD80 [20,33,34]. In addition to the M1 and M2-like phenotypes of macrophages, some other phenotypes have been identified. ATMs are known scavengers of adipocyte debris and they are challenged when adipocytes are enlarged thus, ATMs are unable to engulf the debris in a single step. Instead, macrophages aggregate in WAT forming CLS to envelope and ingest adipocyte debris at the site of adipocyte death. Several phenotypes of macrophages with potential functions are found in the CLS structure. Some ATMs adopt a **Mme** phenotype allowing them to eliminate dead adipocytes through lysosomal exocytosis. Other ATMs, such as iron-rich macrophages (**MFe**) and antioxidant macrophage (**Mox**) are specific to the handling of iron and oxidative stress, respectively [76,78].

4.2. Atms under pathophysiological conditions

In lean subjects, an overall type 2 or T helper 2 (T_H2) state governs the immune cells where master regulators like IL-33 drive the immune response. IL-33 stimulates the secretion of cytokines IL-5 and IL-13 by innate lymphoid cells (ILCs) activating eosinophils. IL-4 is secreted by eosinophils in WAT and it maintains macrophages in a M2-polarized state [21]. The maturation of alternatively activated macrophages and to sustain a M2-phenotype require the activation of peroxisome proliferator-activated receptor (PPAR)γ and PPARδ that promote the expression of anti-inflammatory genes. M2 macrophages improve insulin sensitivity in the tissue via the secretion of many cytokines such as IL-10 and TGF-β, hence, preserving metabolism [19,20,79–81].

In obese subjects, immune cells of the adipose tissue operate in an overall type 1 or T_H1 state where cells coordinate to preserve tissue function while adapting to the overnutrition-associated metabolic needs. In this T_H1 state mediated mostly by LPS and interferon-gamma (IFN-γ), resident and recruited macrophages are inclined to adopt a pro-inflammatory phenotype. M1-polarized macrophages secrete pro-inflammatory cytokines such as TNF-α and IL-1β that further influence the recruitment and polarization of macrophages into M1-like [33,50,60,82–84]. Thus, the number of macrophages in WAT and the M1/M2-like macrophages ratio are increased representing the hallmark of the WAT inflammation accompanied with the development of IR and fibrosis [81,85]. However, the specific role of the novel M2 subtypes phenotypes in adipose tissue under obese conditions is still poorly described.

Recent studies evidence that in obesity, metabolic cues (e.g., free fatty acids, high insulin, high glucose, oxidized phospholipids, oxidized LDL) promote the presence of novel subtypes including metabolically activated (Mme) or oxidized (Mox) macrophages, that are involved in multiple functions [22]. Moreover, adipocytes also contribute to macrophages polarization. Thus, adipocytes can recruit macrophages and polarize them to classical macrophage profile (M1) or alternative macrophage profile (M2) depending on the adipocyte status of inflammation [86]. In obesity, hypertrophic and sometimes dysfunctional adipocytes – through the secretion of cytokines like monocyte chemoattractant protein 1 (MCP-1/CCL2) – attract macrophages and promote M1 polarization. The observed increment of LPS levels also promotes M1 polarization. TLR4 is a crucial mediator and activator of the pathway, and its deficiency was found to prevent the favoring of M1 phenotypes over M2-like macrophages in high fat diet (HFD)-induced environment in obesity [87,88].

Free fatty acids (FFAs), which are found at elevated levels during obesity, are also one of the major activators of the TLR4 signaling pathway in adipocytes and macrophages, promoting a pro-inflammatory profile and an M1 polarization. FFAs can induce the secretion of TNF-α and IL-6 from isolated adipocytes, which is prevented in TLR4 −/- mice. With TLR4 knockout mice, the effect of FFA is inhibited and the adipose tissue along with other insulin-sensitive tissues are partially protected from tissue-specific inflammation and the associated IR [89,90]. In addition to FFAs and due to the positive energy balance in obesity, various molecules are found to be more abundant intervening in several

regulatory pathways. For example, increasing short chain fatty acids intracellular levels through very-low density lipoproteins (VLDLs) in the environment of macrophages induces a pro-inflammatory profile and promotes M1-like macrophage polarization [91].

The effect of high glucose on macrophages polarization should be also considered. When human macrophages were exposed to high glucose, they overexpressed M1 surface markers like CD11c and (iNOS) and M2 markers like ARG1 and IL-10 were downregulated in comparison to macrophages exposed to normal glucose levels [92]. It has been suggested that elevated levels of FFAs, glucose and insulin leading to metabolic alterations can promote the polarization of macrophages into Mme macrophages characterized by an upregulated lipid metabolic profile. Mme macrophages were identified in obese WATs and they overexpress lipid-related genes such as PLIN2 and ABCA1 [22,93]. This is a further indication of a previous statement showing that the increase in macrophages in adipose tissue induced by obesity is not solely attributed to an increase in M1 macrophages.

Furthermore, several other factors involved in macrophages polarization were investigated. In a study focused on the role of IRF5 as a transcriptional factor, it was revealed that the expression of M1 phenotypic markers was upregulated while the expression of the M2 phenotypic markers was downregulated with the upregulation of IRF5 [94]. Inositol-requiring enzyme 1 α (IRE1α) was also identified as a regulator of ATM polarization in WAT. Its knockout in a mouse model inhibited the changes to the M1/M2 ratio induced by HFD through increasing M2 polarization and thus prevented HFD- induced IR and hyperlipidemia. The metabolic syndrome reached by effect of IRE1α was found to be through the impairment of brown adipose tissue (BAT) activity and WAT browning [95]. Another identified player in ATM polarization is 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), an intracellular glucocorticoid reactivating enzyme. It was demonstrated that a phenotypic switch from M2 to mixed M1/M2 phenotype in obese subjects correlated with an upregulation of intracellular 11β-HSD1 [96].

In addition to all the above-mentioned factors affecting the polarization of macrophages, ADSCs and small extracellular vesicles (sEV) were investigated. ADSCs are involved in alterations in the microenvironment of WAT through their secretome and it was reported by many, that ADSCs drive the polarization of macrophages towards a favored anti-inflammatory state. However, under obesogenic conditions, ADSCs demonstrate higher secretion levels of survivin, which is an inhibitory protein of cell apoptosis thus considered a tumor progression marker. It is thought that survivin alters macrophages polarization towards tumor-associated macrophages (TAMs) which triggers an autocrine survivin loop in the WAT microenvironment fed by high abundance of IL-4 [97] Moreover, sEVs are also components of WAT that contribute to modifications to the microenvironment. sEVs are responsible for the transportation of proteins, nucleic acids and/or lipids. sEVs are released by different cells of WAT including ADSCs, adipocytes, fibroblasts and immune cells and several investigations have reported their anti-inflammatory and tissue regeneration role through their ability to turn M1-like macrophages into M2-like macrophages. In a study by Dong *et al.*, the focus was on human adipose tissue-derived small extracellular vesicles and they reported, after the addition of human adipose tissue-derived small extracellular vesicles to WAT, an increase in the percentage of M2 macrophages and a promotion of the polarization of M1 macrophages to M2 macrophages [98].

Finally, recent studies have focused on phenotyping macrophages and classifying them through their metabolic profile. Identification of macrophages phenotypes and polarization under lean and obese conditions has been greatly driven by their glycolytic and oxidative phosphorylation (OXPHOS) capacities. In a simplistic differentiation, classically activated macrophages function almost exclusively through glycolysis while alternatively activated macrophages rely on OXPHOS [93,99–102]. Macrophage polarization and activation have been shown to shift, induced by changes in their metabolism and mitochondria such as alterations in OXPHOS capacity, modifications in mitochondrial structure and membrane potential, as well as levels of mitochondrial reactive oxygen species (ROS) [100,103]. Studies on ATMs from lean and obese mice and on co-cultures with WAT explants, reported increases in glycolysis and OXPHOS of macrophages originating from obesity models thus introducing additional macrophages phenotypes [99,102]. Considering evidence, nowadays, the concept of metabolic flexibility of ATMs has been widely accepted. However, the contribution of the different phenotypes to adipose tissue physiology remains unclear. Further studies will be necessary to understand the full role of macrophages. However, the presence of different phenotypes is highly dependent on microenvironmental stimuli in the WAT, which vary according to physiological conditions. In this line, it was also recently described that changes in the ECM organization could modulate macrophage polarization [104], although less is known about the role of macrophage polarization in WAT in relation to obesity-associated fibrosis.

5. Fibrosis, macrophages and adipose tissue dysfunction

Fibrosis is defined as the excess or dysregulation in deposition of ECM components, especially collagens, leading to severe organ dysfunction associated to a variety of disorders. Increased collagen deposition and fibrosis during obesity-driven chronic low-grade inflammation in WAT has been reported [34,105]. However, the obesity-inflammation-fibrosis link has not been fully explored. It is now clear that many elements of the innate and adaptive immune response participate in the ECM organization mediating differentiation and activation of fibroblasts into actively proliferating ECM-producing myofibroblasts. However, the contribution of macrophages on ECM remodelling and fibrosis are not well elucidated yet.

The ECM is a three-dimensional non-cellular network composed of a variety of multidomain macromolecules with functions ranging from physical support for tissue integrity and elasticity to reservoir of growth factors by sequestering and releasing them. ECM is a highly dynamic structure in constant remodelling to match cellular processes such as proliferation, differentiation, adhesion, migration, apoptosis, etc… Dysregulations in ECM dynamics are linked to pathological conditions and can contribute to fibrosis and further disease progression [34,105,106]. The adipose tissue ECM is mainly formed of collagens (I, II, III, and IV) being the major component contributing considerably to the non-cell mass of WAT. In addition, ECM of WAT includes glycoproteins and proteoglycans (i.e lumican) that contribute to the ECM organization [107]. Continuous remodelling of ECM and an elevated degree of ECM flexibility are key to maintain a healthy adipose tissue profile. During positive energy balance, an adaptive response of cellular and extracellular compartments in the expanding WAT is required for prevention of ectopic lipid deposition and lipotoxicity [108]. Several studies have reported an increased collagen deposition and fibrosis along with reduced elasticity in WATs of diet-induced obese mice and obese humans [34,35,105]. Accumulation of ECM components is paralleled with an increase in the expression of ECM-encoding genes in the obese WAT [109,110].

Regarding their interaction with the ECM, macrophages have been classified into two main groups, the profibrotic and the anti-fibrotic macrophages [111]. Profibrotic macrophages, also referred to as pro-remodelling macrophages, release pro-inflammatory TNF-α and IFN-γ cytokines, wound healing IL-4 and IL-13 cytokines and ECM-producing cells activators IL-10 and TGF-β cytokines, among other cytokines [112–114]. On the other hand, anti-fibrotic macrophages achieve their fibrolytic function through the expression of several ECM degrading proteins like secretory proteases – specifically matrix metalloproteins (MMPs) – and other enzymes and phagocytic receptors involved in intracellular digestion of phagocytosed ECM fragments [115].

5.1. Macrophages and fibrogenesis

Profibrotic macrophages are mostly compared or referred to as M1 and M2c macrophages due to their secretion of pro-inflammatory cytokines and wound healing cytokines, respectively [20,113). In adipose tissue, ATMs were found to release cytokines such as TGF-β1 and PDGF which directly activate fibroblasts. Fibroblast proliferation and activation is deemed crucial for ECM accumulation, since fibroblasts are the major cell type for collagen deposition [116].

Moreover, these macrophages further promote fibrosis by amplifying WAT inflammation through the release of chemokines recruiting more pro-inflammatory cells [117]. During alterations of tissue homeostasis, macrophages recognize inflammation and injury-related factors such as proinflammatory cytokines, pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) leading to a favored M1-like polarization of macrophages [118]. TLR4 was found to be at the center of macrophages-mediated development of obesity-associated WAT fibrosis [119]. The activation of TLR4 in macrophages leads to the activation of the macrophage-inducible C-type lectin (Mincle) which in turn promotes several pathways involved in production and degradation of ECM along with proliferation and differentiation of fibroblasts [119,120]. The study by Vila *et al.* showed that the inhibition of TLR4 signaling in macrophages in mice prevented obesity-associated WAT fibrosis. The impairment of TLR4 prevented the upregulation of collagen genes and the increased deposition of collagens during HFD [119]. The lack of collagens and specifically collagen VI accumulation in human and mouse WAT has been shown to improve WAT expansion, crucial for preventing ectopic fat deposition and improving systemic insulin sensitivity [110,121–123]. In human sWAT, fibrosis and collagen VI accumulation were correlated with IR [18]. In addition, Tanaka *et al.* showed that Mincle expression is localized to macrophages forming the CLS and is activated by residual lipid droplets of dead adipocytes that are phagocytosed by macrophages within the CLS. Mincle expression was found to be low in healthy WAT of lean mice. Thus, Mincle activation is key for CLS formation and fibroblast activation to the expression of fibrosis-associated genes [120].

Important contributors to the inflammation-induced fibrosis are the monocyte-derived macrophages. Through the release of cytokines and chemotaxis, resident macrophages recruit monocyte-derived macrophages which were highly present in fibrotic tissues. However, several investigations on different tissues of mouse models showed that a depletion of monocyte-derived macrophages lead to reduced fibrosis [124–128]. The study on human monocytes and macrophages by Kelly *et al.* revealed that CD14 + macrophages and monocytes as well promote the development of fibrosis through activating ECM-stored latent TGFβ which acts via integrin αvβ8-mediated pathways [129]. Contrary to previous hypotheses considering monocyte-derived macrophages as relatively short-lived, it was revealed that they could assume a tissue-resident macrophages-like phenotype stimulated by the microenvironment [124,130]. Besides the established interaction between macrophages and fibroblasts in fibrosis [111], an improved directionality and increased mobility of macrophages, thus favoring their migration, were induced by fibroblasts and higher substrate stiffness of the tissue [131–134]. Moreover, when human preadipocytes were cultured with conditioned medium from obese adipose tissue macrophages, their adipogenesis was impaired and they showed increased ECM deposition [135].

Furthermore, regarding recruited macrophages, there is a process defined as macrophage-to-myofibroblast transition (MMT) where macrophages differentiate into myofibroblast under the effect of tissue fibrosis. Even though this phenomenon has not been yet investigated in WAT, but it was observed in various human and/or mouse tissues like kidneys, heart and skin [136–139]. In one of these studies, it was also demonstrated that the macrophages that undergo this MMT differentiation were profibrotic macrophages [136]. A study by Shen et al. revealed that recruitment of macrophages in WAT proceeded tissue fibrosis and a feedforward loop mediated by a CCL2/7-macrophage interaction further enhances fibrotic responses [140]. Some of the mentioned studies on macrophages inducing alterations to ECM are not solely based on investigations lead in WAT. There is a lack of information on that front. However, the review by Park *et al.* sheds a light on the most recent studies on the topic of macrophage-ECM interaction in several organs such as liver, lungs, heart and kidney amongst others [141].

Under fibrotic conditions, the macrophages-ECM interaction promotes modifications to the tissue which are mostly represented as a profibrotic loop. In this loop, the interaction leads to further fibrotic responses highlighted by increased recruitment and migration of profibrotic macrophages, activation and differentiation of fibroblasts and increased deposition of ECM components that is associated to fibrosis (Fig. 1). Although further studies are necessary to understand specific ECM remodelling changes associated to profibrotic macrophage activation, these advances could serve to identify novel anti-fibrotic therapies and contribute to reduce fibrosis in adipose tissue.

5.2. Macrophages and fibrolysis

Macrophages contribute to ECM dynamics not solely through promoting fibrogenesis but via ECM clearance through collagen uptake and degradation. Fibrolytic macrophages can be classified into two groups based on their sources; there are the phenotypically altered tissue-resident macrophages and the recruited monocytes. This fibrolytic profile is stimulated by several factors in the microenvironment of the tissue. Anti-profibrotic macrophages prevent ECM accumulation via ECM-degrading enzymes like MMPs, ECM clearance through ECM protein uptake and phagocytosis, and downregulation of ECM-encoding genes [142].

Phagocytosis is a main function of fibrolytic macrophages which execute their role through receptors or soluble proteins such as integrin and mannose receptor C-type 1 (Mrc1) promoting ECM protein uptake [143,144]. The phagocytosis of ECM collagens was found to be highly dependent on receptors and proteins such as Mrc1 and the urokinase plasminogen activator receptor–associated protein (Endo180 and Mrc2) [145]. Another factor secreted by macrophages and important for collagen phagocytosis is the glycoprotein milk fat globule epidermal growth factor 8 (Mfge8) which binds to collagen to be presented and recognized by fibrolytic macrophages [143]. Moreover, the proteolytic capacity of the phagosome of IL-4-activated macrophages has been shown to be highly increased via upregulation of cathepsin S and L and reduced activity of phagosomal NADPH oxidase 2 (NOX2) [146]. In addition, anti-fibrotic macrophages downregulate gene clusters associated to collagen organization and focal adhesion as well as ROS and nitric oxide (NO) synthesis; thus, allowing the resistance of tissue fibrosis and oxidative damage [147].

Fibrolytic macrophages stimulate ECM degradation pathways through the secretion of MMPs and through the ingestion of ECM components [142]. MMPs, a family of zinc-containing endopeptidases that can be produced as soluble or cell membrane-anchored proteinases, are considered the main proteases involved in ECM degradation. They have a wide substrate range which means, collectively, MMPs can degrade all ECM proteins including collagens, fibronectin, proteoglycans, gelatin and laminin [106,148,149]. Inhibitors of most proteases including MMPs are the family of tissue inhibitor of metalloproteinases (TIMPs). The ratio of MMP over TIMP concentrations defines the extent of ECM degradation and specifically protein hydrolysis. This ratio is crucial for the development of angiogenesis, tissue repair, inflammation and fibrosis [150].

Under normal conditions, the activity of MMPs is hindered and it is induced during tissue repair or inflammation [151]. Macrophages are regulators of the production and activity of MMPs. Fibrolytic macrophages modulate MMP production via transcriptional modifications and via secretory regulation. Transcriptional regulation of MMP and TIMP

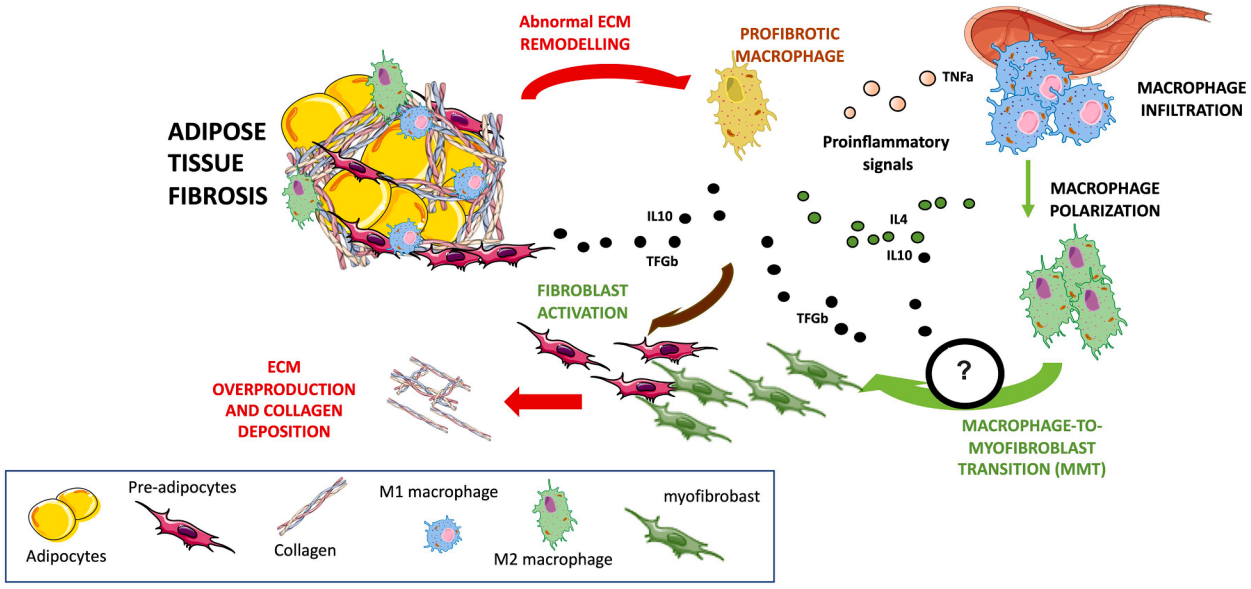

Fig. 1. Profibrotic macrophage and ECM remodelling activity in adipose tissue. Adipose tissue fibrosis leads to abnormal ECM remodelling promoting profibrotic macrophage subtype polarization. These profibrotic macrophages produce pro-inflammatory signals (TNFa, IFNg,..) that induce macrophage recruitment and M1 polarization maintaining adipose tissue inflammation. Profibrotic macrophages also produce other cytokines (IL4, IL13,..) that contribute to i) fibroblast activation and ii) M2 macrophage polarization and macrophage to-myofibroblast transition (MMT), although no additional evidence is observed in MMT in adipose tissue yet, marked on the image with a question mark. Both cell types, fibroblast and myofibroblast are the major source of ECM components. Prolonged exposure to stimulus (TGFb,..) could contribute to aberrant production of ECM proteins and collagen deposition causing adipose tissue fibrosis. This figure has been created by modifying the templates from Servier Medical Art (https://smart.servier.com) and Aldich Design (info@aldichdesign.com).

production is triggered by transcriptional factors such as early growth response factor 1-EGR1, GATA-binding factor 1-GATA1, signal transducer and activator of transcription 3-STAT3C, and nuclear factor kappaB-NF-κB, activator protein 1-AP-1 family [152]. MMP activity is also dependent on MMP secretion and of the cysteine switch of pro-MMP activation mechanism required for the activation of the latent enzyme [153]. Fibrolytic macrophages are key regulators of the cysteine switch of pro-MMP activation via the secretion of thrombin, an important serine protease for this mechanism [154]. The macrophage-MMP interaction is bidirectional since MMPs can also regulate macrophages by inhibiting their recruitment in inflammation [155–158]. In the study by Ramachandran *et al.* fibrolytic macrophages were shown to have increased expression of MMPs and phagocytosis-related genes like Mmp9, Mmp12, Igf1 and Glycoprotein (transmembrane) nmb (Gpnmb)

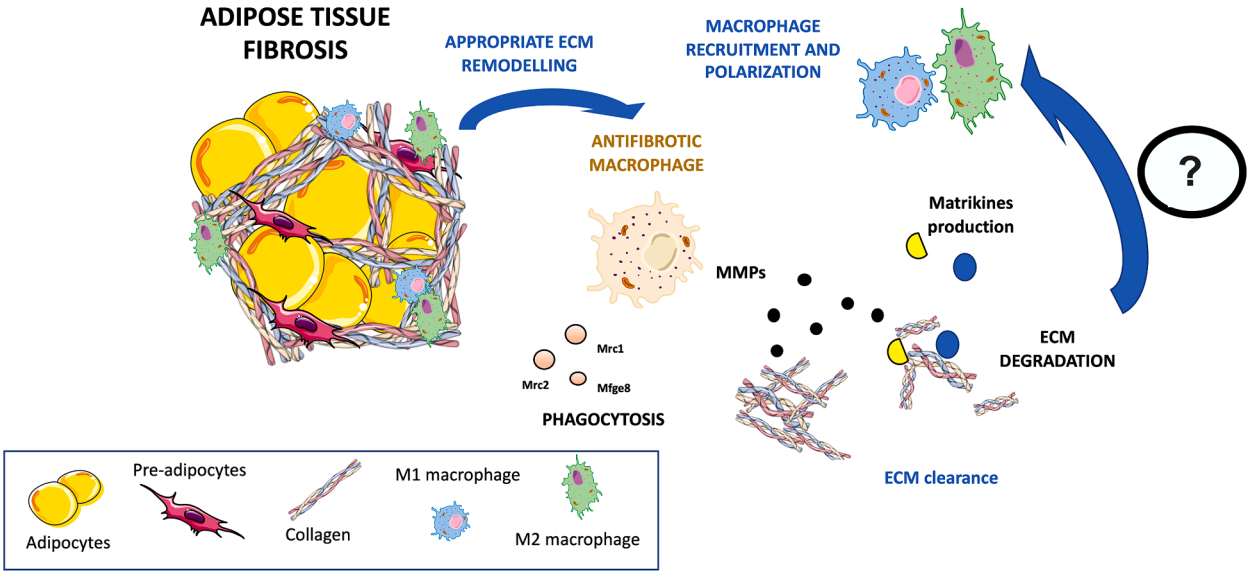

Fig. 2. Antifibrotic macrophages and fibrolytic activity. Changes in ECM composition that surrounds macrophages can also promote the presence of antifibrotic macrophages. This phenotype, also referred to as M2-like phenotype, is characterized by the release of proteases (i.e MMPs, catepsins…) to degrade ECM components (collagen, proteoglycans, glycoproteins…) and promotes ECM clearance of degraded products via phagocytosis. Some of these products, called matrikines (blue and yellow symbols), could serve as signal molecules and participate in different processes (i.e., macrophage recruitment and macrophage polarization). Further studies will be necessary to elucidate the specific macrophage phenotype stimulated under appropriate ECM remodelling and clearance, as well as the possible role of matrikines in macrophage polarization (marked on the image with a question mark). This figure has been created by modifying the templates from Servier Medical Art (https://smart.servier.com) and Aldich Design (info@aldichdesign.com).

[159]. In the classification of macrophages phenotype in fibrosis, the macrophages responsible for phagocytosis were mostly considered similar to M2 macrophages and it was revealed that M1-like macrophages switched to M2-like phenotype in the presence of triggers such as cell debris, IL-1R and prostaglandin E2 [160].

Besides regulating the expression and activity of MMPs, macrophages are also involved in the ingestion of ECM components and their digestion through the lysosomal pathway [142]. During ECM degradation, some of the generated fragments are bioactive exhibiting chemotactic functions and activating effects on monocytes. Injury or inflammation-induced fibrosis stimulates ECM degradation leading to increases in ECM fragments generated causing further interaction with monocytes and macrophages [161]. The products of ECM degradation, which contain structural sites that get activated under pathological ECM conditions, are known as matricryptins or matrikines [162]. Matrikines can be derived from various ECM components like collagens, fibronectin, elastin and laminins and they differ in size. Some matrikines act as chemotractants on monocytes such as tripeptide GHK (a fragment of collagen Iα2) and kappa-elastin peptides (a fragment of elastin) [161]. It was also shown that matrikines are involved in monocytes activation and differentiation into macrophages [163]. However, less is known about the role of matrikines in macrophage polarization (Fig. 2).

In summary, macrophages in adipose tissue are essential for a proper adipose tissue function. Thus, the surrounding microenvironment of adipose tissue macrophages impacts their polarization, metabolic profile and recruitment. Moreover, through mediators, ATMs also communicate with the different adipose tissue cell types and components inducing modifications in adipose tissue homeostasis, that are directly related to adipose tissue dysfunction and associated comorbidities. Unravelling the contribution of macrophage to molecular mechanism involved in adipose tissue homeostasis could elucidate possible novel therapies based on macrophage activation/inactivation, that promote more effective therapies in WAT dysregulation homeostasis as occur in obesity.

CRediT authorship contribution statement

Norma Dahdah: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis. **Carmen Tercero-Alcázar:** Writing – review & editing, Methodology, Investigation, Formal analysis. **María M. Malagón:** . **Pablo Miguel Garcia-Roves:** Writing – review & editing, Supervision, Resources, Funding acquisition, Conceptualization. **Rocío Guzmán-Ruiz:** Writing – review & editing, Writing – original draft, Visualization, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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