Adipose Tissue Inflammation and Metabolic Dysfunction in Obesity

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Word count: 6694

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Abstract

Several lines of preclinical and clinical research have confirmed that chronic low-grade inflammation of adipose tissue is mechanistically linked to metabolic disease and organ tissue complications in the overweight and obese organism. Despite this widely confirmed paradigm, numerous open questions and knowledge gaps remain to be investigated. This is mainly due to the intricately intertwined crosstalk of various pro- and anti- inflammatory signaling cascades involved in the immune response of expanding adipose depots, particularly the visceral adipose tissue. Adipose Tissue inflammation is initiated and sustained over time by dysfunctional adipocytes that secrete inflammatory adipokines and by infiltration of bone-marrow derived immune cells that signal via production of cytokines and chemokines. Despite its low-grade nature, adipose tissue inflammation negatively impacts remote organ function, a phenomenon that is considered causative of the complications of obesity. The aim of this review is to broadly present an overview of adipose tissue inflammation by highlighting the most recent reports in the scientific literature and summarizing our overall understanding of the field. We also discuss key endogenous antiinflammatory mediators and analyze their mechanistic role(s) in the pathogenesis and treatment of adipose tissue inflammation. In doing so, we hope to stimulate studies to uncover novel physiologic, cellular, and molecular targets for the treatment of obesity.

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Introduction

Obesity is now considered as a worldwide epidemic (171) and a strong risk factor for insulin resistance, type 2 diabetes mellitus (T2DM), cardiovascular diseases (CVD), immune disorders, and non-alcoholic fatty liver disease (NAFLD), in addition to several type of cancers. Overall, obesity is associated with a reduction of quality of life, shortened life span and increased healthcare costs (17, 52, 112, 189). Because of a pathophysiology that recapitulates the more complicated picture of multifactorial chronic disease similar to the aging process, obviously obesity cannot be simply considered the result of an energy imbalance between calorie intake and expenditure. Thus, a host of metabolic abnormalities, oxidative stress, mitochondrial dysfunction, immune dysfunction and chronic low-grade inflammation have been identified in the overweight obese organism (153, 158). While it has been almost universally established that adipose tissue (AT) responds to overnutrition by mounting an immune response, the initial inflammatory trigger remains unfortunately unknown. As a result, the clinical efficacy of drugs targeting the presently discovered inflammatory pathways has been disappointing. Perhaps, as discussed later in this review, little attention has been devoted to endogenous antiinflammatory mediators, other potentially intriguing therapeutic targets in AT inflammation. In this review, we summarize the most recent findings about AT inflammation and obesity, highlighting physiologic, cellular and molecular mechanisms through which AT inflammation contributes to AT dysfunction and related systemic complications.

The inflammatory phenotype of white adipose tissue

White adipose tissue (WAT) is the major fat storing depot and also serves as the largest endocrine organ to secrete adipokines and cytokines systemically. Adipokines are involved in various metabolic and physiologic signaling cascades and regulate insulin signaling, glucose uptake, fatty acid oxidation, and other energy producing and metabolic processes (2). Cytokines regulate inflammation and resolution of inflammation along with adaptive and reparative angiogenesis. Weight gain and obesity cause a phenotypic switch of WAT which is characterized by the appearance of inflamed dysfunctional adipocytes along with infiltration of immune cells in the stromal vascular fraction (80, 81). Inflamed adipocytes secrete, both locally and systemically, pro-inflammatory cytokines which in turn disrupt the normal function of AT itself as well as that of remote organs (79). From this standpoint AT can be considered as an immune and secretory organ, and obesity as an inflammatory immune disease (Figure 1).

Both animal and human studies have confirmed the association between increased adiposity and AT inflammation following excessive caloric intake. Using several immunocompromised mouse models, Lee YS et al. demonstrated the essential role of inflammation in the establishment of insulin resistance following long-term consumption of an obesogenic western-type diet (115). A unique feature of the inflammatory responses of expanding WAT is its duration and intensity, i.e., a persistent, low-grade inflammation that fails to resolve. Such obesity-related chronic low-grade inflammation and subsequent altered metabolism has been termed

"*metaflammation*" (80). Inflammation in general is an energy wasting process that enhances energy expenditure and reduce energy intake in direct and indirect manners. Directly, inflammatory cytokines, such as TNF-α, IL-1, and IL-6, induce energy expenditure by binding to signaling receptors located in the central nervous system or in the tissue of metabolic active organs. Indeed, they are provided with leptin-like properties that promote energy expenditure (9, 217) (151). Induction of leptin expression represents a molecular mechanism of the inflammatory activity. Leptin expression is increased in adipose tissue by inflammation. Leptin transcription is induced by hypoxia (66) and inflammatory mediators (67), all of which is experienced by expanding adipose depots. Furthermore, leptin receptor expression is induced by TNF-α (60), which provides a mechanism by which pro-inflammatory cytokines enhance leptin activity for energy expenditure. Leptin is an adipokine that inhibits appetite and induces energy expenditure (131), thus indirectly increasing energy expenditure.

Surprisingly, the unique features of AT inflammation induced by over nutrition are not associated with a significant increase in energy expenditure, which permits the coexistence of inflammation and weight gain in obese people (31). Nonetheless, inflammation of AT still shares several commonalities with the traditional inflammatory response, that is the infiltration of bone marrow derived immune cells and the secretion of inflammatory mediators including, but not limited to, chemokines and cytokines by adipocytes and resident immune cells. Moreover, because of its conspicuous mass and

distribution, even in the apparently healthy normal weight individual, the inflamed WAT can cause widespread systemic inflammation via release of cytokines (147).

Based on its anatomic location and morphological structure (reviewed in (176)), WAT develops diverse and unique inflammatory phenotypes. Accordingly, it is currently well established that obesity instigates a more complex and intense inflammatory reaction in visceral WAT (VAT) than in subcutaneous WAT (SAT). Indeed, VAT contains more macrophages compared with SAT in obese mice (6, 130, 145) and obese humans (28, 75, 76). With obesity and insulin resistance VAT adipocytes experiences a much higher degree of hypertrophy than SAT in both humans (74, 138) and animal models (94). Furthermore, VAT inflammation in obese humans is associated with decreased expression of lipogenic markers (166), probably due to the fact that more cells are switched to an inflammatory rather than to a lipid storage phenotype, which leads to the development of metabolic complications, such as ectopic lipid deposition in skeletal muscle and liver (166). Since ectopic lipid deposition dampens peripheral insulin signaling, VAT inflammation is considered to play a major impact on obesity-related metabolic disorders such as systemic insulin resistance and development of type 2 diabetes (74, 96, 148). While these lines of research support a higher involvement of VAT inflammation in obesity-related complications, it should be nonetheless noted that many investigators have reported convincing evidence of a role for SAT inflammation in metabolic complications (1, 148, 210). The ongoing controversy on the role that different WAT depots play in metaflammation has been partially addressed in mice. To explain the mechanism underlying the different impact of VAT

and SAT on metabolism, Rytka et al. artificially increased fat mass in mice by transplanting epididymal VAT obtained from littermates C57Bl6/J donor mice into the parietal peritoneum that drains in the caval system or the mesenterium that drains in the liver portal system. The procedure induced AT inflammation in both experimental groups of transplanted mice. However, only the mice with mesenterium transplanted fat experienced elevated IL-6 levels and FFA in the portal vein and developed impaired glucose tolerance (172). Human studies of meal FFA uptake further confirm the heterogeneity in the metabolism of VAT and SAT. Expressed relative to the same mass of adipose tissue, meal FFA uptake is greater in intra-abdominal than abdominal subcutaneous fat in both sexes (87) (124). The direct uptake of plasma FFA is also greater in omental compared to abdominal subcutaneous fat of women (99). These data suggest that the anatomical location and the unique structural feature of VAT enable it to directly feed inflammatory cytokines and metabolites to important organs, such as the liver, which play a role in the regulation of insulin action and systemic metabolism.

In the next sections, we will summarize our current understanding of the cellular and molecular mechanisms implicated in the inflammatory response of the WAT in obesity.

The role of bone marrow adipose tissue (MAT).

In healthy adults, the approximatively 10% of adipose tissue located in the bone marrow also regulates whole body energy metabolism, along with local and systemic inflammatory responses. The role of MAT role in energy metabolism and inflammation

has been recently reviewed (16, 21); thus, here we will briefly discuss key relevant aspects of MAT's role in obesity. In terms of metabolic responses, MAT expresses and secretes both adiponectin and leptin. While in vitro studies have reported that primary cultured MAT express lower level of adiponectin (119, 163), studies in mice and humans have found higher levels of adiponectin expression and secretion in MAT over WAT (36). Furthermore, modulation of MAT mass is correlated to serum adiponectin abundance following caloric restriction (36) or treatment with thiazolidinediones (195). MAT also express and secrete leptin (110, 208).

The contribution though of bone marrow adipocytes to the metabolic and inflammatory complications of obesity remains somewhat controversial. Differently than visceral fat adipocytes, bone marrow adipocytes are characterized by lower expression levels of adipose-specific gene such as PPARg and FABP4, and higher abundance of inflammatory response signaling pathways. In vitro studies have shown that primary cultured bone marrow adipocytes secrete significant levels of IL-6, but only small levels of IL-1 and TNF alpha (109). Others instead have reported increased expression of inflammatory response genes such as TNF alpha, IL-6 and IL-1 beta (119). With high fat feeding, mice experience increases bone marrow adiposity with adipocytes that surprisingly express decreased inflammatory genes such as TNF alpha and IL-1 beta, (202). It should be noted though that MAT is unquestionably the prevalent source of immune cells for other adipose depots and metabolic organs in obesity. Thus, it is reasonable to conclude that cytokine production by MAT adipocytes might be mainly important to regulate bone marrow kinetics and that MAT

196 contribution to systemic inflammation in obesity is indirectly supported by production
197 and release of immune cells.
198
199 ***Macrophages, Master Regulators of WAT Inflammation***
200 Infiltration of bone marrow derived inflammatory cells is a key feature of the
201 WAT metaflammation. It is well established that infiltration of inflammatory cells in
202 expanding WAT almost invariably causes adipocyte dysfunction and metabolic
203 dysfunction, such as glucose intolerance and insulin resistance. AT Macrophages
204 (ATMs) were the first immune cell population to be discovered and studied in this
205 process (223), although more recent reports have emphasized the role of earlier
206 neutrophil infiltration (discussed later). During local and systemic inflammatory
207 responses, tissue resident macrophages present antigens to initiate recruitment of other
208 immune cells and secrete cytokines to regulate inflammatory signaling cascades in the
209 host tissue. This physiological role of macrophages appears to be maintained also in the
210 metaflammation of expanding WAT depots (146, 224). The relevance of this
211 phenomenon is confirmed by several clinical reports demonstrating ATMs infiltration
212 in the WAT of obese humans (23, 42, 43, 76, 148, 238). Furthermore, clinical studies have
213 also clarified the relationship between ATMs infiltration in WAT and insulin resistance.
214 WAT obtained from insulin resistant and obese patients contains more macrophages
215 with increased expression of pro-inflammatory mediators (74), and this phenomenon
216 strongly correlates with metabolic dysfunction (96, 226).

Activated ATMs are the main source of pro-inflammatory mediators such as TNF-alpha, iNOS, MCP-1 and IL-6 (224, 232). Hotamisligil et al. initially reported in 1993 that the gene and protein expression of TNF-a are upregulated in AT, especially in ATMs, obtained from obese animal models (82). This first observation was followed by many confirmatory studies in laboratory animals and humans showing the upregulation of proinflammatory adipokines including TNF alpha, IL6, IL18 and MCP-1 in obesity, and their role in the development of insulin resistance and type 2 diabetes (82, 83, 194, 224, 232). The importance of cytokines secreted by ATMs in whole-body metabolisms was mechanistically elucidated by Aouadi M et al. who showed that ATMs-specific silencing of TNF-a and osteopontin using siRNA improves insulin sensitivity and glucose tolerance (10). Osteopontin is a more recently studied inflammatory mediator that appears to favor infiltration, survival, and proliferation of monocytes/macrophages in WAT (201). IL-1 beta produced by the NOD-, LRR- and pyrin domain-containing 3 (NLRP3) inflammasome regulates adipose tissue inflammation during obesity (212) (113) (236). And inhibition of NLRP3 reduces pro-inflammatory cytokines and subsequent macrophage infiltration (240). Proteoglycans are also known to regulate inflammation. Recent report revealed that, in obese condition, adipocytes produce versican and macrophages produce biglycan, and the crosstalk between these proteoglycans affect adipose tissue inflammation and insulin resistance (73).

Recent studies have also emphasized the existence of a complex interplay between WAT signaling and the CNS, an organ that contributes to regulation of

metabolism at multiple steps (reviewed in (85)). A recent line of research demonstrates that factors involved in axonal growth are also implicated in WAT inflammation. Neuroimmune guidance cue netrin-1 and semaphorin 3E (SEMA3E) with its receptor olexinD1 are regulators of the development of neuronal system that are upregulated in the obese WAT where they function as chemoattractant for macrophages (169, 181, 185), also by inhibiting macrophage egression (211). Similarly, the neuronal cytokine fractalkine (CX3CL1) and its receptor modulate monocyte adhesion to adipocyte (179).

The classic accepted paradigm is that tissue resident macrophages originate from bone marrow monocytes that infiltrate tissue during physiologic immunosurveillance or in response to inflammatory events. Interestingly, diet-induce obesity increases the circulating levels of CD11b(+) monocytes, which express the chemoattractant receptor leukotriene B(4) receptor (BLT-1) and BLT-1 has been shown to sustain monocyte trafficking to WAT (191). More recently it has been shown that proinflammatory ATMs express genes involved in myelopoiesis and immune cell recruitment, a process that affects circulating levels of monocytes and neutrophils (19, 132). Thus, obesity generates a self-feeding cycle of monocyte/macrophage infiltration to sustain low-grade chronic inflammation of WAT.

While this classic monocyte/macrophage recruitment remains a confirmed mechanism of inflammatory cell infiltration in expanding WAT, a new emerging concept in the field is that of local macrophage proliferation. Cytokines such as IL-4 are reported to stimulate local macrophage proliferation in AT (86). This local proliferation of ATMs occurs mainly at crown-like structures (CLS) that surround necrotic

adipocytes, resulting in a preferential increase of M2 macrophage in WAT (69). The consequence and impact of local ATMs proliferation, especially of the M2 type, in the pathophysiology of AT dysfunction and metaflammation remains uncharacterized and fertile ground for future research in the field.

The phenotype of obese ATMs is polarized to a pro-inflammatory state, a phenomenon that has been associated to metabolic complications (58, 121, 183, 226). In lean, insulin sensitive mice, ATMs express anti-inflammatory genes such as IL-10 and arginase 1, whereas ATMs in obese mice highly express pro-inflammatory genes such as TNF-a and iNOS (120). Similarly, the major characteristic of WAT obtained from patients with metabolic abnormalities, such as type 2 diabetes patients, is adipocyte hypertrophy with high infiltration of pro-inflammatory macrophages (1). These "metabolically activated" pro-inflammatory ATMs function within the context of low-grade inflammation and therefore appear to have important distinctions compared with classically activated M1 macrophages that occur within the context of a full-fledged inflammatory reaction. In fact while M1 macrophages in acute inflammatory reactions highly express CD38, CD274 and CD319 on their cell surface, the ATMs of the obese organism do not (102); they actually show less inflammatory phenotype with different gene expression profile compared with classically activated M1 macrophages (233). As result, the expression of pro-inflammatory cytokines such as TNF-a and IL-6 in obese ATMs remains lower than classically activated M1 macrophages (102). While these observations are consistent with the occurrence of low-grade inflammation in obesity, the question remains as to how this lower degree of immune cell activation is achieved

283 and maintained. Current research supports the concept that the concomitant activation
284 of endogenous anti-inflammatory cascades is responsible for dampening macrophage
285 activation and overall WAT inflammation in obesity. Thus, recruitment of anti-
286 inflammatory macrophages via increased IL-10 expression has been observed in WAT
287 after HFD (58), and deletion of IL-10 from the hematopoietic system worsened HFD-
288 induced inflammation and insulin resistance as one may have predicted (101). Similarly,
289 we have observed increased expression levels of the proangiogenic and anti-
290 inflammatory cytokine IL-19 in stromal vascular fraction and visceral adipocytes of
291 mice given a HFD (unpublished observation and Figure 2). Others have implicated a
292 role for IFN-gamma, another key regulator of macrophage activation and phenotypic
293 switches. Thus, IFN-gamma knockout mice exhibit less inflammatory ATMs in
294 conjunction with decreased adipocyte size and increased insulin sensitivity following
295 HFD (141). Furthermore, interferon regulatory factor (IRF)-5 expression is upregulated
296 in obesity, and IRF-5 expression is positively correlated with macrophage infiltration
297 and the secretion of proinflammatory adipokines (188).

298 Molecular mechanisms operating within macrophages themselves have also been
299 investigated. Thus, it has been reported that suppression of macrophage activation in
300 obesity is partially controlled via adenosine receptors expressed on macrophages, and
301 that these receptors could respond to accumulation of local catabolites (47, 157). In a
302 similar line of research, the inositol-requiring enzyme 1 alpha (IRE1alpha), a key
303 regulator of endoplasmic reticulum stress in metabolic organs, has been recently
304 investigated. Shan B et al. have implicated IRE1alpha in the regulation of WAT

inflammation (180) by showing that myeloid-specific IRE1alpha knockout mice have a reduced inflammatory phenotype and are protected from HFD-induced obesity, insulin resistance, hyperlipidemia and hepatic steatosis (180). More clinically relevant, the peroxisome proliferator-activated receptor (PPAR)-gamma has also been implicated in regulation of insulin resistance as well as inflammation. PPAR-gamma is essential for modulation of metabolically activated macrophages, suggesting that PPAR-gamma may increase macrophages with an anti-inflammatory phenotype and therefore it improves glucose metabolism via an anti-inflammatory mechanism in addition to its direct metabolic actions (142, 167).

Despite this wealth of knowledge, currently anti-inflammatory therapies have unfortunately failed to correct the metaflammation of obesity, which poses both a puzzling research question and a therapeutic obstacle. To help explain these unexpected negative results, Scherer et al. have recently demonstrated that inflammatory cytokines signaling is paradoxically required for appropriate expansion and metabolic flexibility of WAT. They found that congenital silencing of TNF-a or IL1-beta function in diet induced obese mice further exacerbates insulin resistance and glucose intolerance due to loss of compensatory angiogenesis and insufficient WAT remodeling (227). Consistent with this study, clinical data have yielded contrasting evidence on the effect of TNF-□ and IL1- beta blocking therapy on glycemic control and insulin sensitivity in obese, diabetic patients. Thus, systemic blockade of TNF-a does not improve insulin resistance in humans and blockade of IL1-beta with Canakinumab was not associated with any reduction in the rate of incident diabetes in prediabetic insulin resistance

patients (48, 56). Overall, how the balance between pro- and anti-inflammatory cytokines ultimately determines whether or not an expanding adipose depot develops a dysfunctional degree of inflammation which impairs its metabolic activity remains insufficiently explored and poorly understood. Further studies are needed to fully understand the link between cytokines and metabolism to identify new therapeutic targets.

Infiltration of Other Immune Cells

While macrophages are the most studied and undoubtedly important immune cell type involved in AT inflammation, other immune cells such as neutrophils and lymphocytes appear to play relevant mechanistic roles (125, 170) (Figure 1). Animal studies demonstrate that administration of an HFD to lean mice causes a very early infiltration of neutrophils in VAT, before the onset of insulin resistance and obesity (51). These infiltrated neutrophils initiate recruitment of macrophages and other antigen-presenting cells. Bi-directional crosstalk between adipocytes and neutrophils has been recently reported to cause WAT inflammation via IL1-beta production with the involvement of infiltrating macrophage (221). This neutrophil-dominated early inflammatory cascade was found causal to the development of hepatic insulin resistance and metabolic disorders (70, 197). Prevention of WAT neutrophil infiltration by inhibiting cytosolic phospholipase A2 alpha (cPLA2a) or the endothelial cell adhesion molecule ICAM-1 reduced TNF-a secretion from adipocytes, preserved hepatic insulin signaling, and prevented abnormal gluconeogenesis (70). Neutrophil

elastase secreted from infiltrated neutrophils was found to be one of the key components affecting metabolic functions. Neutrophil elastase inhibitors or the deletion of neutrophil elastase in mice preserved insulin sensitivity and attenuates ATMs infiltration in HFD-fed mice (197).

The infiltration of T cells into expanding adipose depots is also considered to be another important, although controversial (115), mechanism for macrophage recruitment and WAT inflammation (95, 136). Similar to ATMs, views on the immunomodulation of T-cells in expanding adipose depots remains somewhat controversial, especially for the role of regulatory T cells (Tregs). Some studies reported down regulation of Tregs in obese states, potentially resulting in chronic WAT inflammation and subsequent insulin resistance (46, 57, 152, 229). Others have negated a role for Tregs in obesity (206, 239). The natural killer T (NKT) cells have also been implicated, with more recent reports suggesting that HFD increases invariant NKT-1 cells (iNKT1) along with pro-inflammatory ATMs and decreases invariant NKT cells 10 (iNKT10) along with anti-inflammatory ATMs indicating a role for iNKT cells in the amount of M1 ATMs that invade WAT depots (37, 139). The readier should be aware also of the fact that T-cell infiltration in WAT fluctuates with weight cycling between obese states and weight loss states (8). Interestingly, weight loss induces WAT inflammation, which in turn impairs insulin sensitivity by decreasing PI3K, phosphorylated protein kinase B (PKB) and glucose transporter (GLUT) 4 expression (116). In contrast, long-term ketogenic diet containing extremely high fat causes the depletion of gamma delta T cells, and mice lacking gamma delta T cells show impaired

371 glucose metabolisms (63). These results suggested that gamma delta T cells had
372 protective effects on adipose tissue inflammation.

373 Obesity has been also associated with upregulation of B cells (228), which,
374 although based on limited studies, induces insulin resistance via the activation of T-cell
375 and AMTs in obese conditions (50, 228). B cell cytokine production appears to be
376 regulated by activation of the toll like receptors (TLRs) in type 2 diabetes inflammation
377 (84).

378 Mast cells and dendritic cells also accumulate in obese AT (18, 118). Dendric
379 cells promote macrophage infiltration into WAT and liver (193), or maintain T cell
380 homeostasis in WAT (165).

381 Lastly, the role of eosinophils has been also explored by Wu et al., who reported
382 that eosinophils play unique roles in metabolic homeostasis by regulating alternatively
383 activated macrophages (230).

384

385 ***The contribution of Adipokines.***

386 Expanding adipocytes themselves produce various mediators in an autocrine
387 fashion, which are able to promote or attenuate WAT inflammation (Figure 2). These
388 mediators have both immunomodulating and metabolic functions and are collectively
389 termed adipokines. Although the functions of adipokines and their crosstalk are not
390 fully understood, adipokines have emerged as key regulators of WAT metabolic
391 homeostasis, and perhaps systemic inflammation. Adipokines secreted from adipocytes
392 not only contributed to localized WAT inflammation (108), but can also induce systemic

393 elevation of cytokines responsible for peripheral insulin resistance (209, 213).
394 Adipokines also facilitate infiltration of macrophage in WAT via IRF7-mediated
395 upregulation of MCP-1 (106) and its receptor C-C chemokine receptor-2 (CCR2) (26, 91,
396 128, 200, 222). An important example of this paradigm is offered by Chemerin, an
397 adipokine associated with obesity, inflammation, angiogenesis, and metabolic
398 syndrome. Chemerin regulates leukocyte recruitment into inflamed organs (24, 25, 34);
399 adipose depots expressing low level of chemerin maintains normal insulin signaling
400 and a non-inflammatory phenotype (32, 196). Calprotectin has been elucidated as
401 another adipokine upregulated in obesity, implicated in WAT inflammation via
402 enhancing adhesion of circulating monocytes or recruitment of macrophages (22, 33,
403 127).

404 Along with proinflammatory cytokines, adipocytes also secrete anti-
405 inflammatory cytokines, whose abundance and secretion appear to be reduced with
406 weight gain since obesity definitively skews the balance in favor of inflammatory
407 adipokines. Adiponectin is considered the most important of these mediators with
408 several seminal findings by our laboratory and others elucidating its anti-inflammatory
409 actions (149). Silencing of adiponectin exacerbates insulin sensitivity (39, 105). Of note,
410 the expression of adiponectin in WAT is suppressed in acute inflammatory conditions
411 as well as in chronic obesity (53, 234), while its overexpression reduces WAT
412 inflammation and improves insulin sensitivity (94). Several molecules have been
413 involved in the regulation of adiponectin expression, which may represent targets of
414 antiinflammatory drug therapy. Thus, treatment of adipocytes with glucagon-like

peptide-1 (GLP-1) analogs increase adiponectin expression (156). Estrogen also increases adiponectin expression and attenuates WAT inflammation (144, 168), which protects from insulin resistance. Notably, recent study reported women with metabolic syndrome show lower adiponectin and IL-6 level compared to men with metabolic syndrome (203), suggesting that there were sex-specific pathways regulating obesity-induced inflammation. Fat-specific deletion of Fsp27, a lipid droplet-associated protein expressed in adipocytes in mice causes attenuation of WAT inflammation via upregulation of adiponectin (241). However, Fsp27 null mice model remain insulin resistant, possibly because of hepatic steatosis (241), which underscore the complexity of multi-organ integrated functions such as the metaflammation of obesity, and the challenge of interpretation of genetic mouse models.

Taken together, these data suggested the existence of a vicious cycle between dysfunctional adipocytes and the immune system that helps perpetuate low-grade chronic inflammation in the obese organism. Time-course studies aimed at dissecting the temporal relationship between activation of relevant WAT cell types, including those found in the stromal vascular fraction, during feeding studies may provide important mechanistic information to help resolve the pathophysiology conundrum of WAT inflammation by uncovering potential therapeutic targets and intervention timing.

Molecular Mechanisms Regulating Adipocyte Inflammation

Many molecular mechanisms operating within adipocytes have been suggested as possible regulators of WAT inflammation, including endoplasmic reticulum (ER) stress, hypoxia, and cellular senescence (Figure 2). With long standing knowledge

linking ER stress with the insulin resistance of obesity and diabetes (133, 150), several recent studies have explored this field and uncovered a number of important data. In mice, a high fat diet induces ER stress and chronic inflammation in WAT via FFA-mediated increase of reactive oxygen species (ROS) (92). A more direct causal role for ER stress was demonstrated with genetic manipulation of the ER chaperone GRP78 an essential ER chaperone and a master regulator of ER homeostasis that operates as a repressor of the unfolded protein response (UPR) stress sensors. Macrophage-selective ER chaperone GRP78 knockout mice are protected from HFD-induced AT inflammation and insulin resistance (93). In addition, ER stress preconditioning protects against FFA-induced adipocyte inflammation through inhibition of the IKK/NF-kB pathway via X-box binding protein 1 (XBP1), a modulator of the UPR (219). Interestingly, obese, insulin resistant humans also experience higher levels of circulating saturated fatty acid (FFAs) compared with lean individuals (44, 77, 134, 184). Furthermore, in obese patients adipocyte markers of ER stress significantly correlate with BMI or percent body fat (182), and a recent clinical study reported that the amount and types of FFAs in cell membrane phospholipids is related to the inflammatory phenotype of ATMs; for instance, the proportion of pro-inflammatory ATMs increased with the proportions of palmitic or palmitoleic acids (162). Conversely, omega-3 fatty acids have been shown to exert protective effects on WAT inflammation via G protein-coupled receptor 120 (GPR120), an omega-3 fatty acids receptor (143).

Metabolism of FFA is mainly regulated by cell surface expressed lipases and the cytosolic fatty acid binding protein 4 (FABP4). In mice, WAT deletion of the hormone-

sensitive lipase (HSL) that regulates mobilization of stored fat induces WAT dysfunction and fatty liver (231), which is consistent with clinical observations showing that null mutation in the HSL gene is associated with WAT inflammation or increased risk of type 2 diabetes (3). FABP4 is secreted from adipocytes where it controls lipolysis and circulating FABP4 is elevated in metabolic disorders. In vitro treatment of adipocytes with FABP4 inhibits adipocyte differentiation and instigate adipocytes inflammation via the p38/NF-kB pathway (49). In a similar line of research, Koliwad SK et al. reported that overexpression of DGAT1 in adipocytes, the enzyme that catalyzes the conversion of diacylglycerol and FFAs to triglyceride (TG), attenuates AT inflammation with improved insulin sensitivity and glucose tolerance in HFD-fed mice, despite the exacerbated accumulation of triglycerides in liver or skeletal muscle (97). Hematopoietic deletion of the fatty acid translocase and the scavenger receptor CD36 that uptakes long chain fatty acids (FA) also attenuates WAT inflammation (135).

Research has focused on the Toll Like Receptor- 4 (TLR4) in the inflammatory action of FFAs in obesity. Earlier reports suggested that FFAs serve as chemokine inducers to initiate macrophage infiltration via IKK beta and JNK pathways, and this effect of FFAs is partially through TLR4 (89). More recently it has been reported that FFAs more directly stimulate TLR4, and initiate TLR4-dependent gene expression of lipid metabolic pathways and membrane lipid composition that promote the inflammatory cascade (54, 111). Furthermore, the expression level of tenascin C, an endogenous activator of TLR4, is also increased in obese WAT (15, 35). Accordingly, TLR4 mutant mice exhibit reduced AT inflammation, preserved adiponectin expression

and increased insulin sensitivity despite higher epididymal AT mass and adipocyte hypertrophy (161). Furthermore, global TLR4 silencing protects mice from AT inflammation, probably via reduced ER stress, augmented autophagy activity, attenuated senescence (62), and reduction of oxidative stress through metabolic reprogramming of mitochondria (117). On the other hand, TLR4 silencing in myeloid cells alone does not preserve insulin sensitivity, indicating the importance of TLR4 expression in metabolic organs in obesity (88, 173) At the mechanistic level, the high mobility group box protein 1 (HMGB1) initiates TLR4-dependent inflammation via NF-kB and P38 MAPK signaling with subsequent IL-6 secretion (68). TLR4-mediated macrophage activation (7, 29) has also been associated with alterations of gut microbiota due to changes in gut permeability following intake of fat diets (7, 29, 164). Similar to what we have discussed for cytokines, counter regulatory expression of other TLR types appears to take place in obesity. Thus, TLR9 expressed in adipocytes was found to have WAT anti-inflammatory actions, as demonstrated by significantly reduced adiponectin secretion and increased MCP1 secretion in TLR9 knockout mice (204).

Adaptive reactions induced by AT inflammation

Chronic low-grade inflammation mediates not only metabolic dysfunctions, but also the adaptive reactions necessary to maintain physiological conditions in WAT. Interestingly, many of these adaptive reactions are inflammatory in nature. For instance, cellular senescence is another contributor to WAT inflammation, and adipocytes death

503 is enhanced in obese mice and humans (38, 130). Furthermore, accumulation of
504 senescent T cells and endothelial cells occurs in the obese WAT (177, 187, 216), as well
505 as in the insulin resistant organism (126, 177). Upregulation of senescence markers such
506 as p16, EGFP and beta-galactosidase has been reported in expanding VAT depots (177).
507 Since senescent cells are known to secrete pro-inflammatory cytokines (40), it is quite
508 likely that cellular senescence instigates WAT inflammation in obesity. In support of
509 this view, mice lacking programmed cell death-4 (PDCD4), a selective protein
510 translation inhibitor, are protected from HFD-induced obesity and WAT inflammation
511 (220).

512 With expansion, AT becomes also hypoxic due to insufficient vascular supply
513 (reviewed in (207)). The reduced oxygenation of obese fat depots remains even in the
514 face of compensatory angiogenesis (64, 72). The ensuing hypoxia contributes to the
515 increased secretion of inflammatory adipokines, decreased expression of adiponectin,
516 and upregulation of hypoxia-inducible factor 1 alpha (HIF-1alpha) (78, 140, 235). HIF-
517 1alpha increases macrophage infiltration and WAT inflammation (155). Relevant to
518 what we discussed in the section above, Snodgrass et al. reported that FFAs exacerbated
519 macrophage-mediated inflammation in response to HIF-1alpha (190). Indeed, HIF-
520 1alpha favors the M1 ATMs switch by increasing saturated fatty acid stimulation of the
521 adenine nucleotide translocase 2 (ANT2) (114), and activation of the interleukin-1
522 receptor associated kinase M (160). In addition to macrophages, infiltration of other
523 myeloid cells is also mediated by HIF-1alpha (41).

Hypoxia also negatively impacts adipocytes homeostasis. Thus, hypoxia enhances adipocytokine promoter hypomethylation via HIF1-alpha and ten-eleven translocation-1 (TET1) pathway in human adipocytes (5). Taken together, hypoxia in expanded adipocytes is one of the major regulatory mechanisms regulating WAT inflammation and insulin resistance (59).

Adaptive changes have also been described in the lymphatic system of WAT. The lymphatic system is involved in adipose metabolism by regulating lipid absorption and lipid transport and the trafficking of immune cells. HFD-fed obese mice have impaired lymphatic vessel function (20, 225). Clinical studies also found evidence of lymphatic vessel dysfunction in humans (11, 65). Obesity-induced lymphatic dysfunction appears to be related to perilymphatic inflammation (61, 137, 205) and is causative of WAT and fibrosis (175), via increased lymphatic system permeability (104). Recent publications have linked adipokines such as leptin and adiponectin to lymphatic function. Leptin causes lymphedema in obese patients via morphological change of lymphatic ducts (174). Importantly, adiponectin can improve lymphoedema in obese mice by promoting lymphatics formation via AMPK/ALT/eNOS signaling in lymphatic endothelial cells (186).

Inflammation as a therapeutic target in Obesity

Attenuation of WAT inflammation in obesity has been explored in preclinical and clinical studies as a possible treatment strategy to avert the metabolic and vascular complication of obesity. Unfortunately, the data obtained have yielded controversial

546 results and have also made clear the difficulty of translating results obtained in animal
547 models of obesity to humans.

548 Clinical reports have investigated anti-cytokine therapy in the fight against
549 insulin resistance, based on evidence of elevated TNF-α in the serum of obese patients.
550 The mechanistic value of this correlative association has been confirmed with studies
551 demonstrating that administration of TNF-α to laboratory animals and humans impairs
552 insulin sensitivity [9, 128]. In line with this results, some human studies have reported
553 reduced glucose intolerance in overweight individuals and reduced progression to T2D
554 in patients with rheumatoid arthritis following TNF-α neutralization [132, 133]. To the
555 contrary, others have reported lack of improved insulin sensitivity in people with T2D
556 patients [129, 130] or rheumatoid arthritis [131] following anti-TNF-α therapy.
557 Discrepant results have been reported also in healthy volunteers in which TNF-a
558 infusion increased glucose uptake in skeletal muscle [134]. Recent evidence in humans
559 have also implicated IL1-beta. However, in the recent CANTOS trial, IL1-beta inhibition
560 with canakinumab failed to reduce HbA1c, glucose or insulin levels in diabetic patients
561 [150]. This dichotomy between WAT inflammation and metabolism is also observed at
562 the cellular level and in response to diet and lifestyle intervention and even bariatric
563 surgery. Although it is well-established that obesity causes infiltration of ATMs in WAT,
564 calorie restriction or rapid weight loss, which improve insulin sensitivity, paradoxically
565 increase the number of ATMs or pro-inflammatory cytokines both in animal models (98,
566 107, 237) and human obesity (4, 30, 71, 103, 198, 215). Thus, in spite of improvement of
567 systemic metabolic functions, WAT inflammation or the infiltration of resident

macrophages are not changed after weight loss (123, 237). Similarly, the expression of pro-inflammatory genes in WAT is unchanged in the early phase of a very low calorie diet but increases in the later phase (192). Instead, high-intensity exercise improves macrophage polarization toward the anti-inflammatory phenotypes (14). Calorie restriction accompanied with eccentric exercise is also reported to upregulate anti-inflammatory macrophages and downregulate pro-inflammatory macrophages (122). To complicate matters, short-term overfeeding to healthy normal or overweight individuals did not cause upregulation of pro-inflammatory gene expression or macrophage infiltration in SAT, despite the increased body weight and reduction in insulin sensitivity (90, 199). What appears to be important in reducing ATMs infiltration and WT tissue inflammation is the duration of weight loss more than its total reduction (13, 27, 30, 100). Future studies should focus on understanding how chronic adaptation to weight gain and weight cycling links WAT inflammation to insulin resistance. More importantly, integrative physiological studies should be undertaken to fully evaluate the interplay between diet induced WAT inflammation and the function of other metabolic organs such as the cardiovascular system, skeletal muscle and liver.

Many researchers have also investigated the impact of rapid weight loss with bariatric surgery on WAT inflammation, but the results are not consistent. Some studies reported the reduction of WAT inflammation with the improvement of insulin sensitivity after bariatric surgery (12, 27, 214). Conversely other studies show no or only minor changes in AT inflammation after surgery (71, 103, 154). Schmitz J et al.

590 reported that improved inflammation and insulin action in liver could improve
591 systemic glucose homeostasis such as insulin sensitivity after bariatric surgeries, even if
592 the WAT inflammation parameters including the number of ATMs were not
593 significantly affected (178). Others have reported increased neutrophil infiltration in
594 WAT after bariatric surgery (71, 103).

595 Several pharmacological and genetic modification strategies have also been
596 investigated in the fight against obesity and metaflammation. In this context, melatonin,
597 a potent antioxidant that improves inflammatory responses and energy metabolism, has
598 been shown to attenuate obesity-associated complications via decreasing inflammatory
599 adipokines including IL-6, MCP-1, leptin and TNF-a (45, 55). Inhibition of glycogen
600 synthase kinase 3 (GSK3), a protein-serine kinase that lies downstream of multiple cell
601 signaling pathways, also reduces WAT inflammation by suppressing migration of
602 monocytes, favoring apoptosis of macrophage, inactivating STAT3, and reducing the
603 levels of FFAs or chemokines secreted by VAT (218).

604 Genetic modifications have been performed in several mouse models in which
605 the link between WAT inflammation and insulin resistance has been carefully
606 investigated. For example, mice overexpressing calpastatin, the endogenous inhibitor of
607 the calcium-dependent protease calpain, show reduced adipocyte apoptosis and
608 macrophage infiltration in WAT (129). Deletion of C1q/TNF-related protein 7 (CTRP7),
609 a secretory protein of the C1q family, in mice is also improve WAT inflammation,
610 insulin resistance probably via decreased oxidative and ER stress (159).

611

612 ***Conclusion and future direction***

613 In this this review article we have attempted to summarize our current
614 understanding of the role that WAT inflammation plays in the metabolic complications
615 of obesity by highlighting the most recent preclinical and clinical studies. The last
616 decade has clearly demonstrated the existence of a strong relationship between WAT
617 inflammation and insulin resistance, glucose intolerance, type 2 diabetes and obesity.
618 However, numerous knowledge gaps continue to limit our understanding of the
619 complex interactions among adipokines and systemic pathophysiology. Investigation
620 in WAT inflammation have several difficulties to overcome. First, other organs such as
621 brain, liver, and skeletal muscles also contribute to metabolic dysfunction, and an
622 improvement of WAT inflammation is usually associated with an improvement of other
623 organ function that also impact on insulin sensitivity. These integrative metabolic
624 responses make difficult, if not almost impossible, to isolate the mechanistic
625 contribution of WAT inflammation to obesity complications in intact physiologic
626 system. Second, a current limitation of the research in the field is that the fragility of
627 adipocytes makes it difficult to preserve the integrity of the tissue under study. Thus,
628 our current models of the basic mechanisms governing WAT remodeling in obesity are
629 mostly based on extrapolations from *in vitro* or *ex vivo* biochemical approaches or
630 conventional histological analysis. Although these approaches remain useful, they yield
631 limited translational value, as they are inadequate to study integrated physiological
632 responses. Obviously, our understanding of these phenomena would greatly benefit
633 from the availability of tools enabling *in vivo* analysis. Third, there are substantial

differences in characteristics and cell surface markers of immune cells between rodents and humans, and therefore careful interpretation of data obtained in animal models of obesity are warranted. More importantly, genetically modified mice should be validated with the use of wild-type mice in which changes in the target gene byproducts should be observed following induction of obesity. Finally, clinical studies have a limited view of WT tissue inflammation due to the fact that they are largely based on omental fat pad because of accessibility. Since fat depots in different region of the body assume diverse inflammatory phenotypes inclusion of additional adipose depots in future studies may provide a more comprehensive view in the field. We hope the current review will stimulate new interest in this field and will promote obesity research.

Acknowledgments

This work was supported by grant DK096521 to R. Scalia and grants HL141108 and HL117724 to M.V. Autieri.

651 **Figure legends**
652
653 **Figure 1.** The inflammatory phenotype of expanding adipose tissue. Hypertrophic
654 adipocytes and tissue resident immune cells experience phenotype changes that halt
655 secretion of antiinflammatory, protective cytokines to begin secretion of inflammatory
656 adipokines and cytokines that act both locally and systemically to induce peripheral
657 insulin resistance. The inflammatory reaction is sustained by adipocyte-derived
658 chemoattractants such as CCR2, MCP, and SEMA3A.

659
660 **Figure 2.** With increased energy storage and FFAs cargo, white adipocytes undergo
661 abnormal expansion, which results in hypoxia and remodeling-induced senescence.
662 Hypoxia and senescence initiate and sustain chronic low-grade inflammation. Under
663 these condition, adipocytes experience ER stress and increased ROS production.
664 Dysfunctional adipocytes also secrete inflammatory cytokines at the expenses of
665 production of protective adipokines, such as adiponectin. Noteworthy, inflamed
666 adipose depots also express antiinflammatory mediators, such as IL10 and IL19, whose
667 role in the overall regulation of the immunometabolic response of adipose tissue
668 adipose tissue remains largely unexplored.
669

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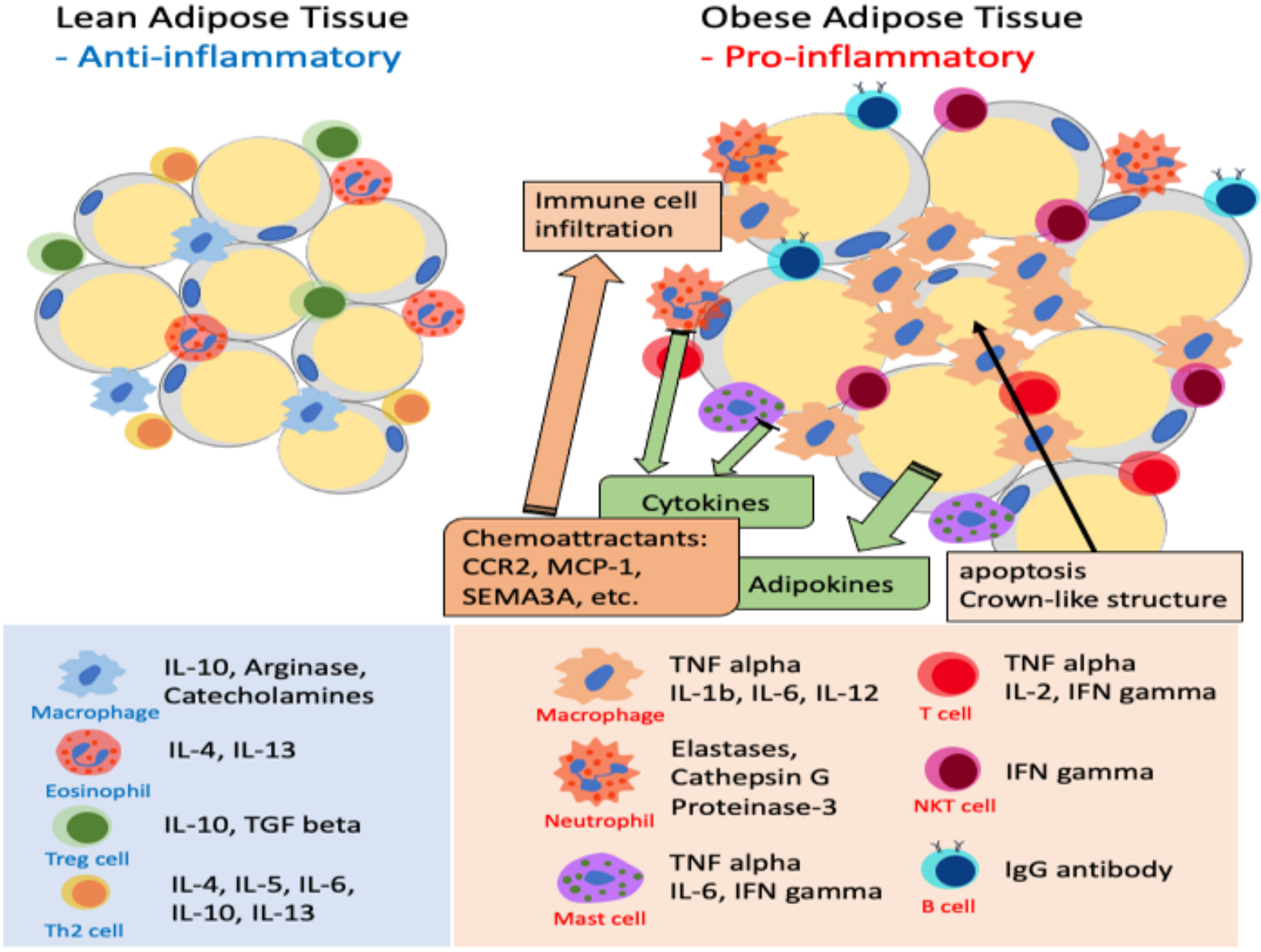
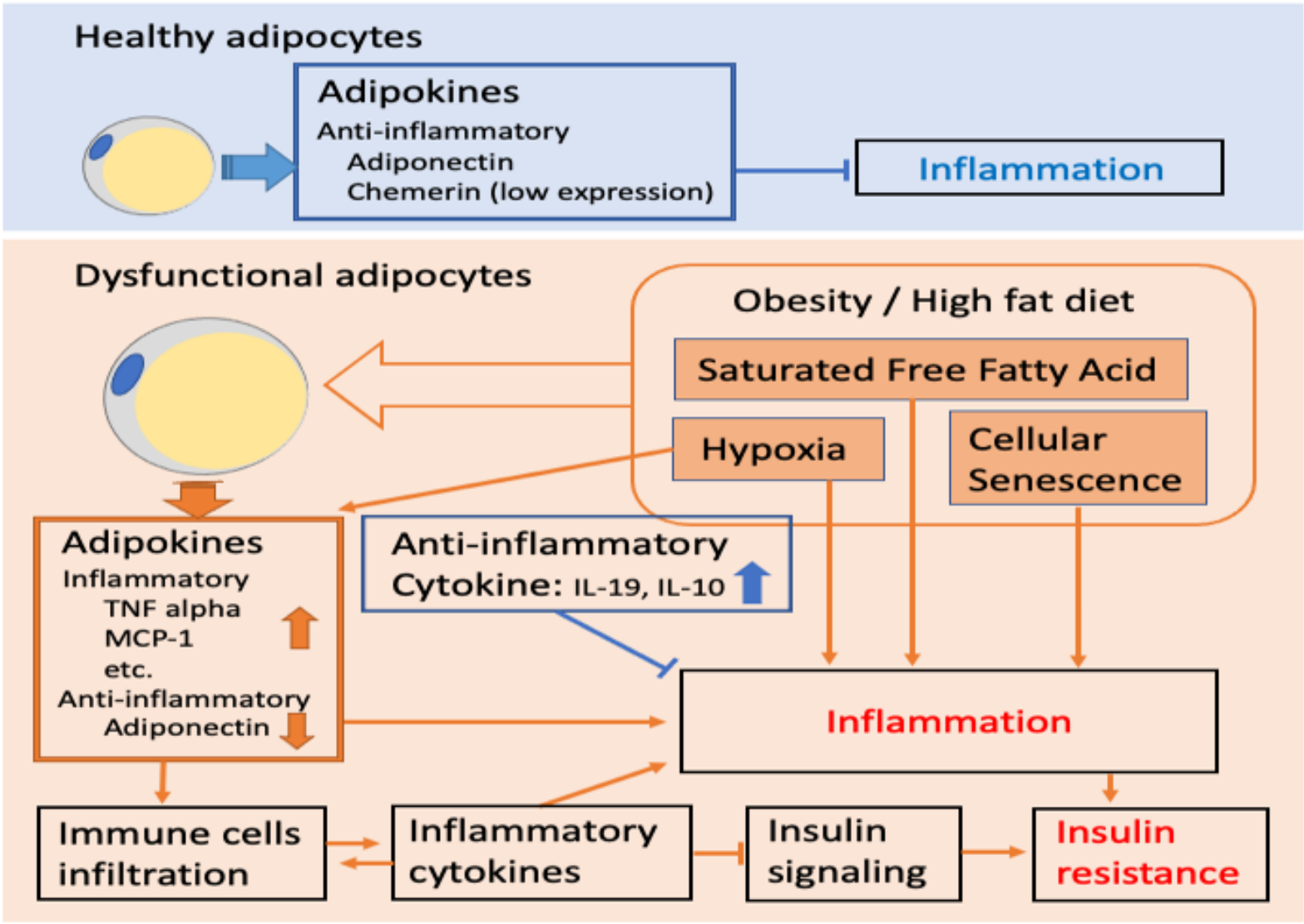

Lean Adipose Tissue
- Anti-inflammatory
Obese Adipose Tissue
- Pro-inflammatory
Immune cell infiltration
Cytokines
Chemoattractants: CCR2, MCP-1, SEMA3A, etc.
Adipokines
apoptosis
Crown-like structure
Macrophage
IL-10, Arginase, Catecholamines
Eosinophil
IL-4, IL-13
Treg cell
IL-10, TGF beta
Th2 cell
IL-4, IL-5, IL-6, IL-10, IL-13
Macrophage
TNF alpha IL-1b, IL-6, IL-12
Neutrophil
Elastases, Cathepsin G Proteinase-3
Mast cell
TNF alpha IL-6, IFN gamma
T cell
TNF alpha IL-2, IFN gamma
NKT cell
IFN gamma
B cell
IgG antibody


Healthy adipocytes
Adipokines
Anti-inflammatory
Adiponectin
Chemerin (low expression)
Inflammation
Dysfunctional adipocytes
Obesity / High fat diet
Saturated Free Fatty Acid
Hypoxia
Cellular Senescence
Adipokines
Inflammatory
TNF alpha
MCP-1
etc.
Anti-inflammatory
Adiponectin
Anti-inflammatory Cytokine: IL-19, IL-10
Inflammation
Immune cells infiltration
Inflammatory cytokines
Insulin signaling
Insulin resistance