


Review

# Adipose Tissue Paracrine-, Autocrine-, and Matrix-Dependent Signaling during the Development and Progression of Obesity

Elizabeth K. Johnston and Rosalyn D. Abbott \* 

Department of Biomedical Engineering, Carnegie Mellon University, Pittsburgh, PA 15213, USA

\* Correspondence: rabbott@andrew.cmu.edu

**Abstract:** Obesity is an ever-increasing phenomenon, with 42% of Americans being considered obese (BMI  $\geq 30$ ) and 9.2% being considered morbidly obese (BMI  $\geq 40$ ) as of 2016. With obesity being characterized by an abundance of adipose tissue expansion, abnormal tissue remodeling is a typical consequence. Importantly, this pathological tissue expansion is associated with many alterations in the cellular populations and phenotypes within the tissue, lending to cellular, paracrine, mechanical, and metabolic alterations that have local and systemic effects, including diabetes and cardiovascular disease. In particular, vascular dynamics shift during the progression of obesity, providing signaling cues that drive metabolic dysfunction. In this review, paracrine-, autocrine-, and matrix-dependent signaling between adipocytes and endothelial cells is discussed in the context of the development and progression of obesity and its consequential diseases, including adipose fibrosis, diabetes, and cardiovascular disease.

**Keywords:** white adipose tissue; angiogenesis; paracrine signaling; inflammation; vasoregulation; extracellular matrix; adipokine; obesity; fibrosis; atherosclerosis



**Citation:** Johnston, E.K.; Abbott, R.D. Adipose Tissue Paracrine-, Autocrine-, and Matrix-Dependent Signaling during the Development and Progression of Obesity. *Cells* **2023**, *12*, 407. <https://doi.org/10.3390/cells12030407>

Academic Editors: Meilian Liu and Weiqin Chen

Received: 20 December 2022

Revised: 19 January 2023

Accepted: 23 January 2023

Published: 25 January 2023



**Copyright:** © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

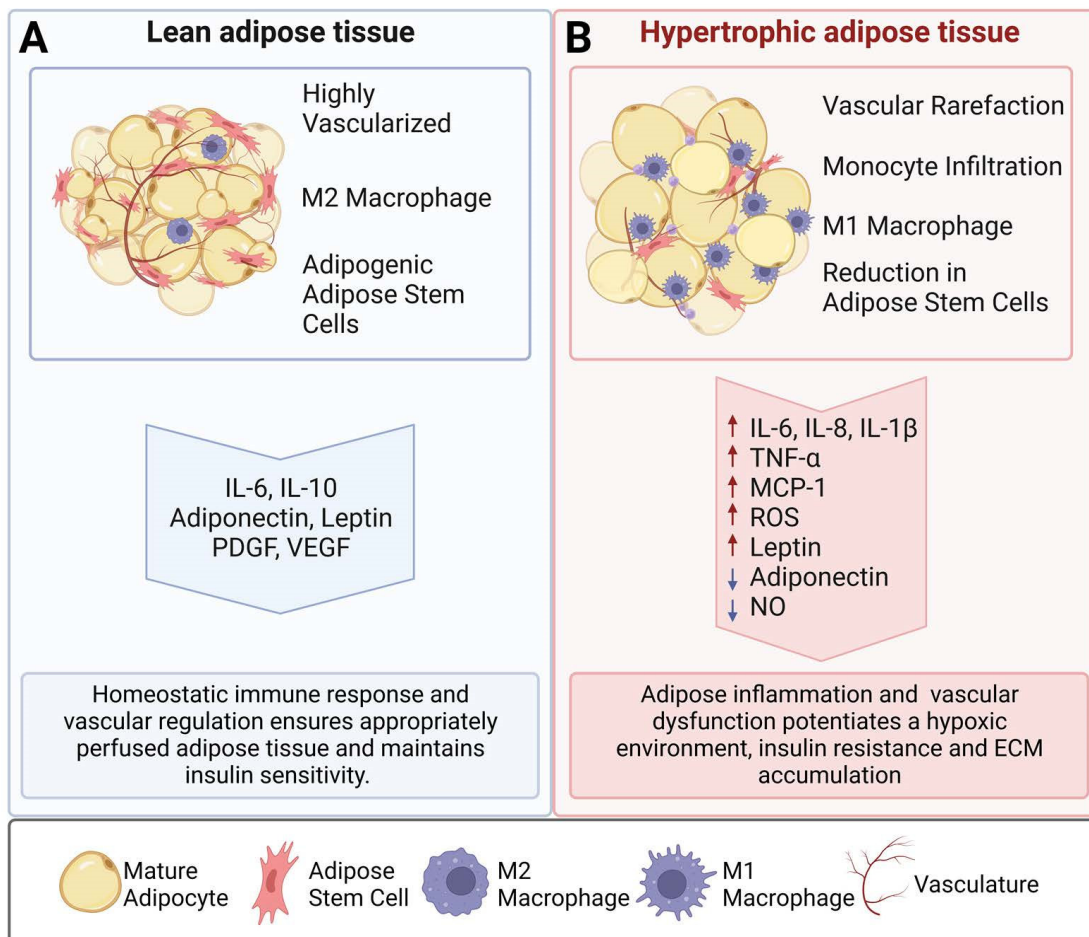
## 1. Introduction

Obesity is a complex phenomenon involving the accumulation of excess body fat. While there are genetic, behavioral, environmental, and hormonal influences on the development and progression of obesity, the basis of the disease lies in the premise of caloric excess, with this surplus being stored as triacylglycerols within adipose depots [1]. The prevalence of obesity has been continuously increasing, with approximately 42% of Americans being considered obese (body mass index (BMI)  $\geq 30$ ) and 9.2% being considered morbidly obese (BMI  $\geq 40$ ) between 2017 and 2018 [1,2]. With obesity being characterized as a chronic low-grade inflammatory disease, there are many alterations in the cellular populations within the tissue, lending to cellular, paracrine, mechanical, and metabolic alterations that have local and systemic effects, including cardiovascular and metabolic diseases. In particular, vascular dynamics shift during the progression of obesity, providing signaling cues that drive metabolic dysfunction [3].

Adipose tissue has a high degree of plasticity, whereby it can accommodate normal fluctuations in the body's energy intake and demand by regulating tissue size. Adipose tissue can expand either through adipocyte hypertrophy or hyperplasia, and it can shrink in a state of fasting or exercise in order to supply the necessary free fatty acids to other organs. This shrinkage occurs through a lipolytic mechanism, where triacylglycerols are broken down into free fatty acids and glycerol. Adipocyte hypertrophy, the growth of adipocyte cell size, occurs through lipogenesis; this converts free fatty acids into triacylglycerols, which are stored within the cell's lipid vacuole. Adipocyte hyperplasia occurs through the recruitment and differentiation of adipose-derived stem cells and preadipocytes into new adipocytes, thus increasing the overall adipocyte number. A unique feature of adipose tissue is the coordination between angiogenesis and adipogenesis with adult stem cells [3–5]. By modulating the vascularity of the tissue, the overall quantity of fat mass can

be regulated [6]. For example, Rupnick et al. showed that angiogenesis inhibitors induced endothelial cell apoptosis, which resulted in adipose tissue regression and weight loss in *ob/ob* mice [7].

As demonstrated in Figure 1, with progressive obesity, there is a reduction in the quantity of adipogenic stem cells and an impairment in adipogenesis, resulting in hypertrophic lipid accumulation [8,9]. As a result, the uncontrolled adipocyte expansion reduces the overall capillary density (rarefaction) within the tissue, limits the diffusion of nutrients and oxygen, and creates a hypoxic and proinflammatory environment [6,9–12]. Epidemiological studies have shown that subcutaneous adipocyte cell size is negatively correlated with insulin sensitivity [8,13–15]. Additionally, these hypoxic, hypertrophic adipocytes are more likely to become necrotic, contributing to a cycle of hypoxia, cell death, and inflammation [16]. With the influx of inflammatory cells, including macrophages, into obese adipose tissue, cells within this environment, including adipocytes and endothelial cells, start to behave aberrantly, communicating with neighboring cells and their environment through paracrine- and matrix-derived signals, including inflammatory cytokines, adipokines, and vasoregulators [17]. In this review, paracrine-, autocrine-, and matrix-dependent signaling between adipocytes and endothelial cells is discussed in the context of the development and progression of obesity and its consequential diseases.



**Figure 1.** Cellular and functional differences in lean and obese adipose tissue. (A) Lean adipose tissue displays functional adipocytes that maintain a homeostatic balance of lipolysis and lipogenesis and is sufficiently vascularized to maintain the nutrient supply required for adipose tissue. (B) Obese adipose tissue is characterized by hypertrophic adipocytes that have a lower capillary density to supply the necessary nutrients, resulting in a hypoxic and proinflammatory environment.

## 2. Paracrine Signals Involved in Obesity

In response to sustained hypoxia due to hypertrophied adipocytes, resident macrophages undergo a phenotypic switch toward an M1 phenotype. There is then the further recruitment and infiltration of circulating monocytes that are then directed toward this proinflammatory phenotype [18]. These macrophages are notorious for their pernicious cytokines, including Interleukin-6 (IL-6) and Tumor Necrosis Factor- $\alpha$  (TNF). These potent molecules run rampant in obesity, having direct adverse effects on the adipocyte niche, as well as on the stromal vascular fraction, as summarized in Table 1. Additionally, these two cytokines are primary regulators for the release of other adipokines and vasoregulators, as noted in Figure 2, including adiponectin, leptin, nitric oxide (NO), and endothelin-1 (ET-1).

### 2.1. Inflammatory Cytokines

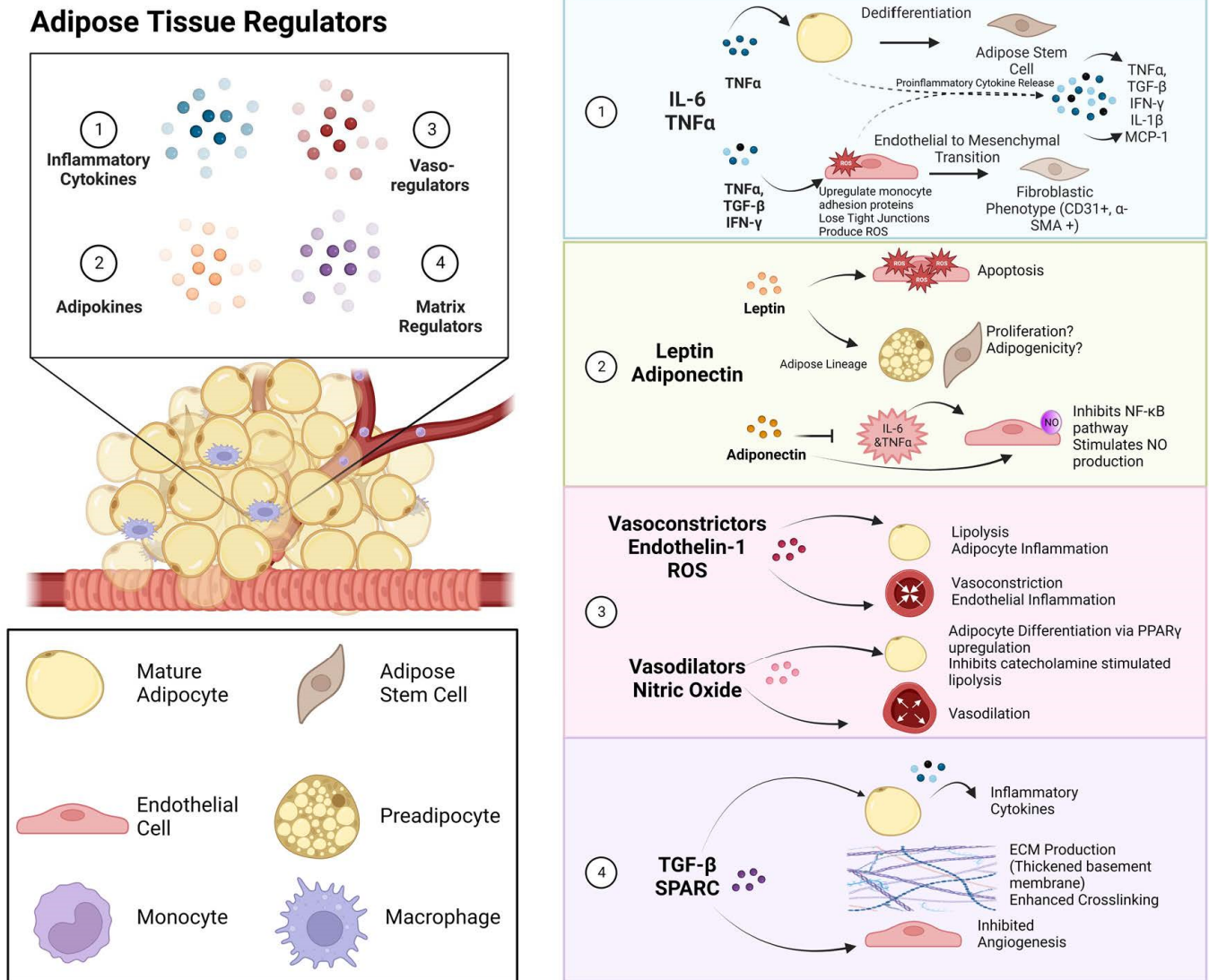
TNF is synthesized as a transmembrane protein that presents on the cell surface [19]. Upon cleavage by the TNF-converting enzyme, the soluble form of TNF is shed from the cell surface [19,20]. While transmembrane TNF is prevalent on obese adipocytes, the primary producers of soluble TNF are preadipocytes and macrophages within obese tissue [19]. Clinical studies have shown that individuals with obesity have increased levels of TNF- $\alpha$  in their sera and that these levels decrease with weight loss [21].

The implications of this chronic TNF elevation in adipose tissue during obesity have been studied *in vitro* through the addition of soluble TNF to the tissue's cellular constituents, including adipocytes, preadipocytes, and endothelial cells. TNF has been shown to be a lipolytic stimulant of adipose cells cultured *in vitro*, including adipocytes and preadipocytes [22,23]. Additionally, Weiner et al. found that 3T3-L1-derived adipocytes dedifferentiated and subsequently upregulated transforming growth factor- $\beta$  (TGF- $\beta$ ) secretion in the presence of 5 nM TNF [24]. This further resulted in the upregulation of extracellular matrix secretions, including collagen types I, III, and IV [24]. This transdifferentiation phenomenon was similarly seen when preadipocytes cultured with TNF- $\alpha$  experienced preferential differentiation toward a macrophage-like phenotype, as indicated by the expressions of Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF), Interleukin-1 $\beta$  (IL-1 $\beta$ ), Macrophage Inflammatory Protein-1 $\alpha$  (MIP-1 $\alpha$ ), TNF- $\alpha$ , CD68, and matrix metalloprotease 3 (MMP3) [25–27].

The development of endothelial dysfunction has been reported to occur as a result of adipose-tissue-derived TNF. Upon incubation with obese adipocyte-derived infranatant, human umbilical vein endothelial cells (HUVECs) significantly upregulated their VCAM-1, ICAM-1, and E-selectin receptors in a TNF-dependent manner [28]. Not only do these endothelial cells become more receptive to inflammatory cells in response to TNF, but they also begin to have a more proinflammatory secretome, as signified by the secretion of IL-8, MIP-1 $\beta$ , MIP-3 $\alpha$ , Monocyte Chemoattractant Protein-1 (MCP-1), and IL-6 [29,30]. Finally, Haynes et al. identified the occurrence of endothelial-to-mesenchymal transition in obese adipose tissue, as indicated by the colocalization of CD31 and  $\alpha$ -SMA in the capillaries of obese adipose tissue [31]. This phenomenon was also seen when healthy adipose-tissue-derived endothelial cells were exposed *in vitro* to either TNF, TGF- $\beta$ , or IFN- $\gamma$ . These endothelial cells exposed to inflammatory signals underwent this transition to obtain a mesenchymal-like phenotype, where they were unable to maintain tight barriers in the culture, had enhanced migration and reduced angiogenesis, released proinflammatory extracellular vesicles, and experienced reductions in oxidative phosphorylation and glycolysis [31]. It is apparent that there is potential for the inflammatory signal TNF to induce both local and systemic effects.

However, the role of TNF in the initiation of insulin resistance remains unclear. While TNF secretion has been speculated to be involved in the initiation of insulin resistance [32], much of the research has been performed in high-fat diet-fed animals [33] or with differentiated murine cells lacking cellular interactions [34], both of which do not mimic human physiology or pathophysiology. Human adipocytes in co-culture with stromal vascular cells (endothelial cells, stem cells, and pericytes [35]) responded to TNF stimulation with

an increase in glucose uptake [36]. Despite the positive correlations found between plasma TNF levels and peripheral insulin resistance, the neutralization and antagonization of TNF have not been shown to improve insulin resistance in humans [37–39].



**Figure 2.** Paracrine, autocrine, and matrix signaling present in adipose tissue. Adipose tissue contains many subpopulations of cells, including inflammatory cells, stem cells and progenitors, and endothelial cells, which are in constant communication with each other and their surroundings. These signals occur in the following contexts: (1) Inflammatory cytokines, including IL-6 and TNF, tend to be abundantly present in obese adipose tissue. These cytokines stimulate a proinflammatory cascade in both adipocytes and the vasculature while also stimulating dedifferentiation within both adipocytes and endothelial cells. (2) Adipokines, leptin, and adiponectin are readily released from adipocytes but act in both an autocrine and paracrine manner, and leptin, a cytokine upregulated in obese adipose tissue, induces the production of reactive oxygen species in endothelial cells while affecting the proliferative capacity and adipogenicity of adipose precursor cells. (3) Vasocrine factors, including vasoconstrictors and vasodilators, are released by both adipocytes and endothelial cells to regulate vascular tone while also altering adipocyte functionality. (4) Matrix-regulating molecules are released by adipocytes and endothelial cells to alter the microenvironment of adipose tissue.

While TNF- $\alpha$  acts locally, adipose-derived interleukins have metabolic and inflammatory effects both locally and systemically [40,41]. Interleukins are cytokines largely secreted by leukocytes, but, more recently, they have been found to both be produced by and act upon adipose-specific cells, including adipose stem and progenitor cells [42]. Composed of close to 50 different interleukins, this family of cytokines plays a crucial role in regulating both the innate and adaptive immune systems, as well as in both metabolic and regenerative processes [40,43]. For more information regarding the breakdown of these adipose-relevant interleukins, please refer to the following review articles: [43,44].

It is well-documented that IL-6 secretion is upregulated in obesity, with positive relationships being found between adipose tissue mass, adipocyte cell size, and IL-6 secretion [45–49]. This proinflammatory cytokine induces effects on adipocytes similar to those of TNF, including lipolytic stimulation and leptin secretion [22,46,50]. Importantly, this cytokine has been found to be strongly positively correlated with the amount of non-esterified free fatty acids in the serum and negatively correlated with whole-body insulin sensitivity, showing the detrimental effects of this cytokine [45].

Many cells, including adipocytes, macrophages, and endothelial cells, both secrete and respond to IL-6, giving them autocrine, paracrine, and endocrine effects [46,51,52]. However, the cellular origin of the cytokine determines the effect that it has within adipose tissue. Han et al. used IL-6 knockout mice to study the source-specific role of IL-6 in the development of obesity. Here, it was found that adipocyte-derived IL-6 promotes high-fat diet-induced adipose tissue inflammation, while myeloid-derived, adipocyte-targeted IL-6 prevents adipose tissue macrophage accumulation and improves glucose and insulin tolerance through the canonical pathway [48]. Further, it was found that these differential responses are determined by the signaling pathway that they go through. The classical signaling pathway is conducted through the membrane-bound IL-6 receptor (IL-6R) and is characterized by PI3K-Akt and ERK 1/2 activation, resulting in anti-inflammatory responses [43,48,53]. It is also possible for signaling to go through the trans-signaling pathway, which depends on the ADAM 10/17-cleaved, soluble IL-6 receptor, which then activates the STAT3 pathway if the soluble form of the IL-6 receptor is present [54]. This IL-6 *trans*-signaling pathway has proinflammatory results [43,48,53].

Cytokines IL-1, TNF, and IFN- $\gamma$  have been shown to stimulate IL-6 release from HUVECs [55]. However, this stimulated IL-6 did not have an autocrine effect despite the known presence of an IL-6R on endothelial cells [54,55]. By culturing endothelial cells with or without IL-6 or IL-6+soluble IL-6R, Montgomery et al. was able to observe the differential effects of the classical signaling and trans-signaling in endothelial cells [54]. The activation of the classical pathway in endothelial cells results in the inhibition of cell death induced via serum deprivation, but the activation of the trans-signaling pathway encourages the secretion of proinflammatory cytokines, such as MCP-1, and the upregulation of monocyte adhesion molecules on endothelial cells [54].

**Table 1.** Prominent signaling molecules in adipose tissue.

Signaling Molecule	Physiological Role in Adipose Tissue	Obese State	Regulation	Citation	
<b>Inflammatory Cytokines</b>	<b>TNF</b>	Involved in immunity Regulates the functions of immune cells, but is found in low levels	Increase in TNF in obesity <b>Stimulates:</b> Adipocyte lipolysis Leptin production IL-6 secretion Plasminogen Activator Inhibitor-1 (PAI-1) biosynthesis ROS production Activates NFκB Inhibits adipocyte differentiation	Triggered through adipocyte cell death	[10,19,25,46,56,57]
	<b>Interleukins</b>	Classical signaling through the IL-6 canonical pathway is anti-inflammatory and regulates glucose and insulin sensitivity IL-10 is a more prominent interleukin in lean adipose tissue	IL-1β, IL-6, and IL-8 increase adipose inflammation during obesity IL-6 induces lipolytic stimulation and leptin secretion from adipocytes through the trans-signaling pathway while upregulating MCP-1 secretion from endothelial cells that then upregulate their expression of monocyte adhesion molecules	Cellular source of IL-6 production regulates response Endothelial cells release IL-6 in response to TNF, IFN-γ, and IL-1	[10,46,54,58–60]
	<b>Interferons</b>	A balance in pro and anti-inflammatory interferons is maintained in order to properly identify and combat invading viruses. This is done through communication between the immune system and the target cells.	Type 1 interferons are upregulated through obesity-derived metabolic endotoxemia. Lipopolysaccharide (LPS) stimulates the production of IFN-β in mouse adipocytes Type II interferon, IFN-γ, is upregulated in obesity due to the influx of IFN-γ-secreting T cells in obese adipose tissue Promotes both a local and systemic inflammatory network between immune cells, adipocytes, and endothelial cells	Adiponectin limits IFN-γ release from CD4+ T cells	[61–64]
	<b>MCP-1</b>	Chemokine that is secreted by both immune and non-immune cells to attract monocytes/macrophages into the tissue	Increased circulating levels in individuals with obesity Adipocyte progenitors secrete MCP-1 to promote M1 macrophage accumulation in adipose tissue Induces endothelial apoptosis in vitro, thus promoting atherosclerosis	Secreted upon injury or ROS exposure Regulated by TNF and <i>trans</i> -IL-6 signaling Insulin-responsive gene	[25,27,54,65–70]

Table 1. Cont.

Signaling Molecule	Physiological Role in Adipose Tissue	Obese State	Regulation	Citation
<b>Adipose Hormones</b>	<b>Leptin</b>	Produced by adipose tissue and the stomach but acts on the central nervous system (hypothalamus) in order to regulate satiety.	Increase in leptin production alongside an increase in fat mass Chronic hyperleptinemia can result in leptin resistance and atherogenic consequences Induces SPARC and collagen II and IV expressions and increases profibrotic signaling	Regulated by insulin and steroids  [71–74]
	<b>Adiponectin</b>	Encourages angiogenesis through the upregulation of Vascular endothelial growth factor (VEGF)-A, MMP-2 and MMP-9 Regulates glucose and lipid homeostasis and maintains insulin sensitivity	Reduced in obesity	Regulated by peroxisome-proliferator-activated receptor (PPAR)- $\gamma$ ligands Inhibited by endoplasmic reticulum stress and proinflammatory cytokines  [75–84]
<b>Vasoconstrictor</b>	<b>Endothelin-1</b>	Endothelial cells release ET-1 in response to low shear stress and hypoxia to increase blood flow	ET-1 elevation in obesity resulting in vascular vasoconstriction and increased vascular permeability, adipocyte lipolysis, insulin resistance and endothelial inflammation, and perivascular fibrosis Can increase reactive oxidative species (ROS) production	Regulated by blood flow, leptin, and insulin  [85–88]
<b>Vasodilator</b>	<b>Nitric Oxide</b>	Adipose-derived nitric oxide inhibits lipolytic activity and promotes endothelial relaxation and vasodilation Adiponectin stimulates NO production	NO is reduced in obesity through TNF-mediated destabilization and free fatty acid (FFA) inhibition of NOS3 phosphorylation Increased ROS will quench NO	ROS FFA TNF  [89,90]
<b>Serpin (serine protease inhibitor)</b>	<b>PAI-1</b>	Induces fibrinogenesis by suppressing intravascular fibrinolysis	Marked increase in PAI-1 in individuals with obesity and diabetes (positive correlation with insulin resistance) When released into the blood stream, it negatively impacts vascular metabolism Fibrinolytic activities decrease in individuals with obesity individuals. Sustained impairment accelerates atherosclerosis	TNF TGF- $\beta$ 1 and Angiotensin II promote PAI-1 production in adipocytes and stromal cells Insulin responsive  [25,79,91–93]

Table 1. Cont.

Signaling Molecule	Physiological Role in Adipose Tissue	Obese State	Regulation	Citation	
Growth Factors	VEGF	<p>Secreted by endothelial cells and adipocytes</p> <p>Acts as a chemotactic factor</p> <p>VEGF-A increases vascularization</p> <p>VEGF-B controls endothelial uptake of fatty acids</p>	<p>Suggestions of a positive VEGF correlation with BMI in humans</p> <p>Dysfunctional VEGF signaling results in impaired vascularization, increased vascular permeability, and endothelial dysfunction in individuals with obesity</p>	<p>SPARC regulates VEGF in individuals with diabetes</p> <p>Leptin modulates VEGF-A expression</p>	[10,79,83,94–98]
	PDGF	<p>Involved in angiogenesis and developmental adipogenesis</p> <p>ASCs become pro angiogenic in response to Platelet-derived growth factor (PDGF)</p>	<p>M1 macrophages overexpress PDGF-B during obesity</p> <p>PDGF-B induces proliferation and migration of aortic smooth muscle cells in vitro, which results in the thickening of the artery</p> <p>Myofibroblast mitogen that contributes to adipose fibrosis</p>	<p>Stromal-cell-derived factor 1</p> <p>Positively regulated by IL-1<math>\beta</math> and TGF-<math>\beta</math>1</p>	[99–105]
	TGF- $\beta$	<p>Regulates the rate of adipogenesis</p>	<p>TGF-<math>\beta</math>1 and TGF-<math>\beta</math>3 increase and can cause mesenchymal transitions and dedifferentiation during obesity</p> <p>These isoforms increase basement membrane production, crosslinking, and inflammatory cytokine production in both adipocytes and endothelial cells</p>	<p>TNF can promote TGF-<math>\beta</math> secretion in differentiated adipocytes</p>	[24,31,106,107]



## 2.2. Adipokine Secretion

There are several proteins produced by adipose tissue that function to regulate its energy balance. Leptin works through the central nervous system in order to regulate satiety [108]. This peptide hormone is primarily released from adipocytes, indicating that the amount in circulation has a positive correlation with the fat mass of the individual [109,110]. In obesity, where there is an elevated triacylglycerol level and an increased fat mass, leptin is elevated [72]. In healthy individuals, leptin works through the hypothalamus to reduce hunger, but in obesity, leptin resistance is not uncommon [111]. An individual with leptin resistance expresses a lack of satiety, resulting in further over-consumption and an increase in total body mass [112]. This hyperleptinemia that occurs in obesity has adverse cellular effects and has been implicated in the development and progression of atherosclerosis by stimulating the production and accumulation of ROS from endothelial cells [73,113,114].

It has been shown that many cells express the leptin receptor. Unsurprisingly, the paracrine effects of leptin are seen within the immune system, within the vasculature, and within the adipose lineage itself [115,116]. Importantly, leptin regulates the adipogenicity and insulin sensitivity of both adipose stem cells and adipocytes through Pre-B-cell leukemia homeobox (Pbx)-regulating protein-1 (PREP1). Notably, the administration of leptin on adipocytes and adipose stem cells reduced PREP1 while increasing TLR4 to limit the adipogenicity [116]. Leptin has been shown to have biphasic effects on preadipocyte and stromal vascular fraction (SVF) proliferation, with lower concentrations promoting proliferation but higher concentrations reducing proliferation [117].

It is known that insulin regulates the release of leptin from adipocytes; however, the effects remain inconsistent. When treated with 100 nM insulin, rat explants and rat-isolated adipocytes experienced a 30–50% reduction in leptin secretion, dependent upon co-treatment with steroids, dexamethasone or hydrocortisone, which elevated leptin secretion [118]. However, Wabitsch found a stimulatory dose-dependent response of insulin on leptin release from differentiated human adipocytes [71], and this was substantiated when 100 nM of insulin was administered to isolated adipocytes, resulting in a 10-fold increase in the secretion of leptin [119]. Further, Kolaczynski found that insulin did not stimulate leptin production acutely; however, over time, insulin increased the production of leptin [120,121].

There are contradictory results surrounding the relationship between leptin and VEGF. Morad et al. explored this relationship in the context of breast tissue and found that the exogenous inhibition of VEGF resulted in a decrease in adipocyte-derived leptin but that the inhibition of leptin did not alter VEGF secretion [122]. However, Nigro et al. showed that the administration of leptin to HUVECs drastically inhibited endothelial tube formation and cellular migration. This leptin administration was also shown to reduce VEGF-A, MMP2, and MMP9 protein levels [83]. This leptin-derived vascular dysregulation was corroborated by Cao et al. [123]. However, it was found that leptin induced angiogenesis and an increased vascular permeability through the upregulation of VEGF and fibroblast growth factor-2 (FGF-2) [123]. Further, obese adipose tissue has an increased secretion of VEGF that results in vascular smooth muscle proliferation, which contributes to vascular dysfunction [98]. However, this dysfunction has been shown to be ameliorated by the activity of adiponectin, an adipokine abundantly present in healthy individuals and lowered with obesity [97].

Adiponectin has been shown to have positive effects on adipocyte differentiation, promoting the more favorable hyperplastic growth rather than hypertrophic growth, and to assist in insulin sensitization [124,125]. In healthy individuals, adiponectin also has paracrine effects on both endothelial cells and macrophages. It has been demonstrated that adiponectin protects endothelial cells from the adverse effects of TNF through the inhibition of the NF- $\kappa$ B pathway [76]. For example, Kobashi et al. showed that adiponectin inhibits Interleukin-8 (IL-8) synthesis through the inhibition of the NF- $\kappa$ B pathway [126]. Additionally, adiponectin reduces the recruitment and restricts the lysis of infiltrating T cells, reducing obesity-induced adipose inflammation [63,127]. Individuals with obesity experience a reduction in adiponectin, allowing for a more proinflammatory and insulin-

resistant environment [84]. While it is apparent that adiponectin has protective effects that contribute to insulin sensitization, the actions of adiponectin seem to be comparable to those of insulin in regard to its ability to encourage vasodilation and increase blood flow through its direct activation of endothelial nitric oxide synthase (eNOS), a regulator of vascular tone [128].

### 2.3. Vasoregulators in Obesity

Vascular tone is regulated by a series of vasodilators and vasoconstrictors. Under normal circumstances, these regulators work together to maintain homeostasis. However, in obesity, dysfunctional and inflamed adipose tissue secretes proinflammatory adipokines that impair normal vasoactivity, resulting in an imbalance in constrictors and dilators, including endothelin-1 and nitric oxide, respectively [85,89].

The vasoconstrictor, endothelin-1, is primarily secreted by endothelial cells and acts in both an autocrine and paracrine manner in adipose tissue, affecting both endothelial cells and adipocytes [129]. In obesity, ET-1 tends to be elevated, resulting in vasoconstriction, adipocyte lipolysis due to hormone sensitive lipase (HSL) phosphorylation, insulin resistance, and endothelial inflammation [130–132]. Similarly, reactive oxygen species are vasoconstrictors that exist as byproducts of aerobic metabolism [133]. It is well-founded that these entities, including hydrogen peroxide, hydroxyl radicals, and superoxide anions, induce cellular damage and inflammation [133,134]. The additional effects of ROS on the vasculature include a surge in intracellular  $Ca^{2+}$ , which results in vascular contraction, increased permeability, and NO quenching, resulting in additional constriction [135]. Further, TNF activates the generation of ROS in HUVECs while also inducing the transcription of NF- $\kappa$ B and ERK 1/2 phosphorylation, which both upregulate ICAM-1 and VCAM-1 expressions on the endothelial surface to promote monocyte attachment, as previously mentioned [28,136–138].

Human adipose tissue expresses several enzymes responsible for the production of NO, a paracrine molecule whose primary function is to mediate endothelial relaxation, including membrane-bound eNOS and cytoplasmic inducible NO synthase (iNOS) [139]. It has been suggested that NO production in adipose tissue promotes the differentiation of adipose preadipocytes through the upregulation of PPAR $\gamma$  but that it also inhibits both basal- and catecholamine-stimulated lipolysis in subcutaneous tissue [140–142]. However, the bioavailability of NO is reduced during obesity. This occurs due to either TNF-mediated destabilization, the FFA-mediated inhibition of NOS3 phosphorylation, or through ROS-mediated quenching [89,90]. More explanation on this can be found in Sansbury et al.'s review on the subject [90]. As a consequence, this reduction in nitric oxide results in impaired vasodilation and tends to have pro-hypertensive effects [143].

Adiponectin has also been shown to be released from healthy perivascular adipose tissue and to travel trans-luminally in order to stimulate nitric oxide production and encourage the vasodilation of blood vessels [76,82,134]. However, this vasodilatory activity is inhibited in obese perivascular adipose tissue (PVAT), with low levels of adiponectin being correlated with impaired vasodilation [144]. Similar phenotypes were seen when an exogenous adiponectin blocker, a NO synthase inhibitor, TNF, and IL-6 were applied to healthy PVAT+vessels, indicating the role of inflammation and free radicals in PVAT-induced endothelial contractility [134]. This protective paracrine role of adiponectin on endothelial cells has been further shown to prevent the detrimental inflammatory activity of TNF on endothelial cells, as previously discussed [75,76].

### 3. Extracellular Matrix Remodeling during Obesity

Filamentous actin (f-actin) is the primary cytoskeletal filament that provides structural integrity within most cells. As an adipose progenitor cell matures into a unilocular adipocyte, there is a normal reduction in the filamentous actin to accommodate intracellular lipid storage. However, one characteristic of mice fed a high-fat diet was the massive increase in f-actin, actin polymerization machinery, and Rho Kinase activity in adipocytes

that resulted in a reduction in insulin sensitivity, indicating that the mechanical stretch of the cell was transduced toward a pathological phenotype [13,145].

In order to accommodate cell size fluctuations, the tissue's extracellular matrix (ECM) will dynamically remodel and allow for cell and tissue expansion, with healthy subcutaneous and omental adipose tissue expressing elevated levels of enzymes involved in ECM remodeling [146]. However, it has been shown that a consequence of obesity is a gradual accumulation of ECM. Henegar et al.'s transcriptomic analysis indicated that the chronic inflammation that occurs in obesity encourages macrophages to stimulate ECM production from neighboring pathological preadipocytes [147]. This ECM regulates the further expandability of the tissue, as well as nutrient diffusion to the cells, and future angiogenesis.

With the pericellular fibrosis of adipocytes and the vasculature being a consequence of obesity, Reggio et al. investigated both the composition and quantity of basement membrane proteins in the endothelial cells and adipocytes from lean, obese, and morbidly obese subcutaneous adipose tissue [106]. Here, it was found that both isolated endothelial cells and adipocytes express common basement membrane components, such as collagen IV and laminin; however, it was also found that adipocytes displayed more Heparan Sulfate Proteoglycan 2 (HSPG2/Perlecan) and Secreted Protein, Acidic, Rich in Cysteine (SPARC) than endothelial cells [106]. This suggests the existence of more crosslinks in the adipocyte matrix [148]. Further, TGF- $\beta$ 1 and TGF- $\beta$ 3 isoforms were upregulated alongside all basement membrane proteins in cellular fractions from individuals with obesity. The treatment of lean adipocytes and endothelial cells with these recombinant isoforms resulted in the upregulation of both inflammatory- and ECM-related genes, including, PAI-1, TGF- $\beta$ 1, connective tissue growth factor (CTGF), IL-6, collagen VI, SPARC, and lysyl oxidase (LOX). This indicates the involvement of both adipocytes and endothelial cells in the thickening of their respective basement membranes and releasing pro-fibrotic stimuli during obesity [106]. For further implications, please see our recent review on coordinated ECM remodeling, angiogenesis, and adipogenesis [149].

To corroborate the finding that basement membrane components derived from adipocytes and endothelial cells serve as pro-fibrotic stimuli, Kos et al. found positive correlations with SPARC levels and adipose fibrosis and metabolic dysfunction [150]. It was shown that leptin induces SPARC expression in adipose tissue and that SPARC expression was then correlated with IL-6 and fasting insulin levels [150]. SPARC has also been shown to further retinopathy in individuals with diabetes by interacting with VEGF and PAI-1 in endothelial cells [151]. In a 3D *in vitro* vasculature model, leptin was also shown to have profibrotic effects, indicated by the upregulation of collagens II and IV and the downregulation of MMPs 2 and 9 [28,80]. These pro-fibrotic effects were mitigated with the simultaneous addition of a counteracting adipokine, adiponectin (which is downregulated in obesity) [80]. This perivascular fibrosis has been shown to occur in individuals with obesity, where Spencer et al. showed that individuals with obesity have 58% less CD31-positive capillaries that were surrounded by more collagen V and less elastin [152]. Further, with the addition of collagen V to an HUVEC culture, angiogenesis was inhibited [152].

These matrix and paracrine alterations that occur in adipocytes and the vasculature during obesity can have severe implications if weight loss measures are not taken and the condition of low-grade inflammation is not resolved. Sasso et al. found an association between the adipose tissue elastography measurements on individuals with obesity taken prior to bariatric surgery and their degree of pericellular fibrosis, indicating the prominence of tissue stiffening and fibrosis in these same individuals [153]. These alterations also play a role in the development of obesity-induced comorbidities, including metabolic dysfunction and hypertension [154,155].

#### 4. Obesity-Related Comorbidities: The Role of Adipose Tissue

It has been shown that the state of adipose tissue influences the behavior of endothelial cells, with obesity inducing endothelial dysfunction and interrupting the homeostatic paracrine signaling that occurs within healthy tissue [82]. It has also been indicated that

endothelial cells from subjects with obesity tend to disrupt adipocyte function through the inflammatory signaling of IL-6 and IL-1 $\beta$  when co-cultured in vitro [156]. These obese endothelial cells reduced insulin sensitivity and lipolytic function of the adipocyte [156]. It is apparent that the crosstalk between cells in the obese state promotes a cycle of compounded inflammation that leads to other comorbidities, including cardiovascular disease and diabetes.

Adipose tissue has continuous capillaries with endothelial cells that form tight junctions and a persistent basement membrane in order to closely regulate the transport of molecules [157]. When dysfunctional, endothelial cells have an increased permeability and cause arterial stiffening. If endothelial dysfunction persists, there is a continuation of oxidative stress that leads to the elevation of ET-1, the reduction of NO, and the cycle of proinflammatory cytokines [89,158,159]. This impaired vasocrine signaling is characterized by the imbalance of vasoconstricting, and the released vasodilatory factors contribute to a proatherogenic and prothrombotic environment. The clinical implications of obesity-derived endothelial dysfunction include the development of atherosclerosis and hypertension.

Atherosclerotic lesions result from the deposition of fat into the artery walls, the infiltration of macrophages, and the successive development of macrophage foam cells. Notably, atherosclerosis may be accelerated by obese adipose tissue in both direct and indirect manners. It has been shown that the adipokine resistin happens to be elevated in obesity [160]. When applied to endothelial cells in vitro, this adipokine was observed to upregulate the expression of the monocyte chemoattractant chemokine, as well as monocyte adhesion proteins, while also increasing the production of ET-1 [161]. Additionally, adipocyte-derived inflammatory cytokines, including IL-6 and TNF, may have similar endothelial dysregulation effects that stimulate the development and progression of an atherosclerotic plaque [162]. In this regard, there is a direct pathological process that provokes inflammatory cell infiltration and lipid deposition [163–165]. Further, when an individual is obese, there is more tissue to supply blood to. Thus, the body attempts to increase blood flow in order to support the increased tissue mass, coinciding with arterial stiffening and chronic vasoconstriction and resulting in an elevated arterial blood pressure, also referred to as hypertension [143,166]. This condition can, in turn, result in exacerbated arterial stiffening, and, in conjunction with other obesity-related comorbidities, such as atherosclerosis, it can result in heart disease and/or thrombosis.

Moreover, the concomitant development of adipose fibrosis during obesity can result in detrimental metabolic consequences, including the deposition of ectopic lipids in other organs and insulin resistance [167–170]. Several review papers have delved into the current mechanistic understanding of the development and progression of adipose tissue fibrosis and its relationship with insulin resistance [152,169,171]. Briefly, DeBari et al. discussed the contribution of chronic hypoxia and inflammation to adipose fibrosis [169]. While hypoxia typically encourages angiogenesis as a normal homeostatic response, the vasculature fails to appropriately expand in obese adipose tissue, reducing capillary density and prolonging hypoxia. Further, pathological angiogenesis is a notable characteristic and consequence of insulin resistance. This insulin resistance is characteristic of Type 2 Diabetes, leading to elevated blood glucose, which furthers endothelial damage and impairs angiogenesis through ROS and advanced glycation end-product (AGE)-mediated complications [12,172,173]. The chronic damage to adipose tissue and its vascular supply results in a cyclical deterioration requiring urgent intervention.

## 5. Conclusions

Here, we lay out the current research into the paracrine-, autocrine-, vasocrine-, and matrix-dependent signaling that occurs between adipose tissue and its vasculature in the development and progression of obesity and its consequential diseases. Throughout the progression of obesity, there is an infiltration of inflammatory cells, including monocytes, macrophages, and T cells, that then drive a cycle of local and systemic inflammation [18].

Upon infiltration, proinflammatory signals, including TNF, interleukins, and interferons, promote the transdifferentiation of both adipocytes and endothelial cells into mesenchymal, pro-fibrotic cells that then sustain local inflammation [24,31]. Additionally, the dysregulation of adipose-specific hormones, leptin and adiponectin, in obese adipose tissue has been shown to have atherogenic and fibrotic consequences by stimulating the production of ROS and pericellular collagen, respectively [73,74,174]. With cardiovascular disease and adipose fibrosis developing concomitantly with obesity, it is important to investigate these interactions between adipocytes, the vasculature, and their surrounding matrix. There are still many unknowns regarding this complex communication; for example, there is evidence to suggest an adipocyte-dependent signaling loop revolving around leptin and VEGF; however, the directionalities of autocrine and paracrine activities have yet to be fully elucidated. Further, it has yet to be determined how vascularization impacts adipose fibrosis and metabolic dysfunction in humans. It is imperative that future research expands on these relationships in order to identify adipose-tissue-related therapeutics.

**Author Contributions:** Conceptualization, E.K.J.; Literature Review, E.K.J. and R.D.A.; Figures and Tables, E.K.J.; Writing—Original Draft Preparation, E.K.J.; Writing—Review and Editing, R.D.A. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research was funded by National Science Foundation, funding No. 2128176.

**Institutional Review Board Statement:** Not Applicable.

**Informed Consent Statement:** Not Applicable.

**Data Availability Statement:** Not Applicable.

**Conflicts of Interest:** The authors declare no conflict of interest.

## Abbreviations

BMI	Body Mass Index
PVAT	Perivascular adipose tissue
IL	Interleukin
PDGF	Platelet-derived growth factor
VEGF	Vascular Endothelial Growth Factor
TNF	Tumor Necrosis Factor- $\alpha$
MCP-1	Monocyte Chemoattractant Protein-1
ROS	Reactive oxidative species
NO	Nitric Oxide
ET-1	Endothelin-1
MMP	Matrix Metalloproteinase
GM-CSF	Granulocyte-Macrophage Colony Stimulating Factor
IL-1 $\beta$	Interleukin-1 $\beta$
MIP-1 $\alpha$	Macrophage Inflammatory Protein-1 $\alpha$
HUVECs	Human umbilical vein endothelial cells
NF $\kappa$ B	Nuclear factor kappa B
IFN- $\gamma$	Interferon-Gamma
ECM	Extracellular Matrix
PREP1	Pre-B-cell leukemia homeobox (Pbx)-regulating protein-1
eNOS	Endothelial nitric oxide synthase
HSL	Hormone sensitive lipase
iNOS	Inducible NO synthase
FFA	Free Fatty Acids
f-actin	Filamentous actin
SPARC	Secreted Protein, Acidic, Rich in Cysteine
LOX	Lysyl Oxidase

CTGF	Connective Tissue Growth Factor
PAI-1	Plasminogen Activator Inhibitor-1
AGE	Advanced glycation end products
VCAM	Vascular cell adhesion molecule
ICAM	Intercellular adhesion molecule-1
ERK 1/2	Extracellular signal-regulated kinase 1/2
ADAM	A disintegrin and metalloprotease
STAT3	Signal transducer and activator of transcription 3
PI3K-Akt	Phosphatidylinositol 3-kinase- protein kinase B
LPS	Lipopolysaccharides
PPAR $\gamma$	Peroxisome proliferator-activated receptors
TLR4	Toll-like receptor 4
SVF	Stromal vascular fraction
FGF	Fibroblast growth factor
HSPG2	Heparan sulfate proteoglycan 2
TGF- $\beta$	Transforming growth factor- $\beta$

## References

- Hales, C.M.; Carroll, M.D.; Fryar, C.D.; Ogden, C.L. *Prevalence of Obesity and Severe Obesity Among Adults: United States, 2017–2018*; CDC National Center for Health Statistics: Hyattsville, MD, USA, 2020; pp. 1–8.
- Hales, C.M.; Carroll, M.D.; Fryar, C.D.; Ogden, C.L. *Prevalence of Obesity among Adults and Youth: United States, 2015–2016*; National Center for Health Statistics: Hyattsville, MD, USA, 2017.
- Cao, Y. Adipose tissue angiogenesis as a therapeutic target for obesity and metabolic diseases. *Nat. Rev. Drug Discov.* **2010**, *9*, 107–115. [[CrossRef](#)]
- Christiaens, V.; Lijnen, H.R. Angiogenesis and development of adipose tissue. *Mol. Cell. Endocrinol.* **2010**, *318*, 2–9. [[CrossRef](#)] [[PubMed](#)]
- Nishimura, S.; Manabe, I.; Nagasaki, M.; Hosoya, Y.; Yamashita, H.; Fujita, H.; Ohsugi, M.; Tobe, K.; Kadowaki, T.; Nagai, R.; et al. Adipogenesis in Obesity Requires Close Interplay Between Differentiating Adipocytes, Stromal Cells, and Blood Vessels. *Diabetes* **2007**, *56*, 1517–1526. [[CrossRef](#)] [[PubMed](#)]
- Sung, H.-K.; Doh, K.-O.; Son, J.E.; Park, J.G.; Bae, Y.; Choi, S.; Nelson, S.M.L.; Cowling, R.; Nagy, K.; Michael, I.P.; et al. Adipose vascular endothelial growth factor regulates metabolic homeostasis through angiogenesis. *Cell Metab.* **2013**, *17*, 61–72. [[CrossRef](#)] [[PubMed](#)]
- Rupnick, M.A.; Panigrahy, D.; Zhang, C.-Y.; Dallabrida, S.M.; Lowell, B.B.; Langer, R.; Folkman, M.J. Adipose tissue mass can be regulated through the vasculature. *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 10730–10735. [[CrossRef](#)]
- Hammarstedt, A.; Gogg, S.; Hedjazifar, S.; Nerstedt, A.; Smith, U. Impaired Adipogenesis and Dysfunctional Adipose Tissue in Human Hypertrophic Obesity. *Physiol. Rev.* **2018**, *98*, 1911–1941. [[CrossRef](#)]
- Belligoli, A.; Compagnin, C.; Sanna, M.; Favaretto, F.; Fabris, R.; Busetto, L.; Foletto, M.; Prà, C.D.; Serra, R.; Prevedello, L.; et al. Characterization of subcutaneous and omental adipose tissue in patients with obesity and with different degrees of glucose impairment. *Sci. Rep.* **2019**, *9*, 1–12. [[CrossRef](#)]
- Goossens, G.H.; Bizzarri, A.; Venteclef, N.; Essers, Y.; Cleutjens, J.P.; Konings, E.; Jocken, J.W.E.; Čajlaković, M.; Ribitsch, V.; Clément, K.; et al. Increased adipose tissue oxygen tension in obese compared with lean men is accompanied by insulin resistance, impaired adipose tissue capillarization, and inflammation. *Circulation* **2011**, *124*, 67–76. [[CrossRef](#)]
- Cifarelli, V.; Beeman, S.C.; Smith, G.I.; Yoshino, J.; Morozov, D.; Beals, J.W.; Kayser, B.D.; Watrous, J.D.; Jain, M.; Patterson, B.W.; et al. Decreased adipose tissue oxygenation associates with insulin resistance in individuals with obesity. *J. Clin. Investig.* **2020**, *130*, 6688–6699. [[CrossRef](#)]
- Pasarica, M.; Sereda, O.R.; Redman, L.M.; Albarado, D.C.; Hymel, D.T.; Roan, L.E.; Rood, J.C.; Burk, D.H.; Smith, S.R. Reduced adipose tissue oxygenation in human obesity: Evidence for rarefaction, macrophage chemotaxis, and inflammation without an angiogenic response. *Diabetes* **2009**, *58*, 718–725. [[CrossRef](#)]
- Hansson, B.; Morén, B.; Fryklund, C.; Vliex, L.; Wasserstrom, S.; Albinsson, S.; Berger, K.; Stenkula, K.G. Adipose cell size changes are associated with a drastic actin remodeling. *Sci. Rep.* **2019**, *9*, 1–14. [[CrossRef](#)] [[PubMed](#)]
- Yang, J.; Eliasson, B.; Smith, U.; Cushman, S.W.; Sherman, A.S. The Size of Large Adipose Cells Is a Predictor of Insulin Resistance in First-Degree Relatives of Type 2 Diabetic Patients. *Obesity* **2012**, *20*, 932–938. [[CrossRef](#)] [[PubMed](#)]
- Hammarstedt, A.; E Graham, T.; Kahn, B.B. Adipose tissue dysregulation and reduced insulin sensitivity in non-obese individuals with enlarged abdominal adipose cells. *Diabetol. Metab. Syndr.* **2012**, *4*, 42–49. [[CrossRef](#)]
- Fuster, J.J.; Ouchi, N.; Gokce, N.; Walsh, K. Obesity-Induced Changes in Adipose Tissue Microenvironment and Their Impact on Cardiovascular Disease. *Circ. Res.* **2016**, *118*, 1786–1807. [[CrossRef](#)]
- E Rausch, M.; Weisberg, S.; Vardhana, P.; Tortoriello, D.V. Obesity in C57BL/6J mice is characterized by adipose tissue hypoxia and cytotoxic T-cell infiltration. *Int. J. Obes.* **2007**, *32*, 451–463. [[CrossRef](#)] [[PubMed](#)]

18. Lumeng, C.N.; Bodzin, J.L.; Saltiel, A.R. Obesity induces a phenotypic switch in adipose tissue macrophage polarization. *J. Clin. Investig.* **2007**, *117*, 175–184. [[CrossRef](#)]
19. Xu, H.; Uysal, K.T.; Becherer, J.D.; Arner, P.; Hotamisligil, G.k.S. Altered Tumor Necrosis Factor- $\alpha$  (TNF- $\alpha$ ) Processing in Adipocytes and Increased Expression of Transmembrane TNF- $\alpha$  in Obesity. *Diabetes* **2002**, *51*, 1876–1883. [[CrossRef](#)]
20. Black, R.A. Tumor necrosis factor-alpha converting enzyme. *Int. J. Biochem. Cell Biol.* **2002**, *34*, 1–5. [[CrossRef](#)] [[PubMed](#)]
21. Dandona, P.; Weinstock, R.; Thusu, K.; Abdel-Rahman, E.; Aljada, A.; Wadden, T. Tumor Necrosis Factor- $\alpha$  in Sera of Obese Patients: Fall with Weight Loss. *J. Clin. Endocrinol. Metab.* **1998**, *83*, 2907–2910. [[CrossRef](#)]
22. Feingold, K.R.; Doerrler, W.; A Dinarello, C.; Fiers, W.; Grunfeld, C. Stimulation of lipolysis in cultured fat cells by tumor necrosis factor, interleukin-1, and the interferons is blocked by inhibition of prostaglandin synthesis. *Endocrinology* **1992**, *130*, 10–16. [[CrossRef](#)]
23. Aubin, K.; Safoine, M.; Proulx, M.; Audet-Casgrain, M.-A.; Côté, J.-F.; Têtu, F.-A.; Roy, A.; Fradette, J. Characterization of In Vitro Engineered Human Adipose Tissues: Relevant Adipokine Secretion and Impact of TNF- $\alpha$ . *PLoS ONE* **2015**, *10*, e0137612. [[CrossRef](#)]
24. Weiner, F.R.; Shah, A.; Smith, P.J.; Rubin, C.S.; Zern, M.A. Regulation of collagen gene expression in 3T3-L1 cells. Effects of adipocyte differentiation and tumor necrosis factor alpha. *Biochemistry* **1989**, *28*, 4094–4099. [[CrossRef](#)]
25. Gustafson, B.; Smith, U. Cytokines Promote Wnt Signaling and Inflammation and Impair the Normal Differentiation and Lipid Accumulation in 3T3-L1 Preadipocytes. *J. Biol. Chem.* **2006**, *281*, 9507–9516. [[CrossRef](#)] [[PubMed](#)]
26. Gustafson, B.; Gogg, S.; Hedjazifar, S.; Jenndahl, L.; Hammarstedt, A.; Smith, U. Inflammation and impaired adipogenesis in hypertrophic obesity in man. *Am. J. Physiol.-Endocrinol. Metab.* **2009**, *297*, E999–E1003. [[CrossRef](#)] [[PubMed](#)]
27. Gerhardt, C.; Romero, I.; Canello, R.; Camoin, L.; Strosberg, A. Chemokines control fat accumulation and leptin secretion by cultured human adipocytes. *Mol. Cell. Endocrinol.* **2001**, *175*, 81–92. [[CrossRef](#)]
28. Kralisch, S.; Sommer, G.; Stangl, V.; Köhler, U.; Kratzsch, J.; Stepan, H.; Faber, R.; Schubert, A.; Lössner, U.; Vietzke, A.; et al. Secretory products from human adipocytes impair endothelial function via nuclear factor kappaB. *Atherosclerosis* **2008**, *196*, 523–531. [[CrossRef](#)]
29. Sommer, G.; Kralisch, S.; Stangl, V.; Vietzke, A.; Köhler, U.; Stepan, H.; Faber, R.; Schubert, A.; Lössner, U.; Bluher, M.; et al. Secretory products from human adipocytes stimulate proinflammatory cytokine secretion from human endothelial cells. *J. Cell. Biochem.* **2009**, *106*, 729–737. [[CrossRef](#)]
30. Cousin, B.; Munoz, O.; Andre, M.; Fontanilles, A.M.; Dani, C.; Cousin, J.L.; Laharrague, P.; Casteilla, L.; Énicaud, L.P. A role for preadipocytes as macrophage-like cells. *FASEB J.* **1999**, *13*, 305–312. [[CrossRef](#)]
31. Haynes, B.A.; Yang, L.F.; Huyck, R.W.; Lehrer, E.J.; Turner, J.M.; Barabutis, N.; Correll, V.L.; Mathiesen, A.; McPheat, W.; Semmes, O.J.; et al. Endothelial-to-Mesenchymal Transition in Human Adipose Tissue Vasculature Alters the Particulate Secretome and Induces Endothelial Dysfunction. *Arterioscler. Thromb. Vasc. Biol.* **2019**, *39*, 2168–2191. [[CrossRef](#)] [[PubMed](#)]
32. Nieto-Vazquez, I.; Fernández-Veledo, S.; Krämer, D.K.; Vila, R.; García, L.; Lorenzo, M. Insulin resistance associated to obesity: The link TNF-alpha. *Arch. Physiol. Biochem.* **2008**, *114*, 183–194. [[CrossRef](#)]
33. da Costa, R.M.; Neves, K.B.; Mestriner, F.L.; Louzada-Junior, P.; Bruder-Nascimento, T.; Tostes, R.C. TNF- $\alpha$  induces vascular insulin resistance via positive modulation of PTEN and decreased Akt/eNOS/NO signaling in high fat diet-fed mice. *Cardiovasc. Diabetol.* **2016**, *15*, 119. [[CrossRef](#)] [[PubMed](#)]
34. Mohallem, R.; Aryal, U.K. Regulators of TNF $\alpha$  mediated insulin resistance elucidated by quantitative proteomics. *Sci. Rep.* **2020**, *10*, 1–15. [[CrossRef](#)]
35. Abbott, R.D.; Wang, R.Y.; Reagan, M.R.; Chen, Y.; Borowsky, F.E.; Zieba, A.; Marra, K.G.; Rubin, J.P.; Ghobrial, I.M.; Kaplan, D.L. The Use of Silk as a Scaffold for Mature, Sustainable Unilocular Adipose 3D Tissue Engineered Systems. *Adv. Heal. Mater.* **2016**, *5*, 1667–1677. [[CrossRef](#)]
36. Abbott, R.D.; Borowsky, F.E.; Alonzo, C.A.; Zieba, A.; Georgakoudi, I.; Kaplan, D.L. Variability in responses observed in human white adipose tissue models. *J. Tissue Eng. Regen. Med.* **2017**, *12*, 840–847. [[CrossRef](#)]
37. Miyazaki, Y.; Pipek, R.; Mandarino, L.J.; DeFronzo, R.A. Tumor necrosis factor  $\alpha$  and insulin resistance in obese type 2 diabetic patients. *Int. J. Obes. Relat. Metab. Disord.* **2003**, *27*, 88–94. [[CrossRef](#)]
38. Wascher, T.C.; Lindeman, J.H.N.; Sourij, H.; Kooistra, T.; Pacini, G.; Roden, M. Chronic TNF- $\alpha$  Neutralization Does Not Improve Insulin Resistance or Endothelial Function in “Healthy” Men with Metabolic Syndrome. *Mol. Med.* **2010**, *17*, 189–193. [[CrossRef](#)] [[PubMed](#)]
39. Bernstein, L.E.; Berry, J.; Kim, S.; Canavan, B.; Grinspoon, S.K. Effects of Etanercept in Patients With the Metabolic Syndrome. *Arch. Intern. Med.* **2006**, *166*, 902–908. [[CrossRef](#)]
40. Carey, A.L.; Steinberg, G.R.; Macaulay, S.L.; Thomas, W.G.; Holmes, A.G.; Ramm, G.; Prelovsek, O.; Hohnen-Behrens, C.; Watt, M.J.; James, D.E.; et al. Interleukin-6 Increases Insulin-Stimulated Glucose Disposal in Humans and Glucose Uptake and Fatty Acid Oxidation In Vitro via AMP-Activated Protein Kinase. *Diabetes* **2006**, *55*, 2688–2697. [[CrossRef](#)] [[PubMed](#)]
41. van Hall, G.; Steensberg, A.; Sacchetti, M.; Fischer, C.; Keller, C.; Schjerling, P.; Hiscock, N.; Møller, K.; Saltin, B.; Febbraio, M.A.; et al. Interleukin-6 Stimulates Lipolysis and Fat Oxidation in Humans. *J. Clin. Endocrinol. Metab.* **2003**, *88*, 3005–3010. [[CrossRef](#)]
42. Mahlaköiv, T.; Flamar, A.-L.; Johnston, L.K.; Moriyama, S.; Putzel, G.G.; Bryce, P.J.; Artis, D. Stromal cells maintain immune cell homeostasis in adipose tissue via production of interleukin-33. *Sci. Immunol.* **2019**, *4*. [[CrossRef](#)]

43. Scheller, J.; Chalaris, A.; Schmidt-Arras, D.; Rose-John, S. The pro- and anti-inflammatory properties of the cytokine interleukin-6. *Biochim. Biophys. Acta* **2011**, *1813*, 878–888. [[CrossRef](#)] [[PubMed](#)]
44. Antuna-Puente, B.; Fellahi, S.; McAvoy, C.; Fève, B.; Bastard, J.-P. Interleukins in adipose tissue: Keeping the balance. *Mol. Cell. Endocrinol.* **2022**, *542*, 111531. [[CrossRef](#)]
45. Mohamed-Ali, V.; Goodrick, S.; Rawesh, A.; Katz, D.R.; Miles, J.M.; Yudkin, J.S.; Klein, S.; Coppel, S.W. Subcutaneous Adipose Tissue Releases Interleukin-6, But Not Tumor Necrosis Factor- $\alpha$ , in Vivo. *J. Clin. Endocrinol. Metab.* **1997**, *82*, 4196–4200. [[CrossRef](#)] [[PubMed](#)]
46. Kern, P.A.; Ranganathan, S.; Li, C.; Wood, L.; Ranganathan, G. Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and insulin resistance. *Am. J. Physiol. Metab.* **2001**, *280*, E745–E751. [[CrossRef](#)]
47. Hajer, G.R.; van Haeften, T.W.; Visseren, F.L.J. Adipose tissue dysfunction in obesity, diabetes, and vascular diseases. *Eur. Heart J.* **2008**, *29*, 2959–2971. [[CrossRef](#)] [[PubMed](#)]
48. Han, M.S.; White, A.; Perry, R.J.; Camporez, J.-P.; Hidalgo, J.; Shulman, G.I.; Davis, R.J. Regulation of adipose tissue inflammation by interleukin 6. *Proc. Natl. Acad. Sci. USA* **2020**, *117*, 2751–2760. [[CrossRef](#)]
49. El-Mikkawy, D.M.E.; El-Sadek, M.A.; El-Badawy, M.A.; Samaha, D. Circulating level of interleukin-6 in relation to body mass indices and lipid profile in Egyptian adults with overweight and obesity. *Egypt. Rheumatol. Rehabil.* **2020**, *47*, 1–7. [[CrossRef](#)]
50. Trujillo, M.E.; Sullivan, S.; Harten, I.; Schneider, S.H.; Greenberg, A.S.; Fried, S.K. Interleukin-6 Regulates Human Adipose Tissue Lipid Metabolism and Leptin Production in Vitro. *J. Clin. Endocrinol. Metab.* **2004**, *89*, 5577–5582. [[CrossRef](#)]
51. Sindhu, S.; Thomas, R.; Shihab, P.; Sriraman, D.; Behbehani, K.; Ahmad, R. Obesity Is a Positive Modulator of IL-6R and IL-6 Expression in the Subcutaneous Adipose Tissue: Significance for Metabolic Inflammation. *PLoS ONE* **2015**, *10*, e0133494. [[CrossRef](#)]
52. Meijer, K.; De Vries, M.; Al-Lahham, S.; Bruinenberg, M.; Weening, D.; Dijkstra, M.; Kloosterhuis, N.; Van Der Leij, R.J.; Van Der Want, H.; Kroesen, B.-J.; et al. Human Primary Adipocytes Exhibit Immune Cell Function: Adipocytes Prime Inflammation Independent of Macrophages. *PLoS ONE* **2011**, *6*, e17154. [[CrossRef](#)] [[PubMed](#)]
53. Reeh, H.; Rudolph, N.; Billing, U.; Christen, H.; Streif, S.; Bullinger, E.; Schliemann-Bullinger, M.; Findeisen, R.; Schaper, F.; Huber, H.J.; et al. Response to IL-6 trans- and IL-6 classic signalling is determined by the ratio of the IL-6 receptor  $\alpha$  to gp130 expression: Fusing experimental insights and dynamic modelling. *Cell Commun. Signal.* **2019**, *17*, 1–21. [[CrossRef](#)]
54. Montgomery, A.; Tam, F.; Gursche, C.; Cheneval, C.; Besler, K.; Enns, W.; Manku, S.; Rey, K.; Hanson, P.J.; Rose-John, S.; et al. Overlapping and distinct biological effects of IL-6 classic and trans-signaling in vascular endothelial cells. *Am. J. Physiol. Physiol.* **2021**, *320*, C554–C565. [[CrossRef](#)] [[PubMed](#)]
55. Podor, T.J.; Jirik, F.R.; Loskutoff, D.J.; Carson, D.A.; Lotz, M. Human endothelial cells produce IL-6. Lack of responses to exogenous IL-6. *Ann. N. Y. Acad. Sci.* **1989**, *557*, 374–385, discussion 386–377. [[CrossRef](#)]
56. Cawthorn, W.P.; Sethi, J.K. TNF- $\alpha$  and adipocyte biology. *FEBS Lett.* **2007**, *582*, 117–131. [[CrossRef](#)] [[PubMed](#)]
57. Sethi, J.K.; Hotamisligil, G.S. Metabolic Messengers: Tumour necrosis factor. *Nat. Metab.* **2021**, *3*, 1302–1312. [[CrossRef](#)] [[PubMed](#)]
58. Sopasakis, V.R.; Sandqvist, M.; Gustafson, B.; Hammarstedt, A.; Schmelz, M.; Yang, X.; Jansson, P.-A.; Smith, U. High Local Concentrations and Effects on Differentiation Implicate Interleukin-6 as a Paracrine Regulator. *Obes. Res.* **2004**, *12*, 454–460. [[CrossRef](#)]
59. Sironi, M.; Breviario, F.; Proserpio, P.; Biondi, A.; Vecchi, A.; Van Damme, J.; Dejana, E.; Mantovani, A. IL-1 stimulates IL-6 production in endothelial cells. *J. Immunol.* **1989**, *142*, 549–553. [[CrossRef](#)]
60. Liddle, D.M.; Hutchinson, A.L.; Wellings, H.R.; Power, K.A.; Robinson, L.E.; Monk, J.M. Integrated Immunomodulatory Mechanisms through which Long-Chain n-3 Polyunsaturated Fatty Acids Attenuate Obese Adipose Tissue Dysfunction. *Nutrients* **2017**, *9*, 1289. [[CrossRef](#)] [[PubMed](#)]
61. Chan, C.C.; Damen, M.S.M.A.; Moreno-Fernandez, M.E.; Stankiewicz, T.E.; Cappelletti, M.; Alarcon, P.C.; Oates, J.R.; Doll, J.R.; Mukherjee, R.; Chen, X.; et al. Type I interferon sensing unlocks dormant adipocyte inflammatory potential. *Nat. Commun.* **2020**, *11*, 1–15. [[CrossRef](#)]
62. Rocha, V.Z.; Folco, E.J.; Sukhova, G.; Shimizu, K.; Gotsman, I.; Vernon, A.H.; Libby, P. Interferon- $\gamma$ , a Th1 Cytokine, Regulates Fat Inflammation. *Circ. Res.* **2008**, *103*, 467–476. [[CrossRef](#)]
63. Surendar, J.; Frohberger, S.J.; Karunakaran, I.; Schmitt, V.; Stamminger, W.; Neumann, A.-L.; Wilhelm, C.; Hoerauf, A.; Hübner, M.P. Adiponectin Limits IFN- $\gamma$  and IL-17 Producing CD4 T Cells in Obesity by Restraining Cell Intrinsic Glycolysis. *Front. Immunol.* **2019**, *10*, 2555. [[CrossRef](#)]
64. Zhang, H.; Potter, B.J.; Cao, J.-M.; Zhang, C. Interferon-gamma induced adipose tissue inflammation is linked to endothelial dysfunction in type 2 diabetic mice. *Basic Res. Cardiol.* **2011**, *106*, 1135–1145. [[CrossRef](#)] [[PubMed](#)]
65. Singh, S.; Anshita, D.; Ravichandiran, V. MCP-1: Function, regulation, and involvement in disease. *Int. Immunopharmacol.* **2021**, *101*, 107598. [[CrossRef](#)]
66. Sartipy, P.; Loskutoff, D.J. Monocyte chemoattractant protein 1 in obesity and insulin resistance. *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 7265–7270. [[CrossRef](#)]
67. Dahlman, I.; Kaaman, M.; Olsson, T.; Tan, G.D.; Bickerton, A.S.T.; Wåhlén, K.; Andersson, J.; Nordström, E.A.; Blomqvist, L.; Sjögren, A.; et al. A Unique Role of Monocyte Chemoattractant Protein 1 among Chemokines in Adipose Tissue of Obese Subjects. *J. Clin. Endocrinol. Metab.* **2005**, *90*, 5834–5840. [[CrossRef](#)]



68. Kanda, H.; Tateya, S.; Tamori, Y.; Kotani, K.; Hiasa, K.-I.; Kitazawa, R.; Kitazawa, S.; Miyachi, H.; Maeda, S.; Egashira, K.; et al. MCP-1 contributes to macrophage infiltration into adipose tissue, insulin resistance, and hepatic steatosis in obesity. *J. Clin. Investig.* **2006**, *116*, 1494–1505. [[CrossRef](#)]
69. Zhang, X.; Liu, X.; Shang, H.; Xu, Y.; Qian, M. Monocyte chemoattractant protein-1 induces endothelial cell apoptosis in vitro through a p53-dependent mitochondrial pathway. *Acta Biochim. Biophys. Sin.* **2011**, *43*, 787–795. [[CrossRef](#)] [[PubMed](#)]
70. Kaplan, J.L.; Marshall, M.A.; McSkimming, C.C.; Harmon, D.B.; Garmey, J.C.; Oldham, S.N.; Hallowell, P.; McNamara, C.A. Adipocyte progenitor cells initiate monocyte chemoattractant protein-1-mediated macrophage accumulation in visceral adipose tissue. *Mol. Metab.* **2015**, *4*, 779–794. [[CrossRef](#)] [[PubMed](#)]
71. Wabitsch, M.; Bo Jensen, P.; Blum, W.F.; Christoffersen, C.T.; Englaro, P.; Heinze, E.; Rascher, W.; Teller, W.; Tornqvist, H.; Hauner, H. Insulin and cortisol promote leptin production in cultured human fat cells. *Diabetes* **1996**, *45*, 1435–1438. [[CrossRef](#)]
72. Chrysafi, P.; Perakakis, N.; Farr, O.M.; Stefanakis, K.; Peradze, N.; Sala-Vila, A.; Mantzoros, C.S. Leptin alters energy intake and fat mass but not energy expenditure in lean subjects. *Nat. Commun.* **2020**, *11*, 1–15. [[CrossRef](#)]
73. Bouloumié, A.; Marumo, T.; Lafontan, M.; Busse, R. Leptin induces oxidative stress in human endothelial cells. *FASEB J.* **1999**, *13*, 1231–1238. [[CrossRef](#)]
74. Picó, C.; Oliver, P.; Sánchez, J.; Palou, A. Gastric leptin: A putative role in the short-term regulation of food intake. *Br. J. Nutr.* **2003**, *90*, 735–741. [[CrossRef](#)]
75. Ouchi, N.; Kihara, S.; Arita, Y.; Maeda, K.; Kuriyama, H.; Okamoto, Y.; Hotta, K.; Nishida, M.; Takahashi, M.; Nakamura, T.; et al. Novel modulator for endothelial adhesion molecules: Adipocyte-derived plasma protein adiponectin. *Circulation* **1999**, *100*, 2473–2476. [[CrossRef](#)]
76. Ouchi, N.; Kihara, S.; Arita, Y.; Okamoto, Y.; Maeda, K.; Kuriyama, H.; Hotta, K.; Nishida, M.; Takahashi, M.; Muraguchi, M.; et al. Adiponectin, an adipocyte-derived plasma protein, inhibits endothelial NF-kappaB signaling through a cAMP-dependent pathway. *Circulation* **2000**, *102*, 1296–1301. [[CrossRef](#)] [[PubMed](#)]
77. Chandran, M.; Phillips, S.A.; Ciaraldi, T.; Henry, R.R. Adiponectin: More Than Just Another Fat Cell Hormone? *Diabetes Care* **2003**, *26*, 2442–2450. [[CrossRef](#)] [[PubMed](#)]
78. Kern, P.A.; Di Gregorio, G.B.; Lu, T.; Rassouli, N.; Ranganathan, G. Adiponectin Expression From Human Adipose Tissue. *Diabetes* **2003**, *52*, 1779–1785. [[CrossRef](#)]
79. Hauner, H. Secretory factors from human adipose tissue and their functional role. *Proc. Nutr. Soc.* **2005**, *64*, 163–169. [[CrossRef](#)] [[PubMed](#)]
80. Zhang, Z.; Wang, F.; Wang, B.-J.; Chu, G.; Cao, Q.; Sun, B.-G.; Dai, Q.-Y. Inhibition of leptin-induced vascular extracellular matrix remodelling by adiponectin. *J. Mol. Endocrinol.* **2014**, *53*, 145–154. [[CrossRef](#)] [[PubMed](#)]
81. Adya, R.; Tan, B.K.; Randevara, H.S. Differential Effects of Leptin and Adiponectin in Endothelial Angiogenesis. *J. Diabetes Res.* **2015**, *2015*, 1–12. [[CrossRef](#)]
82. Sena, C.M.; Pereira, A.; Fernandes, R.; Letra, L.; Seica, R.M. Adiponectin improves endothelial function in mesenteric arteries of rats fed a high-fat diet: Role of perivascular adipose tissue. *Br. J. Pharmacol.* **2017**, *174*, 3514–3526. [[CrossRef](#)]
83. Nigro, E.; Mallardo, M.; Polito, R.; Scialò, F.; Bianco, A.; Daniele, A. Adiponectin and Leptin Exert Antagonizing Effects on HUVEC Tube Formation and Migration Modulating the Expression of CXCL1, VEGF, MMP-2 and MMP-9. *Int. J. Mol. Sci.* **2021**, *22*, 7516. [[CrossRef](#)]
84. Hoffstedt, J.; Arvidsson, E.; Sjölin, E.; Wåhlén, K.; Arner, P. Adipose Tissue Adiponectin Production and Adiponectin Serum Concentration in Human Obesity and Insulin Resistance. *J. Clin. Endocrinol. Metab.* **2004**, *89*, 1391–1396. [[CrossRef](#)]
85. Ferri, C.; Bellini, C.; Desideri, G.; Baldoncin, R.; Properzi, G.; Santucci, A.; De Mattia, G. Circulating endothelin-1 levels in obese patients with the metabolic syndrome. *Exp. Clin. Endocrinol. Diabetes* **1997**, *105*, 38–40. [[CrossRef](#)] [[PubMed](#)]
86. Quehenberger, P.; Exner, M.; Sunder-Plassmann, R.; Ruzicka, K.; Bieglmayer, C.; Endler, G.; Muellner, C.; Speiser, W.; Wagner, O. Leptin Induces Endothelin-1 in Endothelial Cells In Vitro. *Circ. Res.* **2002**, *90*, 711–718. [[CrossRef](#)]
87. van Harmelen, V.; Eriksson, A.; Åström, G.; Wåhlén, K.; Näslund, E.; Karpe, F.; Frayn, K.; Olsson, T.; Andersson, J.; Rydén, M.; et al. Vascular Peptide Endothelin-1 Links Fat Accumulation With Alterations of Visceral Adipocyte Lipolysis. *Diabetes* **2008**, *57*, 378–386. [[CrossRef](#)] [[PubMed](#)]
88. Yoshizumi, M.; Kurihara, H.; Sugiyama, T.; Takaku, F.; Yanagisawa, M.; Masaki, T.; Yazaki, Y. Hemodynamic shear stress stimulates endothelin production by cultured endothelial cells. *Biochem. Biophys. Res. Commun.* **1989**, *161*, 859–864. [[CrossRef](#)] [[PubMed](#)]
89. Gruber, H.-J.; Mayer, C.; Mangge, H.; Fauler, G.; Grandits, N.; Wilders-Truschnig, M. Obesity reduces the bioavailability of nitric oxide in juveniles. *Int. J. Obes.* **2008**, *32*, 826–831. [[CrossRef](#)] [[PubMed](#)]
90. Sansbury, B.E.; Hill, B.G. Regulation of obesity and insulin resistance by nitric oxide. *Free. Radic. Biol. Med.* **2014**, *73*, 383–399. [[CrossRef](#)]
91. Alessi, M.C.; Bastelica, D.; Morange, P.; Berthet, B.; Leduc, I.; Verdier, M.; Geel, O.; Juhan-Vague, I. Plasminogen activator inhibitor 1, transforming growth factor-beta1, and BMI are closely associated in human adipose tissue during morbid obesity. *Diabetes* **2000**, *49*, 1374–1380. [[CrossRef](#)] [[PubMed](#)]
92. Kaji, H. Adipose Tissue-Derived Plasminogen Activator Inhibitor-1 Function and Regulation. *Compr. Physiol.* **2016**, *6*, 1873–1896. [[CrossRef](#)]

93. Wang, L.; Chen, L.; Liu, Z.; Liu, Y.; Luo, M.; Chen, N.; Deng, X.; Luo, Y.; He, J.; Zhang, L.; et al. PAI-1 Exacerbates White Adipose Tissue Dysfunction and Metabolic Dysregulation in High Fat Diet-Induced Obesity. *Front. Pharmacol.* **2018**, *9*, 1087. [[CrossRef](#)]
94. Hagberg, C.E.; Falkevall, A.; Wang, X.; Larsson, E.; Huusko, J.; Nilsson, I.; van Meeteren, L.A.; Samen, E.; Lu, L.; Vanwildemeersch, M.; et al. Vascular endothelial growth factor B controls endothelial fatty acid uptake. *Nature* **2010**, *464*, 917–921. [[CrossRef](#)] [[PubMed](#)]
95. Silha, J.V.; Kršek, M.; Sucharda, P.; Murphy, L.J. Angiogenic factors are elevated in overweight and obese individuals. *Int. J. Obes.* **2005**, *29*, 1308–1314. [[CrossRef](#)] [[PubMed](#)]
96. Loebig, M.; Klement, J.; Schmoller, A.; Betz, S.; Heuck, N.; Schweiger, U.; Peters, A.; Schultes, B.; Oltmanns, K.M. Evidence for a Relationship between VEGF and BMI Independent of Insulin Sensitivity by Glucose Clamp Procedure in a Homogenous Group Healthy Young Men. *PLoS ONE* **2010**, *5*, e12610. [[CrossRef](#)]
97. Lamers, D.; Schlich, R.; Greulich, S.; Sasson, S.; Sell, H.; Eckel, J. Oleic acid and adipokines synergize in inducing proliferation and inflammatory signalling in human vascular smooth muscle cells. *J. Cell. Mol. Med.* **2010**, *15*, 1177–1188. [[CrossRef](#)] [[PubMed](#)]
98. Schlich, R.; Willems, M.; Greulich, S.; Ruppe, F.; Knoefel, W.T.; Ouwens, D.M.; Maxhera, B.; Lichtenberg, A.; Eckel, J.; Sell, H. VEGF in the Crosstalk between Human Adipocytes and Smooth Muscle Cells: Depot-Specific Release from Visceral and Perivascular Adipose Tissue. *Mediat. Inflamm.* **2013**, *2013*, 1–10. [[CrossRef](#)]
99. Onogi, Y.; Wada, T.; Kamiya, C.; Inata, K.; Matsuzawa, T.; Inaba, Y.; Kimura, K.; Inoue, H.; Yamamoto, S.; Ishii, Y.; et al. PDGFR $\beta$  Regulates Adipose Tissue Expansion and Glucose Metabolism via Vascular Remodeling in Diet-Induced Obesity. *Diabetes* **2017**, *66*, 1008–1021. [[CrossRef](#)]
100. Watanabe, E.; Wada, T.; Okekawa, A.; Kitamura, F.; Komatsu, G.; Onogi, Y.; Yamamoto, S.; Sasahara, M.; Kitada, M.; Koya, D.; et al. Stromal cell-derived factor 1 (SDF1) attenuates platelet-derived growth factor-B (PDGF-B)-induced vascular remodeling for adipose tissue expansion in obesity. *Angiogenesis* **2020**, *23*, 1–18. [[CrossRef](#)] [[PubMed](#)]
101. Onogi, Y.; Wada, T.; Okekawa, A.; Matsuzawa, T.; Watanabe, E.; Ikeda, K.; Nakano, M.; Kitada, M.; Koya, D.; Tsuneki, H.; et al. Pro-inflammatory macrophages coupled with glycolysis remodel adipose vasculature by producing platelet-derived growth factor-B in obesity. *Sci. Rep.* **2020**, *10*, 1–13. [[CrossRef](#)]
102. Lopatina, T.; Bruno, S.; Tetta, C.; Kalinina, N.; Porta, M.; Camussi, G. Platelet-derived growth factor regulates the secretion of extracellular vesicles by adipose mesenchymal stem cells and enhances their angiogenic potential. *Cell Commun. Signal.* **2014**, *12*, 26. [[CrossRef](#)]
103. Shin, S.; Pang, Y.; Park, J.; Liu, L.; Lukas, B.E.; Kim, S.H.; Kim, K.-W.; Xu, P.; Berry, D.C.; Jiang, Y. Dynamic control of adipose tissue development and adult tissue homeostasis by platelet-derived growth factor receptor alpha. *eLife* **2020**, *9*, e56189. [[CrossRef](#)]
104. Hotamisligil, G.S.; Murray, D.L.; Choy, L.N.; Spiegelman, B.M. Tumor necrosis factor alpha inhibits signaling from the insulin receptor. *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 4854–4858. [[CrossRef](#)]
105. Bonner, J.C. Regulation of PDGF and its receptors in fibrotic diseases. *Cytokine Growth Factor Rev.* **2004**, *15*, 255–273. [[CrossRef](#)] [[PubMed](#)]
106. Reggio, S.; Rouault, C.; Poitou, C.; Bichet, J.-C.; Prifti, E.; Bouillot, J.-L.; Rizkalla, S.; Lacasa, D.; Tordjman, J.; Clément, K. Increased Basement Membrane Components in Adipose Tissue During Obesity: Links With TGF $\beta$  and Metabolic Phenotypes. *J. Clin. Endocrinol. Metab.* **2016**, *101*, 2578–2587. [[CrossRef](#)] [[PubMed](#)]
107. Choy, L.; Skillington, J.; Derynck, R. Roles of Autocrine TGF- $\beta$  Receptor and Smad Signaling in Adipocyte Differentiation. *J. Cell Biol.* **2000**, *149*, 667–682. [[CrossRef](#)]
108. Elmquist, J.K.; Maratos-Flier, E.; Saper, C.B.; Flier, J.S. Unraveling the central nervous system pathways underlying responses to leptin. *Nat. Neurosci.* **1998**, *1*, 445–450. [[CrossRef](#)] [[PubMed](#)]
109. Korbonits, M.; Trainer, P.J.; Little, J.A.; Edwards, R.; Kopelman, P.G.; Besser, G.M.; Svec, F.; Grossman, A.B. Leptin levels do not change acutely with food administration in normal or obese subjects, but are negatively correlated with pituitary-adrenal activity. *Clin. Endocrinol.* **1997**, *46*, 751–757. [[CrossRef](#)]
110. Zhang, Y.; Proenca, R.; Maffei, M.; Barone, M.; Leopold, L.; Friedman, J.M. Positional cloning of the mouse obese gene and its human homologue. *Nature* **1994**, *372*, 425–432. [[CrossRef](#)]
111. Myers, M.G., Jr.; Heymsfield, S.B.; Haft, C.; Kahn, B.B.; Laughlin, M.; Leibel, R.L.; Tschöp, M.H.; Yanovski, J.A. Challenges and Opportunities of Defining Clinical Leptin Resistance. *Cell Metab.* **2012**, *15*, 150–156. [[CrossRef](#)]
112. Saladin, R.; De Vos, P.; Guerre-Millot, M.; Leturque, A.; Girard, J.; Staels, B.; Auwerx, J. Transient increase in obese gene expression after food intake or insulin administration. *Nature* **1995**, *377*, 527–528. [[CrossRef](#)]
113. Park, H.-Y.; Kwon, H.M.; Lim, H.J.; Hong, B.K.; Lee, J.Y.; Park, B.E.; Jang, Y.S.; Cho, S.Y.; Kim, H.-S. Potential role of leptin in angiogenesis: Leptin induces endothelial cell proliferation and expression of matrix metalloproteinases in vivo and in vitro. *Exp. Mol. Med.* **2001**, *33*, 95–102. [[CrossRef](#)]
114. Artwohl, M.; Roden, M.; Hölzenbein, T.; Freudenthaler, A.; Waldhäusl, W.; Baumgartner-Parzer, S. Modulation by leptin of proliferation and apoptosis in vascular endothelial cells. *Int. J. Obes.* **2002**, *26*, 577–580. [[CrossRef](#)]
115. Kiernan, K.; MacIver, N.J. The Role of the Adipokine Leptin in Immune Cell Function in Health and Disease. *Front. Immunol.* **2021**, *11*. [[CrossRef](#)]
116. Bruno, A.; Di Sano, C.; Simon, H.-U.; Chanez, P.; Patti, A.M.; Di Vincenzo, S.; Dino, P.; D’Esposito, V.; Formisano, P.; Beguinot, F.; et al. Leptin and TGF- $\beta$ 1 Downregulate PREP1 Expression in Human Adipose-Derived Mesenchymal Stem Cells and Mature Adipocytes. *Front. Cell Dev. Biol.* **2021**, *9*, 1756. [[CrossRef](#)]

117. Wagoner, B.; Hausman, D.B.; Harris, R.B.S. Direct and indirect effects of leptin on preadipocyte proliferation and differentiation. *Am. J. Physiol. Integr. Comp. Physiol.* **2006**, *290*, R1557–R1564. [[CrossRef](#)]
118. Mick, G.J.; Wang, X.; Fu, C.L.; McCormick, K.L. Inhibition of leptin secretion by insulin and metformin in cultured rat adipose tissue. *Biochim. Biophys. Acta (BBA)-Mol. Basis Dis.* **2000**, *1502*, 426–432. [[CrossRef](#)]
119. Nolan, J.J.; Olefsky, J.M.; Nyce, M.R.; Considine, R.V.; Caro, J.F. Effect of Troglitazone on Leptin Production: Studies In Vitro and in Human Subjects. *Diabetes* **1996**, *45*, 1276–1278. [[CrossRef](#)]
120. Kolaczynski, J.W.; Ohannesian, J.P.; Considine, R.V.; Marco, C.C.; Caro, J.F. Response of leptin to short-term and prolonged overfeeding in humans. *J. Clin. Endocrinol. Metab.* **1996**, *81*, 4162–4165. [[CrossRef](#)]
121. Kolaczynski, J.W.; Nyce, M.R.; Considine, R.V.; Boden, G.; Nolan, J.J.; Henry, R.; Mudaliar, S.R.; Olefsky, J.; Caro, J.F. Acute and Chronic Effect of Insulin on Leptin Production in Humans: Studies In Vivo and In Vitro. *Diabetes* **1996**, *45*, 699–701. [[CrossRef](#)]
122. Morad, V.; Abrahamsson, A.; Kjölhede, P.; Dabrosin, C. Adipokines and Vascular Endothelial Growth Factor in Normal Human Breast Tissue in Vivo – Correlations and Attenuation by Dietary Flaxseed. *J. Mammary Gland. Biol. Neoplasia* **2016**, *21*, 69–76. [[CrossRef](#)]
123. Cao, R.; Brakenhielm, E.; Wahlestedt, C.; Thyberg, J.; Cao, Y. Leptin induces vascular permeability and synergistically stimulates angiogenesis with FGF-2 and VEGF. *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 6390–6395. [[CrossRef](#)]
124. Arita, Y.; Kihara, S.; Ouchi, N.; Takahashi, M.; Maeda, K.; Miyagawa, J.-I.; Hotta, K.; Shimomura, I.; Nakamura, T.; Miyaoka, K.; et al. Paradoxical Decrease of an Adipose-Specific Protein, Adiponectin, in Obesity. *Biochem. Biophys. Res. Commun.* **1999**, *257*, 79–83. [[CrossRef](#)]
125. Fu, Y.; Luo, N.; Klein, R.L.; Garvey, W.T. Adiponectin promotes adipocyte differentiation, insulin sensitivity, and lipid accumulation. *J. Lipid Res.* **2005**, *46*, 1369–1379. [[CrossRef](#)]
126. Kobashi, C.; Urakaze, M.; Kishida, M.; Kibayashi, E.; Kobayashi, H.; Kihara, S.; Funahashi, T.; Takata, M.; Tamaru, R.; Sato, A.; et al. Adiponectin Inhibits Endothelial Synthesis of Interleukin-8. *Circ. Res.* **2005**, *97*, 1245–1252. [[CrossRef](#)]
127. Okamoto, Y.; Folco, E.J.; Minami, M.; Wara, A.K.; Feinberg, M.W.; Sukhova, G.K.; Colvin, R.A.; Kihara, S.; Funahashi, T.; Luster, A.D.; et al. Adiponectin Inhibits the Production of CXC Receptor 3 Chemokine Ligands in Macrophages and Reduces T-Lymphocyte Recruitment in Atherogenesis. *Circ. Res.* **2008**, *102*, 218–225. [[CrossRef](#)]
128. Chen, H.; Montagnani, M.; Funahashi, T.; Shimomura, I.; Quon, M.J. Adiponectin Stimulates Production of Nitric Oxide in Vascular Endothelial Cells. *J. Biol. Chem.* **2003**, *278*, 45021–45026. [[CrossRef](#)]
129. Orlando, A.; Viazzi, F.; Giussani, M.; Nava, E.; Cazzaniga, E.; Bonino, B.; Palestini, P.; Parati, G.; Genovesi, S. Endothelin-1/nitric oxide balance and HOMA index in children with excess weight and hypertension: A pathophysiological model of hypertension. *Hypertens. Res.* **2019**, *42*, 1192–1199. [[CrossRef](#)]
130. Padilla, J.; Carpenter, A.J.; Das, N.A.; Kandikattu, H.K.; López-Ongil, S.; Martinez-Lemus, L.A.; Siebenlist, U.; DeMarco, V.G.; Chandrasekar, B. TRAF3IP2 mediates high glucose-induced endothelin-1 production as well as endothelin-1-induced inflammation in endothelial cells. *Am. J. Physiol.-Heart Circ. Physiol.* **2017**, *314*, H52–H64. [[CrossRef](#)]
131. Jurrissen, T.J.; Grunewald, Z.I.; Woodford, M.L.; Winn, N.C.; Ball, J.R.; Smith, T.N.; Wheeler, A.; Rawlings, A.L.; Staveley-O'Carroll, K.F.; Ji, Y.; et al. Overproduction of endothelin-1 impairs glucose tolerance but does not promote visceral adipose tissue inflammation or limit metabolic adaptations to exercise. *Am. J. Physiol. Metab.* **2019**, *317*, E548–E558. [[CrossRef](#)]
132. Briançon-Marjollet, A.; Monneret, D.; Henri, M.; Puch, F.; Pépin, J.L.; Faure, P.; Godin-Ribuot, D. Endothelin regulates intermittent hypoxia-induced lipolytic remodelling of adipose tissue and phosphorylation of hormone-sensitive lipase. *J. Physiol.* **2016**, *594*, 1727–1740. [[CrossRef](#)]
133. Schieber, M.; Chandel, N.S. ROS Function in Redox Signaling and Oxidative Stress. *Curr. Biol.* **2014**, *24*, R453–R462. [[CrossRef](#)] [[PubMed](#)]
134. Greenstein, A.S.; Khavandi, K.; Withers, S.B.; Sonoyama, K.; Clancy, O.; Jeziorska, M.; Laing, I.; Yates, A.P.; Pemberton, P.W.; Malik, R.A.; et al. Local Inflammation and Hypoxia Abolish the Protective Anticontractile Properties of Perivascular Fat in Obese Patients. *Circulation* **2009**, *119*, 1661–1670. [[CrossRef](#)] [[PubMed](#)]
135. Rodrigo, R.; González, J.; Paoletto, F. The role of oxidative stress in the pathophysiology of hypertension. *Hypertens. Res.* **2011**, *34*, 431–440. [[CrossRef](#)]
136. Williams, C.R.; Lu, X.; Sutliff, R.L.; Hart, C.M. Rosiglitazone attenuates NF- $\kappa$ B-mediated Nox4 upregulation in hyperglycemia-activated endothelial cells. *Am. J. Physiol. Cell Physiol.* **2012**, *303*, C213–C223. [[CrossRef](#)] [[PubMed](#)]
137. Shiraki, A.; Oyama, J.; Komoda, H.; Asaka, M.; Komatsu, A.; Sakuma, M.; Kodama, K.; Sakamoto, Y.; Kotooka, N.; Hirase, T.; et al. The glucagon-like peptide 1 analog liraglutide reduces TNF- $\alpha$ -induced oxidative stress and inflammation in endothelial cells. *Atherosclerosis* **2012**, *221*, 375–382. [[CrossRef](#)]
138. Xia, F.; Wang, C.; Jin, Y.; Liu, Q.; Meng, Q.; Liu, K.; Sun, H. Luteolin Protects HUVECs from TNF- $\alpha$ -induced Oxidative Stress and Inflammation via its Effects on the Nox4/ROS-NF- $\kappa$ B and MAPK Pathways. *J. Atheroscler. Thromb.* **2014**, *21*, 768–783. [[CrossRef](#)]
139. Elizalde, M.; Rydén, M.; van Harmelen, V.; Eneroth, P.; Gyllenhammar, H.; Holm, C.; Ramel, S.; Olund, A.; Arner, P.; Andersson, K. Expression of nitric oxide synthases in subcutaneous adipose tissue of nonobese and obese humans. *J. Lipid Res.* **2000**, *41*, 1244–1251. [[CrossRef](#)]
140. Yan, H.; Aziz, E.; Shillabeer, G.; Wong, A.; Shanghavi, D.; Kermouni, A.; Abdel-Hafez, M.; Lau, D.C. Nitric oxide promotes differentiation of rat white preadipocytes in culture. *J. Lipid Res.* **2002**, *43*, 2123–2129. [[CrossRef](#)]

141. Gaudiot, N.; Jaubert, A.-M.; Charbonnier, E.; Sabourault, D.; Lacasa, D.; Giudicelli, Y.; Ribi re, C. Modulation of White Adipose Tissue Lipolysis by Nitric Oxide. *J. Biol. Chem.* **1998**, *273*, 13475–13481. [[CrossRef](#)]
142. Engeli, S.; Janke, J.; Gorzelnik, K.; B hnke, J.; Ghose, N.; Lindschau, C.; Luft, F.C.; Sharma, A.M. Regulation of the nitric oxide system in human adipose tissue. *J. Lipid Res.* **2004**, *45*, 1640–1648. [[CrossRef](#)]
143. Rajapakse, N.; Head, G.; Kaye, D.M. Say NO to Obesity-Related Hypertension. *Hypertension* **2016**, *67*, 813–819. [[CrossRef](#)]
144. Tan, K.C.B.; Xu, A.; Chow, W.S.; Lam, M.C.W.; Ai, V.H.G.; Tam, S.C.F.; Lam, K.S.L. Hypoadiponectinemia Is Associated with Impaired Endothelium-Dependent Vasodilation. *J. Clin. Endocrinol. Metab.* **2004**, *89*, 765–769. [[CrossRef](#)]
145. Hara, Y.; Wakino, S.; Tanabe, Y.; Saito, M.; Tokuyama, H.; Washida, N.; Tatematsu, S.; Yoshioka, K.; Homma, K.; Hasegawa, K.; et al. Rho and Rho-Kinase Activity in Adipocytes Contributes to a Vicious Cycle in Obesity That May Involve Mechanical Stretch. *Sci. Signal.* **2011**, *4*, ra3. [[CrossRef](#)] [[PubMed](#)]
146. Sot k, M.; Rajan, M.R.; Clark, M.; Bi rserud, C.; Wallenius, V.; Hagberg, C.E.; B rgeson, E. Healthy Subcutaneous and Omental Adipose Tissue Is Associated with High Expression of Extracellular Matrix Components. *Int. J. Mol. Sci.* **2022**, *23*, 520. [[CrossRef](#)]
147. Henegar, C.; Tordjman, J.; Achard, V.; Lacasa, D.; Cremer, I.; Guerre-Millo, M.; Poitou, C.; Basdevant, A.; Stich, V.; Viguerie, N.; et al. Adipose tissue transcriptomic signature highlights the pathological relevance of extracellular matrix in human obesity. *Genome Biol.* **2008**, *9*, R14. [[CrossRef](#)]
148. Bradshaw, A.D. The role of SPARC in extracellular matrix assembly. *J. Cell Commun. Signal.* **2009**, *3*, 239–246. [[CrossRef](#)]
149. Johnston, E.K.; Abbott, R.D. Adipose Tissue Development Relies on Coordinated Extracellular Matrix Remodeling, Angiogenesis, and Adipogenesis. *Biomedicines* **2022**, *10*, 2227. [[CrossRef](#)]
150. Kos, K.; Wong, S.; Tan, B.; Gummesson, A.; Jernas, M.; Franck, N.; Kerrigan, D.; Nystrom, F.H.; Carlsson, L.M.; Randeva, H.S.; et al. Regulation of the Fibrosis and Angiogenesis Promoter SPARC/Osteonectin in Human Adipose Tissue by Weight Change, Leptin, Insulin, and Glucose. *Diabetes* **2009**, *58*, 1780–1788. [[CrossRef](#)]
151. Luo, L.; Sun, X.; Tang, M.; Wu, J.; Qian, T.; Chen, S.; Guan, Z.; Jiang, Y.; Fu, Y.; Zheng, Z. Secreted Protein Acidic and Rich in Cysteine Mediates the Development and Progression of Diabetic Retinopathy. *Front. Endocrinol.* **2022**, *13*. [[CrossRef](#)]
152. Spencer, M.; Unal, R.; Zhu, B.; Rasouli, N.; McGehee, R.E.; Peterson, C.A.; Kern, P.A. Adipose Tissue Extracellular Matrix and Vascular Abnormalities in Obesity and Insulin Resistance. *J. Clin. Endocrinol. Metab.* **2011**, *96*, E1990–E1998. [[CrossRef](#)]
153. Sasso, M.; Abdennour, M.; Liu, Y.; Hazrak, H.; Aron-Wisniewsky, J.; Bouillot, J.-L.; Le Naour, G.; Bedossa, P.; Torjman, J.; Cl ment, K.; et al. Relevance of Adipose Tissue Stiffness Evaluated by Transient Elastography (AdipoScan<sup>TM</sup>) in Morbidly Obese Patients before Bariatric Surgery. *Phys. Procedia* **2015**, *70*, 1264–1268. [[CrossRef](#)]
154. Pi-Sunyer, F.X. Comorbidities of overweight and obesity: Current evidence and research issues. *Med. Sci. Sports Exerc.* **1999**, *31*, S602–S608. [[CrossRef](#)] [[PubMed](#)]
155. Arroyo-Jousse, V.; Jaramillo, A.; Casta o-Moreno, E.; L pez, M.; Carrasco-Neg e, K.; Casanello, P. Adipokines underlie the early origins of obesity and associated metabolic comorbidities in the offspring of women with pregestational obesity. *Biochim. Biophys. Acta (BBA)-Mol. Basis Dis.* **2019**, *1866*, 165558. [[CrossRef](#)] [[PubMed](#)]
156. Pellegrinelli, V.; Rouault, C.; Veyrie, N.; Cl ment, K.; Lacasa, D. Endothelial Cells From Visceral Adipose Tissue Disrupt Adipocyte Functions in a Three-Dimensional Setting: Partial Rescue by Angiopoietin-1. *Diabetes* **2014**, *63*, 535–549. [[CrossRef](#)] [[PubMed](#)]
157. Tornavaca, O.; Chia, M.; Dufton, N.; Almagro, L.O.; Conway, D.E.; Randi, A.M.; Schwartz, M.A.; Matter, K.; Balda, M.S. ZO-1 controls endothelial adherens junctions, cell–cell tension, angiogenesis, and barrier formation. *J. Cell Biol.* **2015**, *208*, 821–838. [[CrossRef](#)]
158. Viridis, A.; Colucci, R.; Bernardini, N.; Blandizzi, C.; Taddei, S.; Masi, S. Microvascular Endothelial Dysfunction in Human Obesity: Role of TNF- . *J. Clin. Endocrinol. Metab.* **2018**, *104*, 341–348.
159. Gogg, S.; Smith, U.; Jansson, P.-A. Increased MAPK Activation and Impaired Insulin Signaling in Subcutaneous Microvascular Endothelial Cells in Type 2 Diabetes: The Role of Endothelin-1. *Diabetes* **2019**, *58*, 2238–2245. [[CrossRef](#)]
160. Steppan, C.M.; Bailey, S.T.; Bhat, S.; Brown, E.J.; Banerjee, R.R.; Wright, C.M.; Patel, H.R.; Ahima, R.S.; Lazar, M.A. The hormone resistin links obesity to diabetes. *Nature* **2001**, *409*, 307–312. [[CrossRef](#)]
161. Verma, S.; Li, S.-H.; Bhat, S.; Wang, C.-H.; Fedak, P.W.; Li, R.-K.; Weisel, R.D.; Mickle, D.A. Resistin promotes endothelial cell activation: Further evidence of adipokine-endothelial interaction. *Circulation* **2003**, *108*, 736–740.
162. Yudkin, J.S.; Eringa, E.; Stehouwer, C.D.A. “Vasocrine” signalling from perivascular fat: A mechanism linking insulin resistance to vascular disease. *Circulation* **2005**, *365*, 1817–1820. [[CrossRef](#)]
163. Calles-Escandon, J.; Cipolla, M. Diabetes and Endothelial Dysfunction: A Clinical Perspective. *Endocr. Rev.* **2001**, *22*, 36–52.
164. Wang, Z.; Wang, D.; Wang, Y. Cigarette Smoking and Adipose Tissue: The Emerging Role in Progression of Atherosclerosis. *Mediat. Inflamm.* **2017**, *2017*, 1–11. [[CrossRef](#)]
165. Antoniadou, C.; Kotanidis, C.; Berman, D.S. State-of-the-art review article. Atherosclerosis affecting fat: What can we learn by imaging perivascular adipose tissue? *J. Cardiovasc. Comput. Tomogr.* **2019**, *13*, 288–296. [[CrossRef](#)]
166. Cai, Z.; Gong, Z.; Li, Z.; Li, L.; Kong, W. Vascular Extracellular Matrix Remodeling and Hypertension. *Antioxidants Redox Signal.* **2021**, *34*, 765–783. [[CrossRef](#)]
167. Savage, D.B.; Petersen, K.F.; Shulman, G.I. Disordered Lipid Metabolism and the Pathogenesis of Insulin Resistance. *Physiol. Rev.* **2007**, *87*, 507–520. [[CrossRef](#)]
168. Sun, K.; Tordjman, J.; Cl ment, K.; Scherer, P.E. Fibrosis and Adipose Tissue Dysfunction. *Cell Metab.* **2013**, *18*, 470–477. [[CrossRef](#)]

169. Debari, M.K.; Abbott, R.D. Adipose Tissue Fibrosis: Mechanisms, Models, and Importance. *Int. J. Mol. Sci.* **2020**, *21*, 6030. [[CrossRef](#)]
170. Chait, A.; den Hartigh, L.J. Adipose Tissue Distribution, Inflammation and Its Metabolic Consequences, Including Diabetes and Cardiovascular Disease. *Front. Cardiovasc. Med.* **2020**, *7*, 22. [[CrossRef](#)]
171. Crewe, C.; An, Y.A.; Scherer, P.E. The ominous triad of adipose tissue dysfunction: Inflammation, fibrosis, and impaired angiogenesis. *J. Clin. Investig.* **2017**, *127*, 74–85. [[CrossRef](#)]
172. Baynes, J.W. Role of Oxidative Stress in Development of Complications in Diabetes. *Diabetes* **1991**, *40*, 405–412.
173. Busik, J.V.; Mohr, S.; Grant, M.B. Hyperglycemia-Induced Reactive Oxygen Species Toxicity to Endothelial Cells Is Dependent on Paracrine Mediators. *Diabetes* **2008**, *57*, 1952–1965. [[CrossRef](#)]
174. Bouloumié, A.; Sengenès, C.; Portolan, G.; Galitzky, J.; Lafontan, M. Adipocyte produces matrix metalloproteinases 2 and 9: Involvement in adipose differentiation. *Diabetes* **2001**, *50*, 2080–2086.

**Disclaimer/Publisher’s Note:** The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.