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Obesity, adipokines and their relationship with insulin resistance

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Abstract

Obesity is one of the main health problems worldwide. It is a disease that is associated with excessive food consumption, although it is also associated with a process of chronic inflammation and with a group of disorders known as metabolic syndrome. Some of the most distinctive characteristics of obesity are that the individual's adipocytes are hypertrophied, have an irregular adipokine secretion profile, have increased recruitment of inflammatory cells, and altered metabolic homeostasis; which eventually results in the development of various important pathologies or conditions, such as insulin resistance and mitochondrial dysfunction. This review aims to present the current knowledge on inflammation of adipose tissue associated with obesity.

Keywords: obesity, inflammation, adipose tissue, adipokines, insulin resistance.

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Obesidad, adipocinas y su relación con la resistencia a la insulina

Resumen

La obesidad es uno de los principales problemas de salud a nivel mundial. Es una enfermedad que se asocia con un consumo excesivo de alimentos, aunque también se asocia con un proceso de inflamación crónica y con un grupo de trastornos conocidos como síndrome metabólico. Algunas de las características más distintivas de la obesidad son que los adipocitos del individuo están hipertrofiados, tienen un perfil de secreción de adipoquinas irregular, tienen un mayor reclutamiento de células inflamatorias y una homeostasis metabólica alterada; lo que eventualmente resulta en el desarrollo de varias patologías o condiciones importantes, como la resistencia a la insulina y la disfunción mitocondrial. Esta revisión tiene como objetivo presentar el conocimiento actual sobre la inflamación del tejido adiposo asociada a la obesidad.

Palabras clave: obesidad, inflamación, tejido adiposo, adipocinas, resistencia a la insulina.

Introduction

For study and analysis, the etiology of obesity can be organized into: demography, behavior, metabolism, hormonal signaling, central and peripheral energy balance, biology of adipose tissue and skeletal muscle, and intestinal dysbiosis (Ghosh & Bouchard, 2017; Green, Arora & Prakash, 2020). In general, obesity is defined as the presence of a disproportionate increase in body weight in relation to height and excessive accumulation of adipose tissue. Obesity is so important in health issues that it is currently considered the epidemic of the 21st century. According to the World Health Organization, in 2016, it was estimated that more than 1.9 billion adults aged 18 years and older globally were overweight (defined as a BMI ≥25 kg/m2), of which 650 million were considered obese (BMI ≥30 Kg/m2) (WHO, 2021). The pathogenesis of this disease involves two interrelated processes: the first, the positive and sustained energy balance; the second, the restoration of the body weight set point to a higher value (Schwartz, et al., 2017) and that requires new approaches for its treatment (Mayoral, et al., 2020).

Obesity is associated with the development of other pathological conditions, such as type 2 diabetes mellitus (DM2), non-alcoholic fatty liver disease, asthma, various types of cancer, cardiovascular diseases, neurodegenerative diseases, etc. In addition, it is usually accompanied by a chronic low-grade inflammatory state manifested by an increase in systemic markers of inflammation (Sikaris, 2004; Piché, et al., 2020).

The inflammation process in obesity is not fully understood; however, it is most likely associated with homeostatic stress caused by a positive energy balance and a general state of increased anabolism, mainly in adipocytes (Reilly & Saltiel, 2017). These cells respond by releasing various mediators that initiate an adaptive inflammatory response, which allows expansion of adipocytes, resulting in adipose tissue remodeling. Simultaneously, energy storage is considerably reduced and the body tends to restore homeostasis, reaching a new balance for various parameters such as weight, blood glucose levels, lipids, hormones, etc. Low-grade obesity associated with inflammation has a three-stage scenario, typical of chronic inflammation, these are: 1) an initial trigger, which is generally a stressor; 2) an adaptive acute inflammatory response and 3) the chronic pathological phase (Kotas & Medzhitov, 2015).

Diet leads to inflammation

A prolonged overnourished diet and sedentary lifestyle evokes a state of chronic inflammation called metaflammation. Metaflammation contributes to the development of prevalent noncommunicable diseases. These lifestyle-associated diseases represent a growing public health problem with global epidemic dimensions (Christ, et al., 2019). Poor eating habits and obesity are associated with cognitive decline and are risk factors in adulthood. While research has shown that both obese humans and rodents exhibit a reduction in the integrity of the blood-brain barrier, the cellular mechanisms that lay the foundation for these cognitive changes to occur are initially induced by diet (Leigh & Morris, 2020). Low-grade inflammation is associated with a high-fat diet and is the result of independent inflammatory processes that affect and feed back on the intestinal microbiota; these involve multiple mechanisms in inflammatory states (Malesza, et al., 2021). Currently, there is sufficient evidence regarding the role that certain foods have in modulating the inflammatory process through various mechanisms. The alterations caused by diet-induced obesity, DIO (Diet Induced Obesity) seem to depend on time and on the components of the diet themselves. In the western-type diet, which includes at least 40% carbohydrates (sucrose, maltodextrin and corn starch), an increase in the levels of IL-1β, IL-6, IL-18, CCL-2 is observed. and CXCL10 (Interleukin-1beta, IL-1β, Interleukin-6, IL-6, Interleukin-18, IL-18, Chemokine C-C motif Ligand 2, CCL-2, C-X-C motif Chemokine Ligand 10, CXCL-10) in the cortex (Carlin, et al., 2016; HFD (High Fat Diet) continues to be the most widely used DIO model. Its impact on neuroinflammation has been extensively studied. HFD feeding induces the activation of the NF-κB (Nuclear Factor kappa B) pathway and the subsequent expression of inflammatory mediators in the hippocampus (Beilharz, et al., 2016; Wang, et al., 2016; in the amygdala (Almeida-Suhett, et al., 2017), as well as increased levels of TNFα (Tumor Necrosis Factor alpha) messenger RNA and IL-1β in the cerebral cortex (Jayaraman, et al., 2014). and found increased levels of IL-6, MCP-1 (Macrophage Chemoattractant Protein-1) and TNFα (Pistell, et al., 2010) and in the brainstem elevated levels of TNFα and IL-1β (Hao, et al., 2016; Speretta, et al., 2016). On the other hand, a low-fat, high-fiber diet decreases inflammation markers and reduces gut dysbiosis (Fritsch, et al., 2021).

Inflammation of adipose tissue in obesity caused by adipokines

In a situation of obesity, the tissues of the liver, pancreas, skeletal muscle, heart and brain present inflammation. While inflammation in other tissues contributes to the development of insulin resistance and metabolic diseases, inflammation of adipose tissue has a key and unique

role in the pathology of obesity: after weight loss, inflammation in the liver is resolve; however, adipose tissue appears to have obesogenic memory and retains its inflammatory state despite weight loss (Schmitz, et al., 2016). It has been observed that the number of macrophages in obese mice is maintained even after weight loss, which could contribute to sustained tissue damage (Zamarrón, et al., 2017). The effect of this obesogenic memory on adipose tissue is unknown, however, being overweight or obese throughout life, regardless of weight loss, increases the risk of mortality (Yu, et al., 2017).

Although the degree of inflammation correlates with the degree of metabolic disease, it appears that initial inflammation is necessary for physiological adaptation in response to overnutrition (Reilly & Saltiel, 2017). Therefore, the inflammatory environment promotes the formation of new blood vessels from the existing ones to prevent adiposity. Furthermore, it induces insulin resistance to protect adipocytes from lipid accumulation. This inflammatory state promotes the expansion of adipose tissue to prevent ectopic lipid deposition in other tissues where it has lipotoxic effects (Tchkonia, et al., 2013; Chung, et al., 2006; Saltiel, 2012; Nov, et al., 2013; Lu, et al., 2014). However, the continued expansion of adipose tissue can lead to fibrosis, which is associated with inflexibility and irregularities in metabolic pathways, thus leading to death of adipocytes.

Adipose tissue is one of the largest endocrine organs in the body, it is an active tissue for cellular reactions and metabolic homeostasis rather than an inert tissue for energy storage (Unamuno, et, al., 2018). In the obese state, the excessive accumulation of visceral fat causes dysfunction of adipose tissue, which contributes to the appearance of obesity-related comorbidities. In obesity there is a greater caloric overload that leads to the accumulation of fat in ectopic tissues (for example: liver, skeletal muscle and heart) and in visceral adipose tissue deposits, an event commonly defined as lipotoxicity (Longo, et al., 2019).

Inflammation of adipose tissue is initiated and sustained by dysfunctional adipocytes that secrete inflammatory adipokines and by infiltration of bone marrow-derived immune cells that signal through cytokine and chemokine production. Despite its low-grade nature, inflammation of adipose tissue negatively affects the function of remote organs, a phenomenon that is considered to cause the complications of obesity (Kawai, et al., 2021). The cell-cell interactions that take place under the stress of obesity are mediated by intracellular contact and cytokine production and constitute a complicated network that drives phenotypic alterations in immune cells and perpetuates a loop of metabolic decline (Liu & Nikolajczyk, 2019).

Insulin resistance in obesity: role of adipokines

Insulin resistance is a common feature of obesity and DM2 (Type 2 Diabetes Mellitus) and comprises dysfunctional adipose tissue, lipotoxic insulin signaling followed by glucotoxicity, oxidative stress, and low-grade inflammation (Mastrototaro & Roden, 2021). Insulin resistance is manifested primarily by unoxidized glucose disposition in response to insulin, as well as reduced suppression of lipolysis and hepatic glucose production. Although insulin resistance often leads to T2DM, it initially develops as an adaptive physiological response to obesity, resisting the anabolic pressure of insulin to reduce excessive nutrient storage (Reilly & Saltiel, 2017; Asghar & Sheikh, 2017).

Numerous studies show a direct link between inflammation and insulin resistance (Hotamisligil, 2006; Olefsky & Glass, 2010). Insulin sensitivity is related to reduced body weight and decreased low-grade systemic inflammation (Roager, et al., 2019). Excessive accumulation of ectopic lipids causes local inflammation and insulin resistance. In fact, overnutrition triggers runaway inflammatory responses that lead to chronic low-grade inflammation and thus encourages the progression of resistance (Longo, et al., 2019). In general, obese individuals with insulin resistance show a high degree of inflammation of adipose tissue, whereas obese individuals who remain insulin sensitive do not.

Several signaling pathways involved between inflammation and metabolism have been suggested, such as the IKKβ/NFκB axis and JNK1 (I-Kappa-B Kinase beta, IKKβ, c-Jun N-terminal Kinase, JNK) that are expressed both in myeloid cells as well as in cells that are targets of insulin action such as adipocytes, hepatocytes, and myocytes (Arkan, et al., 2005; Hirosumi, et al., 2002). JNK activation leads to phosphorylation on serine residues, instead of tyrosine residues, of the IRS-1 receptor (Insulin Receptor Substrate1) which behaves as inhibitory phosphorylation, thus blocking insulin-mediated signaling events (Zick, 2005).

The cytokines TNFα, IL-1β and IL-6 have their local effect on adipocytes, as well as their systemic action on cells in which insulin acts in peripheral tissues such as liver and muscle, playing an important role in the development of insulin resistance (Hotamisligil, 2006). Leukotrienes B4 (LTB4) act as a stimulus for the stabilization of messenger RNA and synthesis and secretion of TNFα and IL-6 and the lectin galectin-3 (Gal-3), produced mainly by macrophages, which favors the secretion of glucose and insulin supporting the phenomenon of insulin resistance (Li, et al., 2015; Li, et al., 2016). Obesity influences the global level of DNA methylation in visceral adipose tissue, mainly DNMT3a methyltransferase, with a positive

correlation between DNA methylation and insulin resistance (Małodobra-Mazur, et al., 2019) as some insulin pathway genes are epigenetically regulated by promoter methylation.

Adenosine Triphosphate (ATP) production is elevated in insulin-sensitive cells under conditions of obesity, regardless of energy demand, which is called mitochondrial overheating. This phenomenon occurs due to excessive supply of substrate to the mitochondria, leading to the production of additional ATP. ATP overproduction contributes to systemic insulin resistance through several inhibition mechanisms (Ye, 2021), such as: a) reduction in AMPK (adenosine-mono-phosphate kinase) activity leading to a negative regulation of the Glut4 glucose transporter and inhibiting insulin-stimulated glucose uptake (Garcia & Shaw, 2017); b) lead to an increase in cytokines such as TNF-α in the liver to inhibit the activity of the IDE enzyme (insulin-degrading-enzyme) and c), promote insulin elimination through direct activation of DIE (Lee, et al., 2017).

On the other hand, adipocyte-derived bioactive factors known as adipokines influence lipid and glucose metabolism, inflammation, vascular function, and insulin sensitivity in skeletal muscle. The distinct action of adipokines and crosstalk with other organ systems play an important part in inducing adverse health effects in obese individuals (Reuter & Mrowka, 2019).

Adipokines. Adipokines are proteins that belong to a group consisting of cytokines, chemokines, and hormones secreted by adipose tissue. Adipokines are classified as either proinflammatory or anti-inflammatory and an imbalance of adipokines is believed to be the link between obesity, metabolic disorders, cardiovascular disease (Ouchi, et al., 2011) and importantly, sensitivity to insulin (Aguilar-Valles, et al., 2015). The most relevant proinflammatory adipokines include: leptin, resistin, TNFα, retinol-binding protein 4, lipocalin 2, angiopoietin-like protein 2, and visfatin, while anti-inflammatory adipokines include: adiponectin, omentin, vaspin, and adipolin. (Nakamura, et al., 2014; Shibata, et al., 2017).

Proinflammatory adipokines

Leptin. Leptin is an adipokine of 16 KDa produced mainly in adipocytes (Zhang, et al., 1994). Leptin regulates appetite and food intake by communicating the body's energy status to the CNS (Friedman, 1998). Leptin improves glucose utilization and insulin sensitivity under normal conditions and improves hyperlipidemia, as shown in experimental and clinical studies (Oral, et al., 2002; Dong & Ren, 2014). However, hyperleptinemia is common in clinical settings and the administration of exogenous leptin does not produce weight loss, indicating that resistance to leptin may be due to the regulation of its receptor downward or its deterioration in signal

transduction (Mittendorfer, et, al., 2011; and Francisco, et, al., 2018).The form of leptin resistance observed mainly in obesity occurs by inhibiting JAK2/STAT3 signaling, (Janus Kinase2, JAK2, Signal Transducer and Activator of Transcription-3, STAT3) which is normally activated once leptin binds to its receptor (Myers, et, al., 2008;). Increased SOCS3 activity (Suppressor of Cytokine Signaling3, SOCS3) inhibits activation of the JAK/STAT3 pathway, which reduces leptin signal transduction (Bjørbaek, et al., 1998; Bjørbaek, et al., 2000; Rahmouni, et al., 2005).

Resistin. Resistin is an adipokine produced mainly in rodent adipocytes and in monocytes and macrophages in humans (Kaser, et al., 2003). Elevated serum levels of resistin are associated with metabolic disorders and diabetic microvascular complications mediated by endothelial dysfunction (Blaslov, et al., 2015). Interestingly, obesity is still observed in mice with resistin deficiency, despite improved glucose tolerance and insulin sensitivity (Banerjee, et, al., 2004). Cytokines such as IL-1β, IL-6 and TNFα induce the transcription of the resistin RETN of resistin in human mononuclear cells, leading to the expression of more proinflammatory cytokines, this results in precipitation of inflammation (Bokarewa, et al., 2005). Resistin activates SOCS3, an inhibitor of the insulin signaling pathway, thus inducing insulin resistance (Steppan, et al., 2005). Supplementation with eNOS (Endothelial Nitric Oxide Syntase) and L-arginine in mice fed with a high-fat diet improves insulin sensitivity without affecting resistin levels (Szulinska, et, al., 2014).

Tumor Necrosis Factor Alpha (TNFα). TNFα is a cytokine that in obesity is largely produced by monocytes and macrophages present in the stromal vascular fraction of adipose tissue. Levels of TNFα have been found to be elevated in obesity and DM2 (Hotamisligil, et., 1993). TNFα plays a central role in the development of insulin resistance and inflammation by inducing a repressive form of IRS-1, effectively stopping the insulin signaling pathway (Hotamisligil, et, al., 1996). However, patients with metabolic syndrome who were treated with α-TNFα blockers for a prolonged period (approximately 6 months) showed lower levels of fasting glucose, indicating an improvement in insulin resistance and glucose uptake (Stanley et al., 2011). In addition, TNFα increases levels of proinflammatory adipocin visfatin and reduces levels of anti-inflammatory adiponectin (Hector, et al., 2007).

Retinol Binding Protein 4 (RBP4). RBP4 (Retinol Binding Protein4) is a blood transporter for retinol secreted by the liver, adipose tissue, and macrophages (Quadro, et al., 1999). Serum levels of RBP4 are increased in metabolic disorders, obesity, insulin resistance and

proatherogenic affectations (Mohapatra, et al., 2011). RBP4 induces insulin resistance by preventing phosphorylation initiated by IRS1 insulin (Öst, et, al., 2007). RBP4 levels can be used to determine patients' predisposition to atherosclerosis because of their positive correlation with obesity and proatherogenic markers (Mohapatra, et., 2011).

Lipocalin 2. Lipocalin 2 is produced mainly by adipocytes and macrophages after activation of the transcription factor NFκB. Lipocalin 2 is a carrier of retinoids, arachidonic acid, steroids, LTB4 and platelet activating factor. Serum lipocalin 2 levels are elevated in metabolic disorders and inflammation (Cowland, et al., 2006; Zhang et al., 2008). Lipocalin 2 has been shown to cause polarization of M1 macrophages while suppressing the formation of the M2 macrophage phenotype, thereby increasing the expression of iNOS (Inducible Nitric Oxide Syntase) and decreasing the activity of arginase 1 in macrophages (Cheng, et al., 2015). Inhibition of iNOS pharmacologically or through gene silencing prevents the expression of lipocalin 2, indicated by IL-1β and interferon gamma (Chang, et al., 2016). Lipocalin 2 deficiency attenuates insulin resistance associated with aging and obesity (Law, et al., 2010).

Angiopoietin-like protein 2 (ANGPTL2). ANGPTL2 is an adipokine produced mainly by adipocytes, macrophages and endothelial cells and is involved in the development of insulin resistance and inflammation (Tabata, et, al., 2009). High serum levels of ANGPTL2 are high in metabolic disorders and inflammation (Tian, et al., 2013). ANGPTL2 transgenic mice have been shown to have reduced eNOS which is indicative of deficient nitric oxide-mediated vessels (Horio, et al., 2014).

Visfatin. Visfatin is mainly produced by adipocytes and macrophages. It is also known as pre-B cell colony enhancer or nicotinamide phosphoribosyltransferase (Revollo, et al., 2007; Garten, et, al., 2015). Administration of visfatin has been shown to improve glucose intolerance and liver insulin sensitivity (Yoshino, et al., 2011). Serum levels of visfatin are higher in obese patients with DM2 (Olszanecka-Glinianowicz, et al., 2012). Studies suggest that visfatin induces the release of proinflammatory cytokines such as TNFα, which contributes to the onset of insulin resistance (Panidis, et al., 2008). In addition, increased levels of visfatin are closely related to atherosclerosis and reduced levels of L-arginine and nitric oxide (Kusku-Kiraz, et al., 2015).

Antiinflammatory adipokines

Adiponectin. Adiponectin is an anti-inflammatory adipokine produced only in adipocytes. Compared to most other adipokines, healthy plasma concentration is high (approximately 3 to

30 µg/mL) (Ouchi, et al., 2003; Ryo, et al., 2004; Li, et al., 2009). Adiponectin improves insulin sensitivity by increasing glucose and fatty acid metabolism by activating AMP kinase (Adenosin Monophosphate Kinase) and PPARα (Perosyxome Proliferator Activated Receptor Alfa) (Kadowaki, et al., 2008; Yamauchi, et al., 2002; Yamauchi, et al., 2003). Plasma levels of adiponectin correlate inversely with plasma lipid peroxidation, a marker of oxidative stress (Furukawa, et al., 2004). In addition, adiponectin exerts an anti-inflammatory effect by suppressing the production of TNFα and promoting eNOS activity; in addition to inhibiting the NFκB transcription factor induced by a toll receptor and limiting the polarization of macrophages to proinflammatory, while simultaneously increasing the number of anti-inflammatory macrophages (Yamaguchi, et al., 2005).

Omentin. Omentin is an anti-inflammatory adipokine produced in adipose tissue that possesses insulin-sensitizing properties by activating the Akt protein signaling pathway (Yang, et al., 2006). It has been shown that serum levels of omentin are decreased in obese patients with insulin resistance (de Souza, et al., 2007). It has been found that the expression of omentin in visceral and subcutaneous adipose tissue correlates positively with the repression of neuropeptide Y, the most potent appetite-stimulating peptide, suggesting that omentin may play a role in modulating appetite (Brunetti, et al., 2013; Nway, et al., 2016). In addition, omentin has been associated with reduced inflammation, improved lipid metabolism, vasodilation and reduced development of obesity-related cardiovascular diseases and atherosclerosis. Omentin induces the expression of adiponectin, which improves fatty acid degradation and increases insulin-mediated glucose absorption (Herder, et al., 2015). Omentin also stimulates the production of nitric oxide derived from the endothelium, which produces reactive vessel, maintains endothelial barrier function and reduces inflammation (Yamawaki, et al., 2010; Yamawaki, et al., 2011). In addition to its positive regulatory functions, omentin has been shown to suppress the production of TNFα (Kazama, et al., 2012).

Vaspin. Vaspin is an anti-inflammatory adipokine that is secreted by adipose tissue. The administration of recombinant vaspin in diet-induced obesity mice significantly improves glucose tolerance and insulin sensitivity. This beneficial effect results in the normalization of plasma glucose levels and the modification of genes involved in the pathogenesis of insulin resistance (Dimova & Tankova, 2015).

Adipolin. Adipolin is an anti-inflammatory adipokine secreted by adipose tissue that improves insulin sensitivity in obese mice through insulin signaling in liver and adipose tissue. The

treatment of cultured hepatocytes and adipocytes with adipoline activates the signaling pathway of the Akt protein, leading to the suppression of gluconeogenesis and increased glucose uptake. Adipolin levels are reduced in obese mice and correlate negatively with insulin resistance (Wei, et al., 2012). Adipolin reduces inflammation by inhibiting macrophage recruitment and secretion of proinflammatory cytokines (Enomoto, et al., 2011).

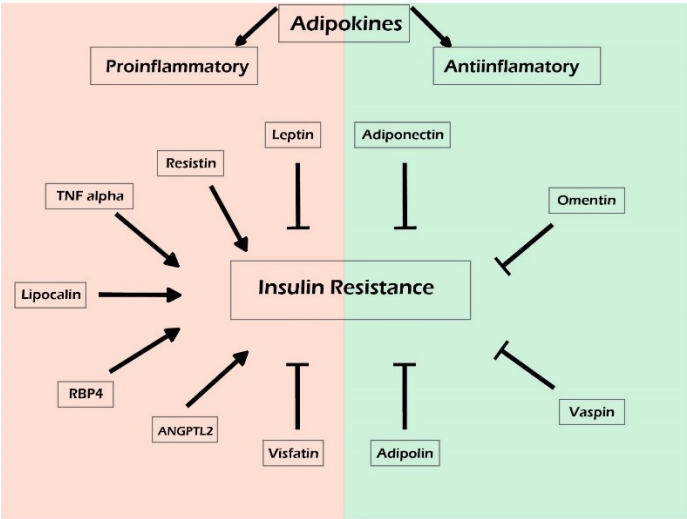

Figure 1. Effect of adipokines on insulin resistance. Insulin resistance is regulated by the effect of proinflammatory and antiinflammatory adipokines. Promotes → inhibits ⊣

Mitochondrial dysfunction in obesity

Mitochondrial dysfunction is a process defined by poor energy production in the form of ATP and often occurs in obesity. Excess nutrients overwhelm the capacity of mitochondrial metabolic processes, resulting in dysfunction (Gao, et al., 2010; Li, et al., 2018). In the mouse preadipocyte cell line, 3T3-L1, mitochondrial dysfunction manifests as a reduction in fatty acid oxidation, resulting in an accumulation of triglycerides and an increase in glucose uptake suggesting an increase in glycerol 3-phosphate synthesis which, in turn, leads to increased lipid accumulation. This increase in lipid accumulation in adipocytes leads to the eventual loss of lipotoxicity buffering capacity in these cells. In a murine model, excess free fatty acids are released into the bloodstream, resulting in an ectopic fat deposit, which is believed to be the underlying cause of the development of insulin resistance in obesity (Hardy, et al., 2012; Crewe et al., 2021; Rytka, et, al. 2011).

In addition to the adverse effects of systemic lipid accumulation and subsequent steatosis, mitochondrial dysfunction also results in increased production of reactive oxygen species

(EROs), as seen in clinical and experimental studies (Talior, et al., 2003; Lin, et al., 2005). The electron transport chain, mainly complexes I, II and III, are also considered to be the main sources of generation of EROs due to electron leakage capacity (Starkov, et al., 2004; Quinlan, et al., 2013; Jastroch, et al., 2010). This electron leakage directly correlates with mitochondrial membrane potential (Suski, et al., 2012).

Activation of the decoupling protein by EROs serves as a feedback mechanism to reduce membrane potential (Cheng, et., 2017). These harmful byproducts of metabolism can induce metabolic dysfunction, inflammation and development of insulin resistance (McMurray, et al., 2016; Forrester, et al., 2018). EROs have also been shown to increase activating transcription factor 3 (ATF-3), a protein responsible for adiponectin expression (Furukawa, et al., 2004). Although adipocytes, unlike other cell types, can support high levels of EROs without substantial damage, chronic elevation of EROs is harmful and decreases the expression of adiponectin (Wang, et al., 2010).

There is an important link between oxidative stress, mitochondrial dysfunction and metabolic dysregulation during obesity. Mitochondrial functions involved in obesity include oxidative functions, renewal and enlargement of adipose tissue through the recruitment and differentiation of adipocyte progenitor cells, affecting the body's metabolic health (Heinonen, et al., 2020).

Death of adipocytes and obesity

Inflammation in obesity can be caused by signaling associated with the death of adipocytes that tend to accumulate in adipose tissue in centers of different crown-shaped structures (Fischer-Posovszky, et al., 2011). Changes in cell numbers mainly involve the generation of new cells or the death of existing cells. The dedifferentiation by which a mature adipocyte reverts to a state similar to that of an undifferentiated parent is a mechanism underlying the plasticity of adipocytes, in some cases culminating in a pathological condition (Song, et al., 2019; Wang, et al., 2020).

Hypertrophic adipocytes have been found to be more susceptible to injury and cell death than normal adipocytes and there are observations suggesting some threshold in adipocyte size and consequently, in their ability to store lipids beyond which they develop intracellular alterations

that affect their functionality; for example, impairment of mitochondrial metabolism (Ortega, et al., 2009) and ultimately lead to cell dysfunction and death (Cotillard, et al., 2014).

Leptin acts directly on macrophages to increase their phagocytic and proinflammatory activity by producing cytokines and exerting an effect on T cells, neutrophils and endothelial cells (Poloni, et al., 2015). Hypertrophic adipocytes produce an increased amount of adipokines that stimulate chemotaxis to recruit macrophages (Guilherme, et al., 2008), being in macrophages where NLR receptor activation occurs (Nod-like Receptors) resulting in the activation of the inflammasome (Vandanmagsar, et al., 2011). These processes undoubtedly contribute significantly to the increase in the number of macrophages in adipose tissue and thus to obesity (Lindhorst, et al., 2021).

Conclusions

The components and time of consumption of a diet rich in fats contribute to low-grade inflammation, which is characterized by the increase of proinflammatory cytokines such as TNF and IL-1β and chemokines such as CCL-2 and CXCL-10 in different cell types. The initial response to inflammation is adapted allowing the reduction of anabolic pressure due to overfeeding and fostering the expansion of adipose tissue over time. In obesity, excessive accumulation of visceral fat causes a dysfunction of adipocytes leading to the secretion of adipokines which, in turn, contribute to the appearance of metabolic diseases such as insulin resistance. Among the signaling pathways present in cells that are targeted for insulin action that lead to this resistance are: 1) the IKβ/NFκB pathway producing key proinflammatory cytokines in its development such as TNF; 2) the JNK pathway by inhibiting the signal by phosphorylation in serine residues instead of tyrosine residues of the IRS1 insulin receptor and 3) overproduction of ATP leading to negative regulation of the Glut4 glucose transporter. Correlations between inflammation, adipose tissue, obesity and comorbidities such as insulin resistance position the aforementioned signaling pathways as a potential target for the treatment or prevention of this pathology. However, a better understanding of the molecules associated with obesity is necessary to develop effective therapeutic measures or prophylactic strategies.

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