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REVIEW ARTICLE

Harnessing the crosstalk of adipocytes, autophagy, and immune cells for immunotherapy in obesity

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ABSTRACT

As a self-degradative and recycling program, autophagy plays an essential role in homeostasis and life. The connection between autophagy and the status of the adipose tissue (white or beige/brown) links to metabolic diseases such as obesity, type two diabetes mellitus (T2DM). Moreover, autophagy and the renin-angiotensin physiological system play a pivotal role in metabolic syndrome, a disease that can disrupt homeostasis in different organs, including adipose tissue. The crosstalk in adipose tissue maintains low inflammation, brown adipocytes, and autophagic machinery under control. The JAK-STAT signalization pathway and the paracrine action of hormones, adipokines, and cytokines play a role in maintaining the status of low inflammation, brown adipocytes, and autophagic machinery to harness the utmost for obesity immunotherapy.

Keywords: Autophagy; Adipocytes; Immune System; Leptin; Obesity; Type Two Diabetes Mellitus (T2DM)

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1. Introduction

Obesity is a condition of excessive fat in adipose tissue. It has become a global problem of concern, especially in young adults (under 20 years old), that represent 25% to 30% of adult people[1,2]. The lack of physical activity, overnutrition, and importantly the diet (rich in carbohydrates and fats) contribute greatly to increase this problem[3–5]. The problem have become ruthless and hard to overcome because those with obesity are predisposed to suffer from other chronic complications, i.e. type 2 diabetes mellitus, hypertension, cardiovascular disease, as well as to suffer from other chronic diseases such as cancer[6–9]. Several studies and efforts have been made to have an adequate management of obesity in different aged populations. Studies at the level of basic clinic research focused to understand the links between obesity and the implication of this condition at the cellular and organismic level. At this point, it is known but not understood clearly that there are key links of the crosstalk between the dysfunction in any of organs or tissues and insulin sensitivity/resistance[8–11].

For example, in obesity, in addition to the surplus of nutrients and energy stored in the adipose tissue and in non-adipose tissue as fat, there are production of inflammatory cytokines, adipokines and reactive oxygen species[12–14]. These provoke damage at tissue (liver, or skeletal muscle) or at cellular levels (adipocytes differentiation)[14,15]. Indeed the surplus of nutrients can provoke systemic lipotoxicity due to the excessive fat accumulation, elevating thus, serum free fatty acid levels[16].

Under these settings, the health condition of the individual is really compromised, because the potential links of the adipose tissue dysfunction with other metabolic organs and cellular processes[9,11,17].

Adipose tissue (AT), considered a dynamic endocrine organ, key in energy and metabolic homeostasis closely related to the energy storage and to the secretion of different components and factors that participate in the regulation of several physiological functions (i.e. metabolism, reproduction coagulation and cardiovascular function). AT secretes a great amount of factors that includes those with endocrine function (adiponectina, leptin, omentin, resistine, visfatine, apeline, vaspine, apelin, various growth factors, sex steroids), and those with immune function (adipsine or factor D of the complement, hepcidine, haptoglobulin)[18,19]. In fact, AT and the lymphoid tissue anatomically is closer to the adipose tissue, generating a microenvironment thus helping the immune system to answer[20,21]. Other components also secreted by AT are the protein 4 ligand of retinol (RBP-4), non-esterified fatty acids (NEFA), inhibitor of the activator of plasminogen (PAI-1), 11 β-dehidroxiesteroide dehidrogenasa, prostaglandins, angiotensinogen that participate in metabolic, cardiovascular function[17,22,23].

Adipose tissue (AT) is conformed by the bona fide cells as pre-adipocytes, adipocytes, endothelial, and immune cells. The two principal types of adipocytes are the white and brown with an intermediate state of adipocytes, and the brown adipocytes that depend mostly of the lipid and mitochondria content. Thus, beige adipocytes are with an intermediate amount of each of these components[15]. Macrophages and eosinophils function in adipose tissue as the yin and yang innate immune cells in AT. Macrophages in obese adipose tissue increase and are associated with inflammation and metabolic disease, specifically insulin resistance[24,25]. Together, all these cells make up AT and contribute to the cellular composition and regulation of obesity and metabolic dysfunction[25,26].

Specifically, brown and white adipocytes (WAT/BAT) secrete several components, enzymes, hormones, and growth factors that activate the JAK-STAT pathway[27,28]. Thus, adipocytes in AT establish paracrine crosstalk of the immune cells and autophagy, representing a platform for immunotherapy[29–32]. Furthermore, adipocyte differentiation is crucial for metabolic homeostasis[13]. In AT, adipogenesis is carried out in two stages: commitment of mesenchymal stem cells to a pre-adipocyte fate and terminal differentiation, and a signalization pathway of WNT and RHO-family GTPase cascade has been involved in this. In the terminal differentiation of committed preadipocytes through the epigenomic activation of peroxisome proliferator-activator receptor-gamma (PPARA-γ) and the adipogenic stimuli[13,15]. The adipocyte gene expression in AT is maintained through the coordination of PPAR-γ and the CCAAT/enhancer binding protein (C/EBP) transcription factors[33]. Understanding this mechanism of adipogenesis and the players involved in it, can also provide therapeutic targets against metabolic diseases[11,33].

Since autophagy is an adaptive eukaryotic process, pivotal for cellular homeostasis, any stress or cellular, organelle damage triggers the induction of autophagy[34,35]. Indeed, there has been a recent study on autophagic response in obesity condition and the links between insulin action and the type 2 diabetes mellitus[29]. Thus, autophagy can be activated either under low nutrients (constitutive activity) intake or in overnutrition[29,35]. A defect or impairment of autophagy machinery program represent a failure and a cause of disease, exacerbated inflammatory responses and organelle dysfunction[36,37]. For example, lipids or glycogen can compromise hepatic metabolic function and affect insulin action, exacerbating insulin resistance and possibly other metabolic pathologies associated to obesity. In obesity, it has been found an impairment in autophagy and insulin signaling[33,38].

Another potential link is that autophagy acts in concert with the immune cells present in AT, and with endocrine renin-angiotensin system (RAS system) for regulation of blood pressure and fluid balance[33,39], dysregulation of which can exhibit abnormalities in obesity. Furthermore, autophagy and obesity connections are related to the ER stress[40,41]. In fact, ER can provide the membranes for the au-

tophagosome formation[15,29,41], and obesity is characterized by ER stress[37]. In experimental ER stress, autophagy is induced, and several canonical UPR (unfolded protein response) pathways are activated[35,39]. ER stress can have an effect in the pancreatic beta cell function, and thereby in insulin secretion. Thus, autophagy also plays a role to keep homeostasis at the level not only of ER but of the beta cell function, critical in metabolic diseases, such as obesity and diabetes[38]. In obesity, insulin action and mTOR, are altered, both of which are autophagy regulators[41,42]. Therefore, dysregulation of autophagy constitutes a critical component of obesity and contribute to metabolite dysfunction.

Current studies and evidence from the literature have shed light on the close crosstalk sustained among different physiological systems to keep homeostasis and individuals functional with life. Work is ongoing in the lab to investigate and determine the status of autophagy, adipokines, and the immune system in obesity in young individuals. These might provide potential therapeutic targets for prevention and immunotherapies.

Adipose tissue and adipogenesis. The adipose tissue is a dynamic endocrine organ that functions in energy storage. It is also the primary site of inflammation in obesity and secretes several participant factors of the immune response[27,43]. The secretion of a great variety of proteins enables it to participate importantly in the regulation of appetite, metabolism, reproduction, coagulation, and cardiovascular function[12,13,44,45]. The deposit sites of adipose tissue can be subcutaneous (80%) or visceral (20%). The vascularized tissue has higher sympathetic innervation and many β adrenergic receptors, enabling it with higher activity and relation with the associated pathology with obesity.

In humans, there are two types of adipose tissue, brown (responsible for thermogenesis) and white adipose tissue (fat storage and secretion of molecules)[12,13,44,45]. In the adipose tissue of obese individuals, the status is characterized by an increase in adipocytes, hypertrophy (increase in size), or hyperplasia (increase in the number). A remarkable anatomical feature is that lymphoid tissue is very close to adipose tissue, generating a microenvironment that helps the immune system[12,13,44] (**Figure 1A**). Both types of tissues interact locally through common mediators—cytokines, adipokines (leptin, adiponectin, resisting, visfatin, apelin, Caspian adipsin), factor D of the complement, hepcidin, retinol ligand protein 4 (RBP4), non-esterified fatty acids—An inhibitor of the plasminogen (PAI-1), 11 β-di-hydroxysteroid dehydrogenase[13,19,42] (**Figure 1B**).

Autophagy is a biological and cellular process of catabolism by recycling products of metabolism. It is a mechanism of autoregulation of renewal to eliminate intracellular components, excessive nutrients, toxic protein aggregates, damaged organelles, and invasive microorganisms[30,46]. This process plays a pivotal role in maintaining energy homeostasis and protection against stress.

Autophagy occurs in specialized vacuoles of double membrane-denominated autophagosomes. It requires the participation of lysosomes[46,47]. Autophagy self-program is formed by a set of associated ATG proteins that conform machinery for cytoplasm checking quality control. The status of autophagy under stress conditions, starvation, or nutrient limitation (glucose, amino acids, growth factors, oxygen, pathogens) is the upregulation of ATG genes, particularly ATG*5*, potentially linked with inflammation[48,49]. Autophagy keeps low levels of homeostasis and survival in anabolic reactions[35]. Activation of autophagy occurs under environmental stress, malnutrition, and other factors, leading to a metabolic dysfunction: at the level of adipocyte differentiation (an increase in white adipose tissue), a dysregulation in lipid metabolism (an imbalance in lipids) and activation of the JAK-STAT signalization pathways)[36,47,50]. (**Figures 1A** and **1B**)

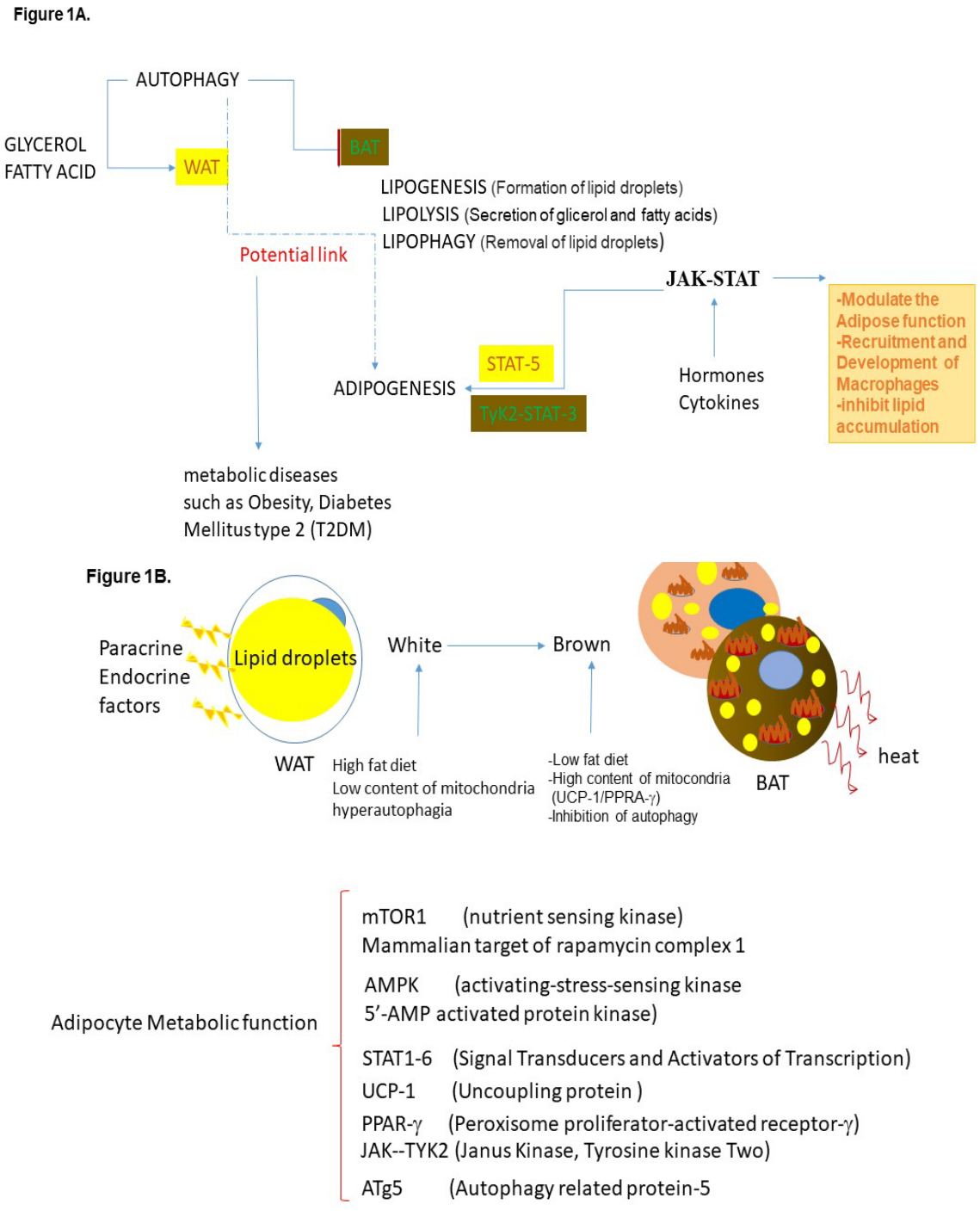

Figure 1. Schematic representation of the metabolic pathways, lipids metabolism, autophagy connected through the JAK-STAT signalization pathway. To maintain homeostasis in adipose tissue makes necessary that all the metabolic pathways function properly connected with autophagy machinery for elimination of unwanted material and cellular damaged organelles. The JAK STAT activators have the enormous responsibility of the functionality of the white and/or brown adipocytes. **(A)** The link are the paracrine secreted components of adipocytes and the immune cells that influence the state of the inflammation status and of the immunometabolic health. **(B)** Features ad hoc of the white and beige/brown adipocytes, the function and development depend of the transcriptional control of the JAK-STAT activator and of the autophagy machinery. White adipocytes are the lipid storage compartment in adipose tissue while brown adipocytes are responsible of the expenditure of the energy, to release energy under cold and beta-adrenergic receptor stimulation.

Regulation of autophagy is necessary to fit an individual metabolic profile and warrant a proper balance in adipose tissue metabolism function. Dysregulation of autophagy correlates with neurodegenerative and cardiovascular disorders. Therefore, the therapeutic implication of the modulation of autophagy constitutes with of the most exciting areas of research[32,35,51]. When autophagy machin-

ery is dysfunctional for a prolonged period (high fat or fructose diet), accumulation of unwanted proteins and organelles in adipose tissue, liver, muscle, and pancreas is observed. Under these settings, autophagy becomes detrimental and eventually induces metabolic dysfunction and metabolic diseases such as obesity and type 2 diabetes mellitus (T2DM) and other effects on health (cachexia, hepatic steatosis, rarosis, atherosclerosis)[27].

2. Autophagy in obesity

Obesity constitutes a health problem, especially in developed countries. In Mexico, around 70% of Mexicans suffer from being overweight, and almost a third proportion develop obesity. Obesity is associated with the development of metabolic syndrome[39,42], leading to diabetes and cardiovascular diseases, but also affects muscular tissue, bones, and some types of cancer[1,2,39]. Hypercaloric foods intake (rich in fat, salt, and sugar) but deficient in minerals and vitamins can cause obesity. Other factors that lead to obesity are some physiological disorders: hypothyroidism and the Cushing disease, pharmacological drugs; anti-depressive, corticosteroids, nutrition diet, smoking habits, genetic factors, age, and race[2,30,52].

Adipogenesis and autophagy have been proposed as potential links to metabolic diseases such as obesity and diabetes mellitus. In referring to the role of autophagy in obesity, it has been reported that there is a combined expression of proteins associated with autophagy ATG5/LC3 (LC3-II)/p62 (ubiquitin-bonding scaffold protein) in obese individuals and mice[53,54]. Autophagy can be involved in the browning of the white adipose tissue. It can affect the metabolism equilibrium of lipids. Furthermore, the role of autophagy in the development of obesity has been related to insulin sensibility. (**Figures 1A** and **1B**)

Autophagy can degrade the cytoplasmic lipids in hepatocytes, a process called “hypophagia”[49]. The equilibrium related to the quantity of white adipose tissue and brown adipose tissue can affect the storage of lipids and the energetic homeostasis of the body. Mice with selective alteration of ATG7 are brown with decreased white adipose mass and are sensible to the insulin, and show an accumulation of lipids due to defects in the elimination process of lipids (lipophagia). In addition, the absence of ATG7 in preadipocytes 3T3-L1 decreased protein levels and factors of adipocyte differentiation. Similarly, the lack of ATG5 or the pharmacological inhibition of autophagy has similar effects[57]. Knockout mice with autophagy genes in adipose tissue show defects in adipocyte differentiation, skeletal muscle, or liver, leading to leanness, obesity resistance, and induced diabetes because of the diet[35]. Therefore, autophagy regulates the accumulation of corporal or body lipids controlling the differentiation of the adipocytes and determining the equilibrium between the white and brown fat[19,24]. By another hand, there is a relationship between some hormones that regulate appetite (ghrelin), and autophagy.

The ghrelin activation of the pathway PI3K/Akt/Bcl-2 inhibits the activation of autophagy. This effect can be interrupted by an inhibitor of the Akt kinase[48]. In referring to the studies approaching the role of the autophagy genes, those described in the mouse and human models were cited. In preclinic models (obese mice)[34,57], deletion in the gene ATG7 causes a phenotype of brown adipose tissue and a high metabolic rate. These knockout mice keep weight and are resistant to obesity. Moreover, obese mice show a decreased expression of ATG5 and ATG7. However, in a clinic model using explants in visceral adipose tissue and subcutaneous tissue (WAT), expression of ATG5, IC3, and IC3B is increased[36]. Autophagy dysregulation leads to problems in overweight, obesity, and diabetes. It predisposes to other neurodegenerative diseases as hypertension and cardiovascular diseases[6,32]. Weight loss and autophagy regulation targeted to improve metabolic health targeting in anti-obese therapies. Adipogenesis increase when autophagy is inhibited facilitating, thus, weight loss and improving metabolic health[6,32]. Furthermore, the role of autophagy in adipocytes differentiation can be through the activation of the autophagy by the angiotensin II pathway modulated by NADPH oxidase and ROS, both targets of cellular stress, inflammation, and cellular infiltration[12,13]. The ad-

ipose autophagy activated regulates the increase in C/EBP, Fabp4, Agpat2, and FAS, related to the differentiation and adipose maturation. The activation of the autophagy could be through NADPH oxidase mediated by the production of angiotensin II and ROS, as well as other triggering factors like cellular stress inflammation and macrophages infiltration[39,42].

3. The status of autophagy in obesity

Autophagy is inactive during obesity conditions because hyper nutrition inhibits AMPK (serine/threonine kinase AMP-activated protein kinase complex) and activates mTOR1 (nutrient-sensing kinase) (mammalian target of rapamycin complex 1)[30]. In obesity, mTOR1 is positively regulated and associated with anabolic metabolism in the liver[34]. The resistance to insulin and hyperinsulinemia is attributed to the inhibition of autophagy in obesity[6]. In recent times, some studies have related autophagy with the regulation of lipids metabolism, and today it is known to be through four pathways. (**Figures 1A** and **1B**).

1) The metabolites released from the lipids metabolism activate the mTOR pathway decreasing the activation of autophagy[30].

2) Changing the morphology of the lipid membrane and the transport of the vesicles of binding to effectors proteins.

3) Some lipidic molecules facilitate the modification of the proteins to regulate autophagy for example in the lipidation of the family of proteins Atg8/LC3.

4) The lipidic molecules regulate autophagy by the control in the distribution of specimens of lipids in the double lipidic membrane.

The resistance to insulin and hyperinsulinemia is associated with the inhibition of autophagy during obesity. Obese mice show a low expression of ATG5 and ATG7 and an inhibition of autophagosome biogenesis[52,55].

Some other studies in humans are related to the increase in the protein expression and the ARNm of ATG5, IC3A, and IC3B[36]. Moreover, the events involved in the acquired pathogenesis of the overweight and obesity condition at the physiological level, the body suffers a significant dysregulation in diverse processes[36,39,56], for example, in mechanisms of recycling and destruction to the cellular level of proteins, cellular remnants or whole organelles, in senescence or anormal, as well as substances in the cytoplasm due to autophagy. This process is activated under different conditions like stress, starvation, and microbial or in the development of anormal cells[35]. In the regulation of the metabolism of lipids, it is proposed that the autophagy machinery intact is necessary for the biogenesis of lipids.

3.1 The status of the immune system in obesity

In the last years, it has been associated obesity with a chronic inflammatory process of low intensity. Obesity alters the metabolism of the adipose tissue and endocrine functions, leading to an increase in the release of hormones, fatty acids, and pro-inflammatory molecules that contribute to the association of own complications of the disease[58–60]. When persons become obese, their adipocytes enlarge, and adipose tissue suffers alterations at the molecular and cellular level affecting systemic metabolism. First, macrophages accumulate inside adipose tissue, which causes local inflammation, but also macrophages act as scavengers of apoptotic adipocytes[28,32,58,61]. (**Figure 2A**)

Several pro-inflammatory factors are produced in adipose tissue (AT) of obese individuals in comparison with AT of lean individuals. Several studies have shown an increase in the secretion of cytokines like TNF-α and IL-6 that stimulate the preadipocytes and the endothelial cells to produce chemo-tactic (MCP-1). These can attract macrophages to the adipose tissue for induction of the inhibitor of titular plasminogen (PA1-1) and some adhesion molecules (P-selectin, ICAM, VCAM-1). It promotes adhesion, migration, and accumulation of monocytes and T lymphocytes in the subendothelial space as a consequence of the impairment in vascular permeability[50]. Autophagy plays a fundamental role in inflammation, which is part of the obesity profile, influences the development, home-

Figure 2A.

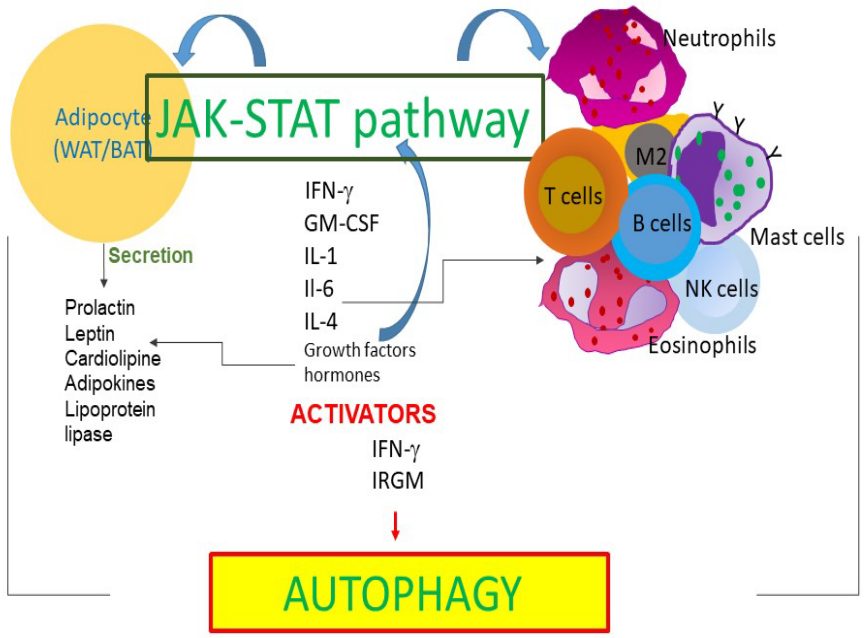

Figure 2B.

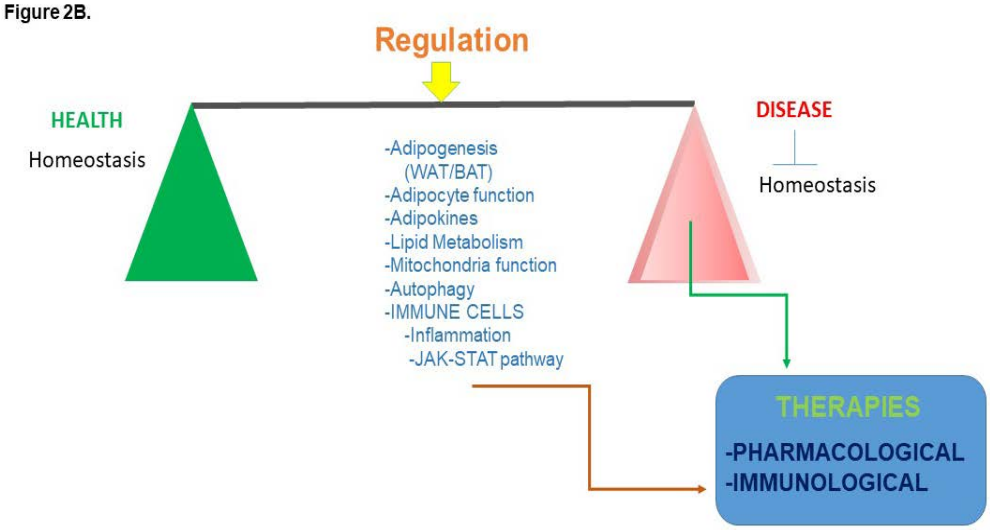

Figure 2. (A) The crosstalk in adipose tissue for modulating adipogenesis, the development, differentiation and the physiological function of adipocytes (white, beige-brown), involves to the immune cells and the cytokines produced, the autophagy machinery and the different secreted components by adipocytes. All of them behave as activators of the JAK-STAT pathway, that influences strongly the status of inflammation, considered as key endocrine immunological factor that trigger immunometabolism diseases. **(B)** The balance in the crosstalk and regulation of the physiological processes in adipose tissue with bias toward health or disease.

ostasis, and survival of the inflammatory cells, including macrophages, neutrophils, and lymphocytes, carried out transcription, processing, and secretion of a series of cytokines, besides to be regulated by other cytokines. It has shown that either IL-1α or IL-1β induce autophagy, which can behave as a negative feedback loop to control the inflammation induction by IL-1. The secretion of Il-18 and TNF-α is regulated by autophagy. The inhibition of autophagy is due to the production of IL-18, reducing the production of IL-6, IL-8 and TNF-α[25,28,32,47].

Indeed, autophagy affect the secretion of cytokines type-TH1 (IFN-γ, TNFα, IL-1, IL-2, IL-6, TGF-β, MCP-1) and of the type-TH2 (IL-4, IL-10 and IL-13) as well as another type cytokines (IL-1β, IL-18, IFN-α, IFN-β and IL-8)[25,28]. The family of STATs or signal transducer activator of transcription (STATS) is activated by phosphorylation of one tyrosine (Tyr) residue near the C-terminus that is catalyzed by a Janus Kinase (JAK), conforming to the JAK-STAT signalization pathway. The STAT family of transcriptional activation play a pivotal

role in transferring the external stimulus to the nucleus for expressing transcription factor that influences and participates in different immunological processes and in connection with endocrine system in adipogenesis development, differentiation and regulation. STAT1-3, STAT5, and STAT6 play a role directly or indirectly in human. For example, STAT1-3 participates through IFN-γ modulation of adipocyte function, while STAT5 participates in the regulation of the differentiation of preadipocytes, adipocytes, myeloid and macrophage in adipose tissue[21]. Another component of the innate immune cells, the GM-CSF (granulocyte-macrophage colony-stimulating factor) functions as a bridge between the innate and adaptive immune response. In normal conditions, GM-CSF secreted by tissue-invading lymphocytes plays a role in immunopathogenesis[21,62]. (**Figures 2A** and **2B**)

The level of the immunological response in adipose tissue refers to obesity. A series of biochemical reactions that are pivotal in the translation of positive or negative signals are the JAK-STAT signalization pathway. This pathway, the Janus kinase activation pathway (non-receptor tyrosine kinases) (JAK1, JAK2, JAK3, and TYK2)[21,51], is formed by a diversity of ligand-, mediated signals, from cytokines and hormones, leads to activation downstream signaling pathways and alterations in gene expression. One of the physiological functions of the JKA activation is the immune effector function. Aberrant activation of JKA signaling plays a critical role in various chronic diseases, such as autoimmune disorders, several malignancies, and rheumatoid arthritis. The inhibitor of the JKA pathway is proposed as a new therapeutic approach[24,63]. The JAK-STAT signalization pathway has a critical role in the crosstalk of adipocytes and immune cells in adipose tissue that might influence obesity pathogenicity. The family of JAKs (1-3) includes Ty2 and STATs (1-6) and is well known as critical in adipocyte differentiation (WAT/BAT) in AT. The immune cells produce pro-inflammatory and anti-inflammatory cytokines signals via the JAK-STAT pathway[21,51]. In other words, the immune cells present in the adipose tissue participate dynamically and modulate the physiological function of either WAT or BAT adipocytes. Target genes of STAT pathways in AT have shed light on the role of the transcription factors in immunometabolism (adipocyte browning and whitening, insulin sensibility, lipid storage, and glucose homeostasis)[58]. (**Figures 2A** and **2B**)

For example, STAT-1 transcriptionally regulates the lipoprotein lipase produced by adipocytes. Indeed, STATs activators play a role in the regulation of adipocyte differentiation. Moreover, these activators exhibit differential expression in conditions of obesity and/or insulin resistance. GM-CSF plays a role in adipose tissue to recruit and activate macrophages that contribute to AT inflammation and insulin resistance. Furthermore, the pro-inflammatory properties of IFN-γ signaling through the JAK-STAT pathways can inhibit pre-adipocytes differentiation[59,60,62,64]. In addition, IFN-g produced from infiltrated immune cells on adjacent adipocytes leads to insulin resistance. It was observed in transgenic mice in the IFN-γ gene that the shift from ATM in WAT toward a phenotype BAT in ATMs results in decreased production of inflammatory cytokines and improved insulin sensitivity[28,32,52,63,65]. (**Figures 2A** and **2B**)

4. Conclusion

For immunometabolism disease therapeutic interventions (i.e. obesity), it makes necessary to take advantage of the crosstalk of the endocrine, immunological, and autophagy programs. One alternative could be to promote the browning of white adipose tissue, possibly through keeping or modulating the inflammation in AT macrophage activation (IL-6 production) and species reactive oxygen, inhibiting fatty acid release but promoting fatty-acid combustion (exercise). A second alternative is to target inflammation modulation by innate cells in AT through the JAK-STAT signalization pathway with the interplay with the autophagy machinery. For example, ATG proteins are associated with autophagy machinery targeted by Chloroquine treatment, and this might influence the outcome of the endocrine-immunological response potentially in AT of obese individuals.

A third one is, to target autophagy, by subtle

inhibition through pharmacological drugs) which will impact adipocyte differentiation. Moreover, to inhibit or modulate autophagy expression proteins (ATG-5), and downregulate IFN-γ production and TLRs expression on macrophages. By another hand, the modulation of ATMs in AT and the products secreted by them is pivotal for insulin sensitivity regulation.

An exciting area of basic and clinical research is the translation of the crosstalk and the status of the adipocytes, immune cells, and autophagy. The three have the enormous task of favoring steady low inflammation and adipocyte browning to get healthier tissues and longer life.

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Conflict of interest

No conflict of interest was declared by the author.

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