Chapter

# Phagocytosis: Inflammation-Obesity Relationship

*Jeanet Serafín López, Ursino Pacheco García, María Eugenia Castro Mussot and Ernesto Pacheco Ramírez*

## Abstract

Obesity is a chronic, multifactorial disease with increasing worldwide prevalence. It is characterized by excessive adipose tissue accumulation in the body, which decreases the patient's life expectancy and has been associated with a higher incidence of chronic degenerative diseases, including type 2 diabetes mellitus, systemic arterial hypertension, cancer, and cardiovascular disease. Several investigations have found that the adipose tissue of obese humans and rodents is infiltrated by a high number of macrophages. These cells interact with apoptotic adipocytes, which internalize and accumulate lipids to become foam cells. These processes lead to the release of proinflammatory mediators that promote insulin resistance. In addition, individuals with obesity have higher levels of circulating neutrophils; however, these individuals also have a higher incidence of infection, indicating that the phagocytic function of these cells is affected. This chapter describes several studies that could partly explain the phagocytic mechanisms affected by obesity. Therapeutic alternatives to favor phagocytic capacity are also discussed.

**Keywords:** obesity, phagocytosis, inflammation, macrophages, insulin, neutrophils

## 1. Introduction

Obesity results from an energetic balance alteration caused by the abnormal or excessive accumulation of triglycerides in the adipose tissue (AT). It is a chronic and multifactorial ailment and is considered a serious public health illness. Its prevalence is on the rise, and the World Health Organization (WHO) estimates that since 1975, obesity has increased almost thrice worldwide, reaching epidemic proportions. It is considered the epidemic of the twenty-first century [1–3].

The body mass index (BMI) is the most accepted parameter to determine clinically overweight and obesity and is frequently used to identify overweight and obesity in adults using the relationship between weight and stature. It is calculated by dividing the person's weight in kilograms by his/her squared stature in meters ($kg/m^2$).

The WHO defines overweight and obesity for adults as follows:

- Overweight: BMI equal to or above 25.

- Obesity: BMI equal to or above 30.

Although the BMI is not an ideal indicator because it does not allow the exact determination of an individual's adiposity, it is the most recommended for clinical use by international health organizations due to its easy usage [4].

Different diseases are associated with obesity because there are alterations in the immune response generated by an inflammatory process, which is also related to the following:

- Metabolic disorders such as insulin resistance (IR), type 2 diabetes mellitus (T2DM), cholesterol or triglycerides increase, and metabolic syndrome (MetS).
- Cardiovascular diseases such as hypertension, atherosclerosis, heart failure, and cerebrovascular disease.
- Respiratory diseases such as hypoventilation or sleep apnea/hypopnea syndrome.
- Increased risk for some cancer types and osteoarticular pathologies [1, 5].

## 2. Inflammation and obesity

The AT can be classified into different compartments: subcutaneous tissue and visceral adipose tissue (VAT). In obesity, VAT is highly associated with the increment of cardiovascular risk and the development of MetS, hypertension, insulin resistance, and T2DM [6].

The VAT is composed of a greater number of adipocytes, but it is a tissue with plentiful immune infiltrate with the presence of eosinophils, neutrophils, macrophages, regulatory T lymphocytes (Treg), CD4+ T lymphocytes, CD8+ T lymphocytes, and type 2 innate lymphoid cells (ILC2). In the VAT in homeostasis, there is a microenvironment rich in IL-4, IL-5, and IL-13, as well as the presence of Treg cells, eosinophils, and ILC2 that promote a Th2 phenotype and M2 macrophage polarization, which express arginase-1 (ARG-1) that inhibits the activity of the inducible enzyme nitric oxide synthase (iNOS) and increase IL-10 production. In obesity, the adipocyte's number and size are increased due to the accumulation of fatty acids inside the cells. This fact demands a higher oxygen concentration, and if it is not attained, it favors the adipocytes' death by apoptosis. That, in turn, causes alterations in the tissue's number and type of immune cells [1, 7–10].

One of the populations that are diminished under the above-described situation is the Treg lymphocytes, which depend on the presence of IL-33 and the nuclear factor PPAR-gamma. In normal conditions, these lymphocytes produce large amounts of IL-10, but when these cells decrease in number, the amount of tumor necrosis factor alpha (TNF alpha), IL-6, and RANTES (CCL5) increases [11]. There is also a mobilization of macrophages into the AT to eliminate dead cells and "remove" their lipid content. These increase the presence of inflammation mediators in the tissue as most of the macrophages change from an M2 phenotype to an M1, which promotes the secretion of proinflammatory cytokines (TNF alpha, IL-6, and IL-12). Other cellular subpopulations (CD8+ T lymphocytes, Th1 CD4+ lymphocytes, B-lymphocytes, and granulocytes) are also activated and secrete cytokines such as TNF alpha, interferon (IFN) gamma, and IL-6, which also contribute to the amplification of the inflammatory response (**Figure 1**) [12–14]. In this way, the increase of these mediators is

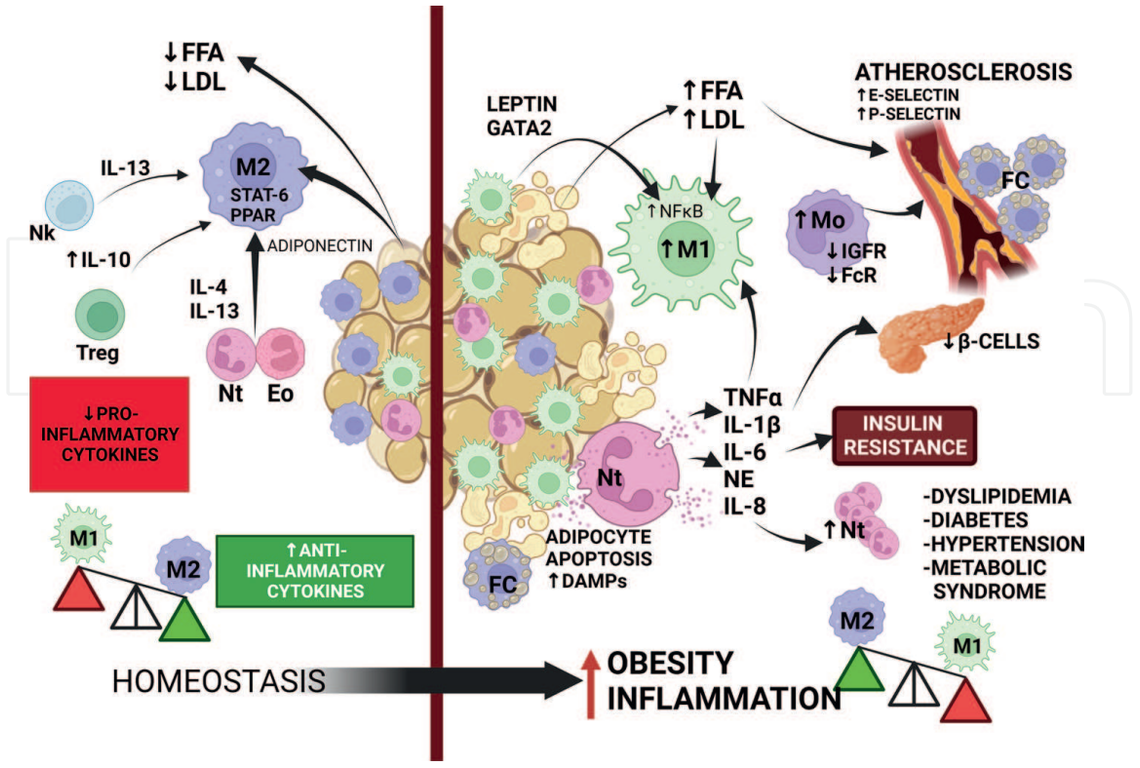


**Figure 1.**
*Adipose tissue in homeostasis and obesity. The adipose tissue (AT) is infiltrated by diverse immune cells that communicate with each other. In homeostatic conditions, the cells present in the tissue include eosinophils (Eo) and neutrophils (Nt), which secrete IL-4 and IL-3; regulatory T lymphocytes (Treg), which produce IL-10; Natural Killers (Nk), which release IL-13; and adipocytes, which release adiponectin. Together, these cytokines generate an anti-inflammatory Th2 microenvironment, and macrophages (Mo) polarize towards an M2 phenotype characterized by the transcription factors STAT-6 and PPAR. In obesity and hyperglycemic states, AT adipocytes undergo hypoxia and cell damage, leading to apoptosis and the release of damage-associated molecular patterns (DAMPs). Moreover, leptin expression increases in obesity, shifting the Mo phenotype towards an inflammatory profile (M1) and increasing transcription factor NFκB. Mo counteract DAMPs through the phagocytosis of apoptotic adipocytes, thereby transforming into foam cells (FC), which are associated with metabolic complications. Upon activation, the cells of this microenvironment secrete more proinflammatory cytokines like TNFα and IL-1β, which, in the long term, decrease insulin production and damage pancreatic β-cells. Higher levels of IL-6 and Nt elastase (NE) produce systemic insulin resistance, and higher IL-8 increases Nt infiltration, further increasing inflammation. Finally, the excess of proinflammatory cytokines, along with the increase in LDL and FFAs, damage the vascular endothelium, increasing the expression of adhesion molecules and the deposition of foam cells that cause atherosclerosis and other pathologies. Created with BioRender.com.*

relevant during the adaptation process to the gain in fat mass [15]. Nevertheless, when this inflammatory process is not resolved, chronic obesity ensues, which leads to tissue fibrosis and discharge of the extracellular matrix, which prevents the adipocyte enlargement and storing of lipids with the consequent liberation of fatty acids that increase the inflammatory process associated with the loss of insulin sensitivity. These alterations help to the establishment of a state of low-degree chronic inflammation characteristic of individuals with obesity [16].

## 3. Insulin resistance, metabolic syndrome, and type 2 diabetes

Insulin is a hormone secreted by the pancreatic beta cell in response to diverse stimuli, glucose being the most relevant. Its principal function is to maintain glycemic homeostasis. In this way, after each meal, insulin suppresses the liberation of fatty acids while favoring triglyceride synthesis in the adipose tissue [17].

Insulin resistance (IR) refers to a state in which cells do not respond normally to insulin, and thus, glucose cannot enter the cells with the same easiness, causing its accumulation in the blood (hyperglycemia) [18].

The changes happening in the VAT that lead to the liberation of proinflammatory mediators promote insulin resistance by interfering with insulin signaling through the activation of the c-JUN N-terminal kinase (JNK) and the nuclear factor kappa B (NF-kB) at a local level (AT and macrophages). When these mediators escape into circulation and reach the insulin target tissues (skeletal muscle and the liver), they unchain a systemic IR diminishing the insulin effect in these organs. This process precedes the development of metabolic diseases such as MetS [19–21].

MetS has been defined as a clinical entity characterized by a combination of risk factors. Individuals suffering from this disease show a metabolic disorder that includes visceral obesity and some of the following alterations: IR, triglycerides increase, high-density lipoproteins (HDL-C) decrease, hypertension, and hyperglycemia. This pathology confers a high risk of suffering from T2DM or cardiovascular diseases [8, 22].

Diabetes mellitus is an endocrine-metabolic disease characterized by raised blood glucose levels or hyperglycemia caused by deficient insulin secretion or action. Evidently, the most severe consequence is the damage caused to beta cells caused by lipotoxicity. The excessive accumulation of triglycerides in the pancreatic islets increases the expression of iNOS, raising nitric oxide (NO) levels, which causes alterations in the beta cells function and, finally, apoptosis of these cells, which gradually lose their capacity to compensate for IR with higher insulin secretion. Glucose blood levels increase progressively in prediabetic stages first, leading finally to T2DM [23].

## 4. Phagocytosis general aspects

The phagocytosis process includes several sequential stages, which are common to macrophages and neutrophils that comprise chemotaxis, adhesion, endocytosis, and the intracellular physical and biochemical changes that prepare the phagocytes to ingest, kill, and digest microorganisms: increment in the cell's general metabolism, phagosome formation, the interaction of the phagosome with endosomes and lysosomes to form the mature phagosome (phagolysosome), phagolysosome acidification, generation of reactive oxygen and nitrogen intermediates, activation of lysosomal hydrolases, and, finally, the elimination of waste materials through exocytosis.

### 4.1 Chemotaxis

An infection or trauma situation favors a tissue microenvironment, which gives rise to the formation of materials, both exogenous (microorganism derived) and endogenous (coming from damaged tissue), with chemotactic activity. In order for the phagocytic cells to go to the injury site, they must come out of the blood vessels, which involves the participation of adhesion molecules both in phagocytic (integrins and selectins) and endothelial (selectins and adhesins) cells. Some of these molecules are constitutive of the cellular membrane, while others are induced by chemotactic factors or some cytokines. Cells come out of the blood vessels by diapedesis, attracted by factors with chemotactic activity [24, 25].

Chemotaxis requires energy in the form of adenosine triphosphate (ATP) and the presence of calcium and magnesium, which indicates that it is an active metabolical

process. As with all cellular functions that imply mobility, chemotaxis depends on the function of contractile structures of the cells that constitute the cytoskeleton.

The interaction of the cells with their external ligand occurs through membrane receptors, which generate biochemical signals that activate several G proteins and protein kinases that result in the polymerization of actin with the consequent cell movement (chemotaxis and phagocytosis) [26].

### 4.2 Opsonization

Opsonization improves the endocytosis process and requires the interaction of the ingestible particles with serum factors called opsonins. These include antibodies (usually IgG), complement components (C3b, C4b, or iC3b), and other proteins present in the serum, such as colectins and C reactive protein. Opsonins promote phagocytosis through specific receptors against them on the membranes of phagocytic cells [27, 28].

### 4.3 Endocytosis

Endocytosis is a process by which particles enter the cells due to the presence of receptors on the surface of the phagocytes. These receptors can be pathogen recognition receptors (PRR), which recognize components that are unique to microorganisms or receptors for opsonins.

The cross-linking of receptors for the immunoglobulin Fc region gives rise to signals with the participation of protein kinases, GTPase, ATPase, adaptor proteins, and other associated proteins that lead to actin polymerization, endocytosis, and cellular movement [29].

Among the PRRs, we can consider the Toll-like receptors (TLRs), which have an intracytoplasmic domain and are able to transmit signals. Ten TLRs have been identified, and although there are cellular activation pathways depending on the involved TLR, the mechanism representative of the events is described as follows:

The interaction of TLR with its ligand promotes the recruitment of the signal adaptors MyD88, a protein associated with the intracellular receptor called Toll/IL-1 (TIR) and the adaptor molecule that contains TIR (TRAM) or TIR domain-containing adaptor molecule inducing interferon-beta (TRIF). These events occur in the TIR domain of the TLRs. Depending on the type of adaptor involved, this binds to the interleukin 1 receptor-associated kinases (IRAKs) are a family of related signaling intermediates (IRAK1, IRAK2, IRAK4), TANK-binding kinase (TBK) 1 and an IkappaB kinase (IKK)-related kinase epsilon, which, in turn, binds to the TNF-6 receptor-associated factor (TRAF-6), which becomes activated and stimulates TAK1. This kinase sets in motion the Mitogen-activated protein kinase (MAPK) kinase protein signalization that phosphorylates other kinases such as JNK, which activates and translocates nuclear factors such as PA-1 and NF-κB, with the consequent transcription of the genes coding for proinflammatory cytokines. The importance of the TLRs lies in the fact that if there are defects in signalization, there will be high susceptibility to infections [30].

Within the metabolic changes associated with endocytosis, we can mention that in the phagocytic cells, as a result of the interaction with the ingestible particle, a series of events occur associated with the morphological and biochemical changes that include engulfment of the particle, formation of the digestive vacuole, and lysosomal degranulation with the release of enzymes and other components inside the vacuole.

The morphological events associated with vacuolization and degranulation are similar both in neutrophils and in macrophages, except for the following differences:

macrophages can synthesize more granules in their Golgi complex, they can get rid of the microorganisms' remains by exocytosis, and, finally, they survive the phagocytosis process, while neutrophils generally die [31].

### 4.4 Phagocytosis events and microbicidal activity

A few seconds after the interaction of the phagocytic cell with chemotactic agents and microorganisms, biochemical alterations are generated, which indicate the presence of metabolic changes related to membrane potential, production and release of cyclic adenosine monophosphate, release of superoxide anion, and later escape of several lysosomal enzymes. Some of these metabolic changes are related to oxygen and nitrogen metabolism, while others are of a nonoxidative nature.

Among the nonoxidative changes accompanying the endocytosis process, we can find an increment in oxygen and glucose consumption and an increase in the activity of the pentose or hexose monophosphates cycle; there is also superoxide anion and hydrogen peroxide production. The set of these changes is what is known as the "respiratory burst" [32].

The destruction of microorganisms occurs through these mechanisms, both oxygen-dependent and independent. The former includes the participation of radicals generated by the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase system, which transforms molecular oxygen into superoxide anion, which, in turn, is transformed into hydrogen peroxide and then into hydroxyl radicals, which, along with the oxygen singlets, constitute the reactive oxygen intermediates (ROIs). The enzymatic system that catalyzes these oxidative changes is named "NADPH oxidase." In neutrophils, the microbicidal activity is increased by the myeloperoxidase that uses hydrogen peroxide as the substrate to produce, along with halide, highly toxic compounds [33].

Nitric oxide (NO) is generated in macrophages from the L-arginine metabolism; generally, its production is regulated by the effects of some cytokines such as gamma interferon. Given its unstable nature and in the same way as the ROI, NO interacts avidly with various chemical groups present in many molecules, causing functional and structural alterations and molecular breakdowns in them. In the target cells, NO inhibits DNA synthesis and respiratory activity [31].

Oxygen-independent mechanisms include lysosomal enzymes that intervene in the digestion of severely damaged microorganisms, and proteins with microbicidal activity. Cathepsin B, cathepsin D, glucuronidase, mannosidase, and phosphatase A2 are acid hydrolases; elastase, cathepsin G, proteinase 3, and collagenase are neutral proteases; and myeloperoxidase, lysozymes, defensins, and lactoferrin are microbicidal factors. Lysosomal hydrolases are activated by the acidification of the phagosomal environment through the activity of an endosomal enzymatic system that functions as a proton pump called "Proton ATPase," which is incorporated into the digestive vacuole's membrane when the phago-endosomal fusion occurs [34, 35].

## 5. Phagocytosis alterations and their relationship with obesity comorbidities

Lymphocyte subpopulations changes, both for those of the innate and the adaptive immune response, have been reported in obese individuals. These cells accumulate in the obese persons' VAT and could result from a survival increment and proliferation

of resident immune cells, as well as greater cellular recruitment toward the VAT or a decrease in the cellular return to peripheral blood [36, 37]. There are also differences in the proportion of these cells among the different fat deposits. It has been observed that there are larger numbers of macrophages, T lymphocytes, and inflammatory molecules in the VAT compared to the subcutaneous tissue of obese individuals. Moreover, it was found that in the VAT from obese individuals with MetS, the number of Tregs is lower [11, 12, 38].

There are several innate immune system cells in the low-intensity chronic inflammation caused by obesity, but since this chapter deals with the phagocytic process and its relation to inflammation obesity, we will focus only on the phagocytic cells.

Alterations of the innate immune system in obesity include, among other aspects, a raised macrophage infiltration in AT, a place where these phagocytes interact with the adipocytes and endothelial cells, forming an inflammatory network. The interaction of these cells promotes the activation of the fat tissue macrophages, which are induced to produce diverse proinflammatory cytokines and chemokines such as TNF alpha and the monocyte chemoattractant protein-1 (MCP-1) [11].

Neutrophils are the first to migrate to the infection sites, and this happens in obesity, where neutrophils are the first cells to respond to inflammation, infiltrate the VAT approximately three days after a high-fat meal, and can stay there for up to 90 days [13, 39, 40].

Neutrophils depend mainly on glucose as the only energy source. In the diabetic patient, there is an excess of advanced glycation end products (AGEs), which are modified proteins that appear at the tissue and plasmatic level as a consequence of the reaction of blood monosaccharides with the protein's amino acids [41]. AGEs are formed in situations of sustained hyperglycemia or high oxidative stress [42]; this is a key part that explains why the neutrophil function is altered in diabetes [43–45].

Several clinical and epidemiological data report a higher incidence and severity of some specific types of infectious diseases, which are more frequent in obese persons than in lean ones. It has also been observed that the risk of developing cutaneous infections is increased, and the capacity to heal wounds is reduced in obese individuals. A decrease in the capacity of polymorphonuclear neutrophils to destroy bacteria was reported, which led to establishing the association of immune system alterations with obesity in children, adolescents, and adults [8, 46].

In obesity, circulating neutrophils are increased (associated with the BMI) as well as in individuals with MetS [47, 48]. These cells present an activated phenotype as indicated by an increase in the plasmatic concentrations of myeloperoxidase and elastase [48–50]. It is not well understood why the activated state of the neutrophils in obese individuals does not result in a more effective antimicrobial function. The following studies might partially explain this conundrum:

Four decades ago, it was described that diabetic patients have defects in their chemotactic response [51, 52]. Nevertheless, other studies showed controversial results, as no differences in the chemotactic response were observed between normal and diabetic patients [45, 53]. On the other hand, experimental studies in alloxan-induced diabetic mice showed that their neutrophils internalized the C-X-C motif chemokine receptor 2, which resulted in a reduced migration [54, 55]. It has also been shown that the administration of insulin to diabetic mice results in the reduction of alfa-1-acid glycoprotein (which is also increased in diabetic persons), restoring cellular migration [54].

Concerning adhesion, hyperglycemic stages increase the adhesion of phagocytic cells, especially for neutrophils, and due to the microenvironment, there is an increment in the protein C kinase (PKC) activator, which favors the expression on the

cell membrane of molecules such as P-selectin, E-selectin, and intercellular adhesion molecule-1. The adhesion mechanisms activated in phagocytic and endothelial cells have been associated with the increment in cytotoxic factors (free radicals and TNF alpha) and with transforming growth factor beta-1, fibroblast growth factor, and platelet-derived growth factor. This set of factors is related to the lesions at the vascular level, a bad reparation process, and they increment the appearance of atherosclerosis. Obese and hyperglycemic patients are characterized by presenting vascular and microvascular pathologies [45, 56, 57]. There are not many studies on the alterations of adhesion molecules that affect phagocytosis; it is only known since the 1970s that the presence of hyperglycemic states leads to phagocyte adherence abnormalities. Neutrophils from hyperglycemic patients showed a lower adherence, which is re-established by insulin [58]. Nevertheless, other studies show the opposite; in a diabetic mice and rat model, hyperglycemia (>500 mg/dL) increases the expression of adhesion molecules such as Fc gamma RII/III, ICAM-1, Mac-1, −2 [59, 60].

C3 is a central component of the complement system, and its activation into C3b is critical for bacterial opsonization and phagocytosis. Diabetic patients have elevated levels of C3 and C4 in addition to having a decreased ability to fix complement by IgG [61]. In hyperglycemic conditions, C3 suffers conformational changes that make it unable to initiate the complement pathway or act as an opsonin, despite the fact that it can adhere to bacteria such as *Staphylococcus aureus* [62, 63].

Phagocytic cells display in their cell membranes different types of Fc receptors (FcR), and depending on the activation of these receptors, the phagocyte will exert a different function through second messengers. Insulin can promote changes in the phosphorylation of second messengers, and therefore, it can modify the phagocytic cell response with respect to the glycemia levels based on the presence of the FcR activity, which uses cAMP for signal transduction. In hyperglycemic states, monovalent cations are altered through the FcR functions in the ionic channels so that phagocytosis would be affected by the modifications in the glycolysis pathway [64].

The production of intracellular ROI is often diminished in neutrophils from diabetic persons, which makes them more susceptible to infections. If the glycolysis pathway is modified, phagosome maturation is also altered, mainly with a reduction in the acidification and bactericidal capacity [65]. The molecule C5a has been found incremented in obesity and T2DM [66]. It has been observed that when neutrophils from critical patients are challenged with *S. aureus*, the molecule C5a impacts the phagosome maturation, preventing their acidification [67].

In diabetic rats, a decrease in the activity of the glyceraldehyde-6-phosphate dehydrogenase enzyme is observed, which indicates that the pentose pathway is diminished in the leukocytes from these animals. Leukocytes with reduced activity of this enzyme present damage in phagocytosis, bactericidal activity, and superoxide anion production. In addition, the decreased glucose flux through the pentose phosphate pathway reduces the NADPH and ribose 5-phosphate production, which might be related to a neutrophil malfunction in the diabetic state [65].

Another pathway that affects the bactericidal capacity is the polyol pathway. In hyperglycemic states and obesity, there is stress due to an increase in free radicals, which affects the endoplasmic reticulum of the phagocytic cells; enzymes such as the aldose reductase are activated, which reduces the glucose excess to sorbitol (polyol pathway). This pathway is characterized by an increase in NADPH consumption, leaving less and less substrate for the phagocytic function [68, 69] (**Figure 2**).

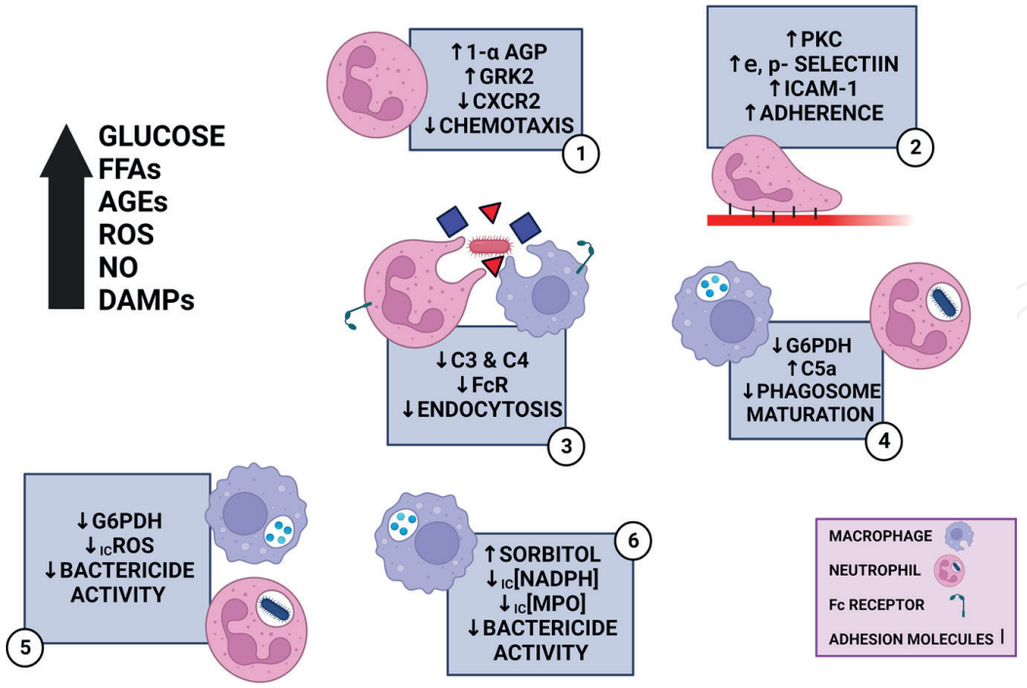


**Figure 2.**
*Phagocytic alterations in obesity. Increased FFAs, ROS, NO, advanced glycation end products (AGEs), DAMPs, and glucose in the microenvironment impact phagocytic cells, especially Nt and Mo. (1) Chemotaxis is decreased due to the high expression of 1 alpha acidic glycoprotein (1-α AGP) and G-2 protein-coupled kinase (GRK-2) and the low expression of the chemotaxis molecule CXCR2. (2) High protein kinase C (PKC) levels increase the expression of adhesion molecules such as e-selectin, p-selectin, and intracellular adhesion molecule 1 (ICAM-1). (3) Endocytosis is affected due to the reduction of opsonins such as C3 and C4 and the decrease in the expression of the immunoglobulin Fc region receptor. (4) Lower function of the enzyme G6PDH and higher C5a prevents the proper maturation of the phagosome. (5) The production of intracellular ROS, which hold bactericidal activity, is also diminished due to decreased G6PDH activity. (6) Excess glucose is reduced to sorbitol, which increases the consumption of NADPH, making it less available for phagocytosis. Created with BioRender.com.*

## 6. Therapeutic strategies

Even though obesity-related metabolic diseases are treated with drugs, some therapeutic alternatives that favor phagocytosis restoration are described here.

In search of improving the phagocytic capacity, which is deficient due to metabolic diseases such as obesity, several solutions have been proposed; among them, the use of probiotics stands out. Probiotics are defined as live microorganisms that have beneficial effects on the host's health when consumed [70]. These beneficial effects result from a wide range of actions that they exert, among which are the regulation of inflammation by increasing IL-10 expression [71] and the modulation of the expression of COX-2, and the activation of TLR4 [72]. In addition, probiotics can modulate insulin sensitivity [73] or decrease the individual's weight or dyslipidemia degree [73, 74], or act directly on the phagocyte, by increasing IFN gamma production, improving phagocytosis and increasing the expression of complement receptors [75].

Probiotics have an immunomodulatory function, and it has been found that their consumption can regulate the macrophage phagocytic activity against several pathogen agents, such as *Aggregatibacter actinomycetemcomitans*, a pathogen bacterium that affects the oral mucosa. When the *Lactobacillus johnsonii* NBRC 13952 probiotic is present, it increments the phagocytic activity and optimizes the bactericidal capacity

of the macrophages, thus avoiding infection [76]. In the same way, the consumption of *Lactobacillus rhamnosus* HN001 and *Lactobacillus acidophilus* for four weeks by elderly subjects incremented their phagocytic capacity. With this immune stimulus, an improvement in the health of this population sector is sought [77].

Some of the mechanisms by which probiotics exert their action are still unknown, not to mention that these mechanisms also differ between the strains used for this purpose. Nevertheless, it has been demonstrated that probiotics secrete molecules that can regulate several functions, as is the case for *L. rhamnosus* strain GG (LGG). When macrophages were exposed to LGG-conditioned media, their phagocytic and bactericidal activity was increased up to sixfold. This activity was associated with an increment in free radicals production, with the activation of NADPH oxidase, and a slight increase in nitric oxide generation [78].

Another way that is being explored to counteract the metabolic changes and improve the phagocytic function is through organic compounds such as resolvins. These are a group of molecules derived from omega-3 fatty acids [79] that have a positive effect on decreasing obesity and increasing the phagocytic and bactericidal capacity. How this effect is attained is still under investigation, though a blockade of the Akt pathway and the mitogen activated protein kinase phosphorylation seems to be involved [80].

Macrophages from obese patients exhibit a deficiency in the expression of growth differentiation factor 15 (GDF-15), which is essential for the oxidative metabolism in M2 macrophages and suppresses M1 macrophages, increasing inflammation and

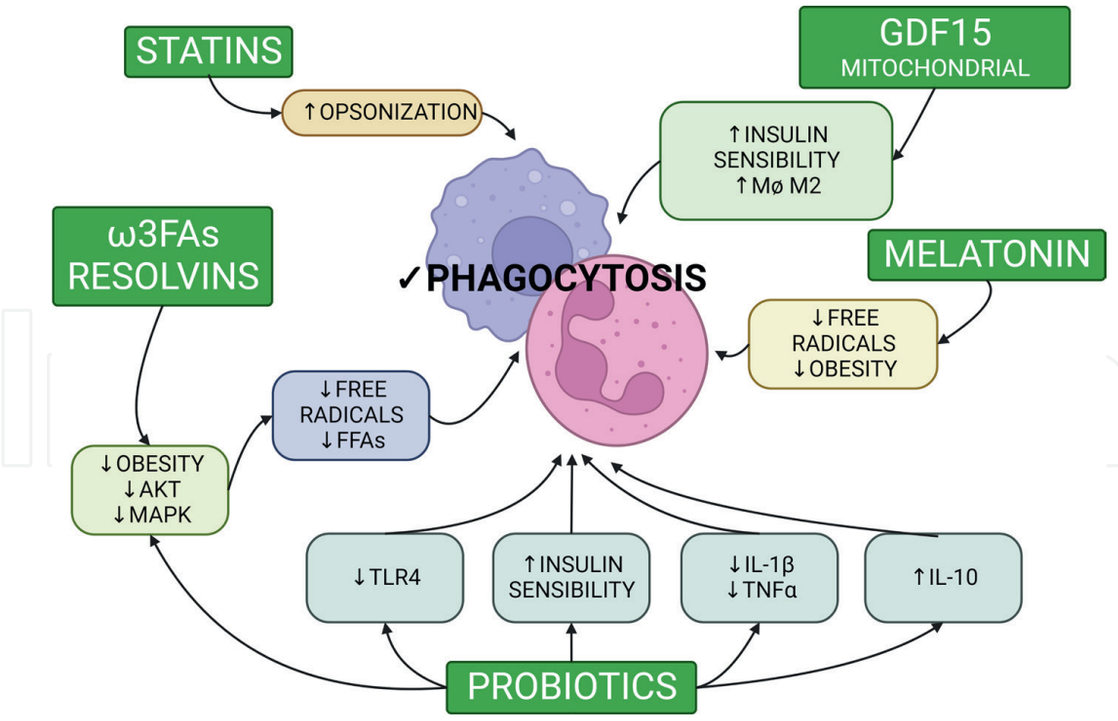


**Figure 3.**
*Alternatives for the recovery of an adequate phagocytosis. Statins increase opsonization improving phagocytosis. The presence of omega-3 fatty acids (ω3FAs) and their derivates, such as the resolvins, reduce obesity, help the M2 differentiation of macrophages, increase phagocytosis, and increase insulin sensitivity. Melatonin increments phagocytosis besides having antioxidant action and modulates obesity. Probiotics generate changes that immunomodulate the microenvironment leading to an improvement in the use of energetic resources, increase the production of anti-inflammatory cytokines (IL-10), diminish the presence of FFAs, and improve all the phagocytic process. Created with BioRender.com*

IR. The administration of GDF-15 to obese mice reverts IR, mitochondrial oxidative alterations (improving bactericidal and phagocytosis capacity), and macrophage differentiation, making it a good prospect for obesity treatment [81].

Another condition that can modify the phagocytosis process is the presence of hormones such as melatonin. There is evidence that lactating obese women possess phagocytes with high melatonin concentrations compared to women with a normal BMI. Melatonin promotes the activity of the colostrum phagocytes through G protein-coupled receptors, improving dectin-1 expression, an important type C lectin receptor crucial in proinflammatory responses such as cytokine production, ROI production, and phagocytosis [82]. The melatonin in the colostrum macrophages increases superoxide release in phagocytosis, but it also has cytoprotective effects with an antioxidant function depending on the dose, cellular targets, and exposition time. Considering these functions, the high levels of melatonin present in the colostrum of high-BMI women could be a mechanism of protection against childhood obesity, as obese individuals have reduced melatonin levels. On the other hand, melatonin promotes colostrum phagocytes' activity, which could be important for the protection of the lactating newborn (**Figure 3**) [83, 84].

## 7. Conclusion

Obesity is a chronic, multifactor illness. Data have been reported that relates obesity to alterations in the immune system in obese children, adolescents, and adults. Neutrophils from obese and diabetic individuals show a deteriorated phagocytic functionality that is manifested by a reduced chemotaxis, phagocytosis, and intracellular reactive oxygen species production.

Some therapeutic alternatives for the recovery of an adequate phagocytosis have been reported, such as probiotics, resolvins, statins, administration of GDF-15, and melatonine, but future research is needed to fully understand the aberrant neutrophil function in obesity and other obesity-related complications.

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## Conflict of interest

The author has no financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter discussed in the manuscript.

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