Macrophage polarization and obesity complications: what we can learn from experimental studies

Polarização de macrófagos e as complicações da obesidade: o que podemos aprender com os modelos experimentais

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RESUMO: Evidências clínicas e experimentais apontam para o papel das células do sistema imunológico e mediadores inflamatórios no desenvolvimento de doenças em pacientes obesos. Nosso objetivo neste trabalho é explorar estudos experimentais que abordam a relação entre os diferentes tipos de reação inflamatória no tecido adiposo, particularmente a polarização de macrófagos e o desenvolvimento de complicações da obesidade. Além disso, temos a intenção de especular como traduzir esse conhecimento, obtido a partir de estudos experimentais, em tratamentos aplicáveis às doenças humanas. Para tanto, foi realizada busca no banco de dados PubMed, usando-se os termos “obesidade”, “macrófago” e “polarização”. Depois de aplicados os filtros “Idioma - Inglês” e “espécies - Animais”, chegamos a 90 referências. Sessenta e duas dessas foram excluídas por serem revisões ou não estarem relacionadas com o assunto principal. Os resultados em modelos experimentais de obesidade indicaram uma correlação significativa entre a polarização de macrófagos para uma resposta do tipo 1 (M1) no interior do tecido adiposo branco e o desenvolvimento de resistência à insulina, diabetes e outras complicações da obesidade. Vários artigos relatam estratégias de mudança para o fenótipo tipo 2 (M2), como uso de drogas ou mudanças de estilo de vida. Ainda é uma questão em aberto o modo como estas descobertas podem ser traduzidas para novos tratamentos em seres humanos, o que só poderá ser respondido por pesquisas bem elaboradas.

Descritores: Macrófagos; Obesidade; Tecido adiposo; Modelos animais.

ABSTRACT: Clinical and experimental evidences pointed to the role of immune cells and inflammatory mediators on the development of diseases in obese patients. Therefore, it is our objective to explore experimental studies that approach the relationship between the different types of inflammatory reaction inside the adipose tissue, particularly the macrophage polarization and the development of obesity complications. Further, we intend to speculate how to translate this knowledge, obtained from experimental studies, to treatments applicable to the human diseases. PubMed database was sought using the terms “obesity”, “macrophage” and “polarization”. After applying the filters “Language - English” and “Species - Animals”, we arrived to 90 references. Sixty-two were excluded for being reviews or not related to the main subject. Results in experimental models of obesity pointed a relevant correlation between the macrophage polarization to a type 1 response (M1) inside white adipose tissue and the development of insulin resistance, diabetes and other complications of obesity. Several articles report strategies to shift to a type 2 phenotype (M2), using drugs or lifestyle changes. How these findings could be translated to new human treatments is still an open question that only well designed researches could answer.

Keywords: Macrophages; Obesity; Adipose tissue; Models, animal.
**BACKGROUND**

Obesity results from an imbalance between caloric intake and energy expenditure, leading to increased storages of fat inside adipocytes throughout the body. This is clinically characterized by an increased Body Mass Index (BMI), defined as the ratio between weight (in kilograms) and the squared height (in meters). Individuals with a BMI higher than 30 kg/m² are considered obese, while the ones between 25 and 30 are classified as overweight.

Recent epidemiologic studies have reported that one third of the United States population is obese and this trend is expanding to developing countries. Several causes have been proposed to account for this phenomenon, particularly the ones related to the comforts of modern life: gradual reduction of manpower in performing labor tasks and daily activities; enhanced offer of industrialized foods, usually rich in sugar and fat; increased income, allowing the families a higher degree of consumption.

Obesity is widely recognized as a major contributing factor to the development of several diseases. There is plenty of clinical and epidemiological evidence of this relationship in diseases such as type 2 diabetes, dyslipidemias and cardiovascular syndromes. In other situations, like cancer and dementia, for example, evidences are more scarce and questionable. As a consequence, vital resources have been allocated to treat these maladies, that, ultimately, have obesity as one of the main causes for their development.

In recent years, much interest has been directed to the relationship between obesity and systemic inflammation. It has been proposed that some of the aforementioned diseases appear in obese patients with high levels of inflammatory circulating markers. Moreover, attention has been caught by patients with high BMI but no other comorbidity. The mechanisms that cause this “healthy obesity” are still being discussed.

Therefore, this review is structured in five main topics, beginning with a brief analysis of the importance of obesity as epidemiological factor in modern society, followed by a short discussion on pathophysiology, approaching in more detail the connection between inflammation and obesity and the onset of diseases. Following, macrophages polarization is conceptualized and is made an exposition on the researching involving some of the major known forms of changing the balance between the M1 and M2 types, including by intracellular signaling pathways, with emphasis on diet, exercise and pharmacological drugs. At the end, based on the revised texts, it is carried the study of translation, assessing which mechanisms could be adopted for the control of obesity and its harmful effects to humans.

**METHODOLOGY**

In order to search for the proposed theme, one database was used (PubMed), accessed on December 15th, 2015.

The key terms were “obesity”, “macrophage” and “polarization”. Using these terms, 132 articles were retrieved (Figure 1). Additionally, two filters were used: “Language - English” and “Species: Animals”. Two articles were ruled out for not being written in English. Another forty articles were excluded by the filter Species.

Therefore, we obtained 90 articles. Initially, reading only the titles and abstracts, additional 62 articles were excluded because were not related to the main objective of our review, or for being reviews themselves.

Although reviews were found with the searched keywords, many specifically address only macrophage polarization mechanisms, the physiology behind macrophage polarization or compounds that act on inflammation and complications of obesity. The few reviews that associate macrophage polarization with obesity are specific to a modulation mechanism of polarization, such as drugs or lifestyle habits.

Our review has a comprehensive and translational approach. We intend to describe, compare and evaluate macrophage polarization mechanisms while linking them to obesity. We focus on describing changes in obesity and its comorbidities framework caused by the numerous modulation possibilities of macrophage polarization.

We arrived at 28 articles, which were read and resumed by the authors. In further discussions, these articles were divided in four topics:

- the role of inflammation on the genesis of clinical complications of obesity;
- the role of macrophage polarization on this phenomenon;
- the signaling pathways and mediators responsible for polarizing macrophages in obesity;
- how to shift macrophage polarization inside the adipose tissue.

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RESULTS

In order to better understand the studies aimed to manipulate the inflammatory response inside the white adipose tissue, we initially describe our current knowledge about the role of inflammation on the obesity complications.

Obesity and inflammation

During human evolutionary pathway, body fat storages meant the difference between life or death in times of starvation or pathogen challenge. However, over the last century, the major threat of energy deficit to living organisms has been replaced by overnutrition.
of humans in the developed world. As a consequence, a chronic imbalance between enhanced calories intake and diminished expenditure led to increased number of individuals with pathological expansion adipose tissue.

In the last decades, it has been demonstrated that these fat deposits are also the source of a chronic low-grade inflammation, which mechanisms are still being discovered. Several processes were proposed to explain inflammation inside the adipose tissue. It is known, for example, that adipocytes may, by themselves, release inflammatory mediators like cytokines and chemokines. Also, hypertrophic adipocytes, overloaded with fat, fail to efficiently store the excess of energy, releasing intracellular antigens that may act also as immune cells activators (Figure 2).

These processes are part of a self-perpetuating inflammatory reaction that is detected through increased circulating markers and leads to adipose tissue dysfunction, dyslipidemia, and insulin resistance.

Clinical and experimental evidences pointed that progression of clinical diseases related to obesity has been strongly linked to chronic inflammation of white adipose tissue and the resultant increased circulating concentrations of inflammatory markers.

Obesity and macrophage polarization

At the center of this inflammatory process inside the adipose tissues are the macrophages. There is plenty of evidence that these cells may be responsible for shifting the adipose tissue inflammation between the Th1 and Th2 responses. Th1 and Th2 helper cells both result from stimulation of naive T CD4+ cells, respectively by IL-12 and IL-4. They differ primarily because the Th1 produce cytokines, such as interferon gamma (INF-γ), IL-2 and Tumor Necrosis Factor alpha (TNF-α), mainly related to defense against intracellular infectious agents, whereas Th2 secrete interleukins mainly related to IgE production and the activation of eosinophils. Th1 responses are mostly proinflammatory, and Th2 counteracts them, reducing inflammation. The consequences of this shifting are observed in the clinical set as a majority of obese patients struggling with multiple metabolic and cardiovascular diseases and, on the other side, those who could be called the “healthy obeses”.

Further, it was demonstrated that adipose tissue macrophages (ATM) differ not only in number, but also in inflammatory phenotype and tissue localization. In a series of seminal works, it was shown that mice fed with high-fat diets present a larger population of macrophages F4/80 (+) CD11c (+), that are not found in mice with normal diet. Those macrophages express TNF-alpha and iNOS-coding genes, known to be pro-inflammatory. On the other side, ATMs of lean mice, express many genes related to M2 macrophages, such as Ym1, arginase 1, and IL10. Besides being an inflammation suppressor, the cytokine IL-10 is associated with stimulation of the influx of glucose by adipocytes and, so, indicates a contribution from those kind to the reduction of insulin resistance.

Inflammatory mediators responsible for M1/M2 shifting in adipose tissue

The mechanisms responsible for macrophage to develop an M1 or M2 phenotype inside the macrophages are still not completely understood, however, the cellular environment and the adipocyte metabolism seem to exert major effects (Figure 2).

The interaction of macrophages and lymphocytes
with adipocytes is associated with inflammation of the adipose tissue found in obese animals. The CD40-CD40L system is costimulatory, being important in inflammatory reactions and activation of T cells. Recently, it was shown that CD40L can promote inflammation of adipose tissue in vivo. To clarify how is the interaction of CD40L with adipocytes and chemokines and its relationship with inflammation in adipose tissue, cells of this kind were stimulated with CD40L, TNF and palmitate, being observed their migration, and that there was no change in the adhesion of adipocytes to T cells. Stimulation with CD40L showed an increase in expression of CD40 and the chemokines MCP-1, CCL4 and CCL5. TNF also stimulated CD40, however palmitate had no effect. Chemokines attracted monocytes and macrophages to the adipose tissue. The presence of the CD40L has also resulted in high migration of lymphocytes and increased expression of proinflammatory genes, i.e., genes capable of stimulating the permanence of M1 macrophages polarization.

Although it does not prevent the accumulation of macrophages, the toll-like receptor 4 deficiency attenuates inflammation in obesity. To demonstrate the effects of TLR4 deficiency in inflammation and insulin resistance, typical of that condition, and determine whether this deficiency promotes the polarization of macrophages in adipose tissue, mice were fed with three different diets: low-fat, rich in saturated or rich in monounsaturated fats, and, in a later step, marrow transplant was performed to assess the influence of TLR4 signaling in hematopoietic cells. It was confirmed that global and hematopoietic deficiency of TLR4 signaling produced changes in the phenotype of macrophages: it inclines them to M2, the anti-inflammatory polarization. The deficiency also reduces body fat and weight gain in small proportion, being one of the main causes of diabetes, is associated to inflammation of the adipose tissue in obesity. The tissues affected by insulin showed increased inflammation and changes in the polarization of macrophages. IL-6 signaling promotes IL-4 receptor expression and increased autonomic response to IL-4 in macrophages, but Il6ra^{−/−} were resistant to alternative polarization mediated by IL-4, and had greater susceptibility to endotoxemia induced by LPS. These results suggest that signaling by IL-6 is an important factor in the alternative activation of macrophages, but also plays an important homeostatic role in limiting the inflammatory state.

Lipid-induced toxicity, related to the distribution of lipids between the ATMs and adipocytes, is another mechanism that may account for the state characteristic of obesity, involving inflammation and insulin resistance. It was observed that the early stages of adipocyte proliferation are most related to the M2 macrophage polarization and the growing accumulation of lipids in adipose tissue induces a polarization conversion to M1 type.

The intracellular signaling pathways activated in macrophages also seem to determine the fate of these cells. When the chemokine MCP1 is overexpressed, phenotype M1 predominates, the same occurring with disruption of signaling by the nuclear receptors PPAR-γ. Both genetic manipulations induce a pro-inflammatory status in the adipose tissue, leading to increased insulin resistance in mice. Interestingly, PPAR-γ is known to be necessary to polarize macrophages to a M2 phenotype. Similar results were obtained when another chemokine is stimulated. The C-C chemokine receptor 5 (CCR5) is crucial in the migration of macrophages to adipose tissue. In obese animals, caused by either by genetic manipulation or food ingestion, it was shown that CCR5, and their ligands are overexpressed. The loss of CCR5 causes not only reduction in macrophages quantity in adipose tissue, but also prevents the M1 polarization. In addition, CCR5 knockout mice have shown to be immune to liver steatosis, diabetes induced by high-fat diet and insulin resistance.

Even signaling pathways not directly related to inflammation control may affect ATM function. RBP4, a retinol carrier, is found in high concentration in insulin resistance states, and this resistance, along to being one of the main causes of diabetes, is associated with inflammation of the adipose tissue in obesity. The increased RBP4 causes inflammation in adipose tissue through the activation of innate immunity, from which derives an adaptive response. By enabling connections between the innate and adaptive immune systems, activating antigen-presenting cells in the adipose tissue to induce polarization of CD4 Th1 cells, RBP-4 contributes to insulin resistance and adipose tissue inflammation.
Pathways known for its ability of controlling metabolism are also able to influence the macrophage polarization. One example is the PPAR, as described above, and other is its counterpart, the C/EBPα transcription factor, that is highly expressed in macrophages. When establishing its role in regulating the function of macrophages and energy homeostasis, it was found that macrophages from C/EBPα knockout mice (McKO) presented impaired polarization response after induction by cytokines, suggesting that C/EBPα controls both polarizations. While in McKO fed normal diet it was observed deterioration in mitochondrial respiration rate and the signals for fatty acid oxidation, findings consistent with lower exercise capacity, in McKO high-fat fed mice the levels of inflammatory cytokines were reduced. These results mean that the C/EBPα is required for the activation of macrophages, and this, in turn, as well as its relative insulin influence, has an important role in the maintenance of skeletal muscle insulin sensitivity and normal metabolism.

The few studies listed above exemplify the complexity and broadness of the signaling pathways controlling the macrophage polarization inside the adipose tissue. Although some of the mechanisms are not completely understood, there is a consensus, however, that macrophages polarized to an M1 response become the individual more prone to obesity complications, like insulin resistance (and diabetes) and cardiovascular diseases. On the other side, macrophages with an M2 phenotype seem to protect individuals to these diseases.

Therefore, finding ways to manage the ATMs phenotype may be an interesting method to prevent obesity complications.

How to shift macrophages inside the adipose tissue from M1 to M2

Weight loss and, particularly, maintenance is a difficult task for doctors and their patients. A combination of low calories intake and exercise is the only method available so far, regardless of the diet prescribed, and its long term adherence is always cause of concern. Therefore, finding treatments that can reduce obesity complications is an urgent goal for researchers, in order to diminish the health burden of these diseases.

As described above, there is a direct relationship between obesity complications and the inflammatory response inside the adipose tissue. Moreover, these complications are more common when adipose tissue macrophages are polarized to an M1 response and are less prevalent when these ATMs express an M2 phenotype.

There is no consensus whether macrophages, once committed to a particular phenotype, can change to another (Figure 3). Nevertheless, in a recent study, it was reported that bone marrow derived macrophages (BMDM) from high fat-fed mice, when placed in culture, retain their ability to secrete cytokines characteristic of a pro-inflammatory (M1) profile. Interestingly, incubation ex vivo with palmitoleate, an omega-7 monounsaturated fatty acid, reverses this trend. When the culture was performed with BMDM from low fat-fed mice, exposure to palmitate, a saturated fatty acid, triggered a marked increased expression of proinflammatory genes associated with M1 polarization. Although these results were obtained ex vivo, under controlled circumstances (cell culture), they are important since they demonstrate the plasticity of BMDM polarization in response to saturated and unsaturated fatty acids. Also, these findings point to the role of diets as therapeutic tools to reverse obesity-linked inflammation in metabolically relevant tissues.

LPS: lipopolysaccharide; IL: interleukin; TNF: tumor necrosis factor; IFN: interferon; NO: nitric oxide; iNOS: nitric oxide synthase 2; ROS: reactive oxygen species; IL1Ra: interleukin 1 receptor antagonist.

In experimental models, macrophages with a phenotype M1 are found in obese animals and correlate with the development of insulin resistance and other metabolic diseases, while M2 macrophages are encountered in lean subjects. This polarization process is not completely understood. In the upper panel we can observe some of the stimuli that shifts macrophage to a M1 phenotype, the intracellular mediators and, on the right, some of the characteristics of these type of cells. On the lower panels, the M2 phenotype. Usually there are various populations of macrophages inside adipose tissues, with plasticity across the entire spectrum of activation states encompassed by the M1 and M2 nomenclature.

Figure 3. Macrophage polarization
The role of fatty acids in ATM polarization was also studied in vivo. Mice fed a high fat diet showed increased F4/80 and CD11b double-positive macrophage staining and elevated IL-6 and MCP-1 levels in the adipose tissue. When the same diet was supplemented with docosahexaenoic acid (DHA), a typical long-chain polyunsaturated fatty acid (PUFA) of the ω-3 series, no difference was observed in the total number of macrophages but significantly reduced the percentage of high CD11b/high F4/80-expressing cells in parallel with the emergence of low-expressing CD11b/F4/80 macrophages in the adipose tissue, suggesting an increased number of M2 cells, compared to animals that did not receive DHA. It seems that resolvins D1, an anti-inflammatory and proresolving mediator biosynthesized from DHA, is the main culprit for this phenomenon. Nonetheless, these results were not confirmed for other PUFAs. Mice were fed a high fat containing different omega-6/omega-3 ratios, manipulated through the α-linolenic and linoleic acid contents. This study concludes that the omega-6:omega-3 ratio reduction with only alpha-linolenic acid (ALA), is not an effective therapy in reducing obesity or retarding the development of type 2 diabetes mellitus, and all high fat diets lead to similar levels of inflammatory markers, although 1:1 ratio reduces the infiltration of macrophages. It is likely that the use of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) for the same purpose are more useful because these acids, besides being potent activators of GPR 120 (a G-protein-coupled receptor), can be stored directly in these acids, besides being potent activators of GPR 120 (a G-protein-coupled receptor), can be stored directly in phospholipids, and, hence, do not compete for enzymes to be incorporated into the cell membrane.

Other strategies to manipulate the macrophage phenotype inside the adipose tissue involve tempering with the immune response. Some inflammatory mediators that may influence the Th1/Th2 response were tested in vitro and in experimental models. Obese mice treated with interferon tau (IFNT), a member of the type 1 interferon family with low cellular toxicity even at high doses, developed enhanced insulin sensitivity compared to control mice. This phenomenon was accompanied by a significant decrease in the levels of proinflammatory cytokines and increased presence of M2 macrophages in adipose tissue.

Another target is the membrane receptor cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that functions as an immune checkpoint, downregulating immune responses. When activated by an immune complex (CTLA-4g) in obese mice, CTLA-4g prevented insulin resistance by changing gene expression to M2 polarization in ATM, elevating arginase expression and decreasing the secretion of cytokines and pro-inflammatory chemokines.

Interleukin-33 and its receptor ST2 are found in adipose tissue and it seems to reduce inflammation in obese mice. In vitro, IL-33 stimulates the production of Th2 cytokines. In vivo, recombinant IL-33 induces, preferably, a M2 polarization, and has several other effects, particularly reduction of adipose tissue and improved insulin tolerance. These findings may be related to the ability of IL-33 of triggers accumulation of M2 macrophages in adipose tissue. Mice that lack the ST2 receptor, when subjected to high-fat diet have a poorer response, with greater weight and fat gain, reduced insulin secretion and worse regulation of glycemia, implying that IL-33 may actually have a significant role in chronic inflammation related to obesity.

Promising also, are the strategies that use helminth proteins to stimulate a Th2 response. Helminths are the largest natural inducer of type 2 immune responses, and there are reports of improvement in glucose tolerance in obese mice after infection with nematodes. It was observed that inducing infection in mice fed with high-fat diet provokes significant reduction in body weight gain, fat mass and size of adipocytes, with lower insulin resistance and glucose intolerance. Peripheral glucose uptake and white adipose tissue sensitivity to insulin were also improved. The same result was obtained with injection of antigens obtained from eggs of *S. mansoni*, which conducts to the conclusion that chronic infections with helminths or contact with molecules derived from them have protective effect against metabolic disorders, obtained through Th2 response, eosinophilia and M2 polarization in white adipose tissue.

Some drugs acting on other pathways, not primarily related to the immune response, have also been tested in obese animals. Telmisartan, an angiotensin receptor blocker II type 1, acts to decrease the number of M1 macrophages in visceral adipose tissue, improving insulin sensitivity and modulating the polarization of macrophages to M2 state in mice with high-fat diets. Rosiglitazone, a PPAR-gamma activator, was able to increase the M2 population whereas reducing the occurrence of damages caused by M1 polarization. Rosiglitazone induces a more homogeneous distribution of lipids between adipocytes, decreasing the M1 response and improving insulin sensitivity in obese mice.

Finally, a few studies also investigated the effect of exercise on adipose tissues macrophage infiltration and function. Obese mice fed a high fat diet submitted to chronic aerobic exercise for 16 weeks did not present differences in body or adipose tissue mass, compared to their sedentary control. However, exercise training markedly impaired TNF-alpha, F4/80, ICAM-1 and CD11c expression in adipose tissue, while increasing CD163 expression, a marker of M2 polarization. More recently it was reported that even acute exercise may interfere with macrophage polarization. Obese rats submitted to forced swimming (two 3-hour of moderate exercise bouts, separated by one 45-minute rest period) presented an improved insulin signaling in white adipose tissue fractions, as detected by enhanced phosphorylation of tyrosine IRbeta and IRS-1-induced insulin release. Moreover, it was observed a phenotypic switch from M1- to M2-macrophages, as...
indicated by a marked increase in macrophage galactose-type C-type lectin 1-positive cells and a reduction in circulating levels of lipopolysaccharide, and toll-like receptor 4 activity along with TNF-alpha, IL-1-beta and MCP-1 mRNA levels in white adipose tissue fractions. Exercised rats also had increased the levels of IL-10, anti-inflammatory cytokine characteristically associated with the stimulation of glucose uptake in adipocytes, setting another possible mechanism by which the polarization of macrophages may reduce inflammation.

Another recent trend in the scientific literature about obesity is the relationship between intestinal flora and obesity complications, particularly insulin resistance. It seems to be a very relevant issue, however, it was out of our scope in this review and it needs a more focused approach than the one we could offer in the available space here.

CONCLUSION

How to translate this knowledge to humans?

In humans, progression of insulin resistance, diabetes and other metabolic diseases in obese individuals has been also strongly linked to obesity-associated chronic inflammation of white adipose tissue and the resultant increased circulating concentrations of inflammatory markers.

Early reports showed a marked decrease in macrophages infiltrating white adipose tissue after a significant weight loss. This finding was related to a diminished inflammatory response, measured by circulating markers, and improvement in periphic insulin resistance. Changes in the phenotype of the macrophages, however, were not reported.

Moreover, in adipose tissues obtained from women submitted to bariatric surgery, there was a direct relationship between the presence of macrophages with a M1 phenotype (expressing more CD11c and CD206 and secreting more interleukins 1beta, 6, 8 and TNF-alfa) and insulin resistance. In addition, sustained weight loss results in reduced total numbers of adipose tissue macrophages, which is accompanied by a decrease in pro-inflammatory profiles of obese individuals.

Nonetheless, to postulate a direct view of these findings may lead to an oversimplification. Usually there are various populations of macrophages inside adipose tissues, with plasticity across the entire spectrum of activation states encompassed by the M1 and M2 nomenclature.

As could be seen throughout this review, polarization of macrophages inside the white adipose tissue is at the center of the pathogenesis of the diseases related to obesity. Above we also described several signaling pathways and inflammatory mediators that are involved in this phenomenon in animal models (Figure 4). More importantly, however, is the fact that these experimental studies provide a series of possible ways to change macrophages phenotypes, from changes in lifestyle to potential new drugs derived from parasites.

How these findings could be translated to new human treatments is still an open question that only well designed researches could answer.

Figure 4. Factors affecting macrophage polarization in adipose tissue

There is no consensus whether macrophages, once committed to a particular phenotype, can change to another. However, several studies described in this review show that some drugs or lifestyle changes (diet and exercise) may shift the balance of this polarization, increasing the number of M2 macrophages inside white adipose tissue.
REFERENCES


