Complex interaction between the immune system and adipose tissue (Review)

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Abstract. We review the studies on the links between obesity, the immune system and lifestyle (limited or excessive calorie intake) that provoke changes in the current therapeutic course. There is no doubt that the positive energy balance of the body affects the immune cells, and consequently, the changes intracellular pathways, leading to the disruption of their function. Research suggests that metformin, a drug long used to treat diabetes, and an alternative remedy in the treatment of obesity, increases the activity of 5-adenosinemonophosphate (AMP)-activated kinase (AMPK). Thus, this review comes to the conclusion that alongside traditional methods, such as reducing calorie intake and increasing the energy expenditure of the body, the therapeutic outcome may be improved by implementing drugs affecting the activity of AMPK. In future, other new therapeutic options may be available. The targeting receptors or immunocompetent cells residing in adipose tissue may help to reduce the effects of obesity.

Contents

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1. Introduction

Since 1986, obesity is considered a chronic disease. Excessive accumulation of body fat causes changes in homeostasis, with the most serious consequence leading to cardiovascular diseases. This is particularly important in the context of a dramatic increase in the prevalence of obesity which counteracts the progress in medicine and efforts made to improve our health and extend the average human life time. Recent studies describe the impact of obesity on the immune system (1-3). In prehistoric times, survival depended on the ability to acquire and accumulate stocks of food, just as important as the ability to recognize and combat harmful microbes. Thus, during the course of evolution, we have formed a link between the energy balance of the body and the functioning of the immune system. The aim of this review was to present the associations between obesity (adipose tissue activity) and immune function.

2. Role of adipose tissue in regulating immune function

The main task of adipose tissue is to collect fat energy reserves. This is not a passive storage. It is known that adipocytes secreting endocrine substances transfer signals regarding energy resources to the central nervous system and thereby participate in the regulation of food intake. In addition to adipocytes, adipose tissue contains connective tissue (stroma), blood vessels, immune cells and nerve tissue elements (1). Through all compounds secreted by these cells and substances collected by numerous receptors that receive signals from the outside, adipose tissue actively participates in the regulation of such important processes, as carbohydrate and lipid management, maintenance of blood pressure, fertility and hemostasis (2,3). Thus far as many as 100 substances synthesized by adipose tissue (preadipocytes, adipocytes, as well as other cell types) have been discovered.

Adipocytes are the main source of leptin and adiponectin. Macrophages produce almost all the tumor necrosis factor

(TNF), resistin and visfatin present in the body, while prostaglandin E2, interleukins (ILs), vascular endothelial growth factor (VEGF) and hepatocyte growth factor are synthesized by stromal and vascular cells.

Adipocytes are the place of synthesis for many proteins involved in inflammatory processes. Cytokines connected with inflammatory process and secreted by adipocyte include, among others, TNF, numerous interleukins (IL-1β, IL-6, IL-8 and IL-10), monocyte chemotactic protein-1 (MCP-1) and macrophage migration inhibitory factor (MIF). Leptin, resistin, VEGF, amyloid A, haptoglobin, plasminogen activation inhibitor type-1 (PAI-1) and acylation stimulating protein (ASP) are also related to the development of inflammatory processes. The concentration of the majority of pro-inflammatory cytokines increases together with the increase in body fat mass.

Adiponectin is responsible for the anti-inflammatory properties of adipokines (4-6). The process of interaction between adipose tissue and the immune system is mediated by adipocytokines. As mentioned above, adipose tissue synthesizes and releases a number of regulatory substances, whose tasks include reading changes in the energy balance of the body and consequently, the regulation of adipose tissue (16). The interdependence of body fat and the immune system is particularly noticeable in situations of excess body fat observed during obesity. It has been observed that in addition to the development of cardiovascular diseases, cancer and increased mortality, obese individuals are also vulnerable to acute and chronic infections of the lower respiratory tract, tuberculosis, sepsis and other infections (6,7). It has also been suggested that obesity increases the risk of peri-operative and in-hospital infections. The serious complications of common usually harmless infections are also more likely to occur (8). It has therefore been suggested that excess body fat can lead to impaired immune function (9), an opinion based on several experimental studies on the association between excess body fat and the functioning of the immune system.

Obese ob/ob mice lacking leptin gene mutations display a markedly involuted thymus and have significant defects in T-cell responsiveness (10,11). The impairment of antigen presentation by dendritic cells has also been observed (12). Similar findings apply to humans with congenital leptin deficiency (13). It is well established that obese dogs have a greater susceptibility and consequently, an increased mortality rate due to canine distemper virus (14). In diet-induced obese (DIO) mice, influenza virus infection has been shown to cause impaired immune response with a six-fold increase in the mortality rate (15).

3. Adipokines, ghrelin and the immune system

The first described compound of this type was leptin, a protein marker of mature adipocytes, whose discovery in 1994 drew attention to the secretory and endocrine role of adipose tissue. This endocrine role, as is known, not only applies to adipose cells, but also to other components of tissues, including macrophages and other immune cells. In obesity, the infiltration of adipose tissue by monocytes/macrophages is observed, and the percentage of these cells increases from 10% to as much as 50%. It has been suggested that resident macrophages in adipose tissue are responsible for secreting most of the IL-6 and TNF-α produced by adipose tissue (9,16,17).

Thus one can distinguish between two types of adipokines: adipose tissue-specific leptin and adiponectin, as well as non-specific, such as TNF, IL-6 and PAI-1 among others. Given the amount of body fat (it may be up to 25-30% of body weight), the total secretory activity of this tissue has a significant effect on the metabolism of the whole body. Adipose tissue can therefore be considered to be the largest endocrine gland in terms of weight (18). Due to the connections shaped by the ongoing evolution between available food supplies (and thus energy storage) and the ability to fight infections resulting from injuries and exposure to germs, it should not be surprising that adipokines actively modulate the function of the immune system.

Thus leptin, a hormone derived almost exclusively from adipose tissue, in addition to controlling food intake, interacts with monocytes and macrophages, resulting in an increased production of pro-inflammatory cytokines, including TNF and IL-6 (19). Leptin also stimulates the chemotaxis of neutrophils and the synthesis of reactive oxygen species (ROS). It also regulates the differentiation, proliferation activation and cytotoxicity of natural killer (NK) cells and can induce T-cell proliferation (4,20).

Adiponectin, another protein highly specific to adipose tissue, significantly affects the functions of monocytes and macrophages. It inhibits the TNF-induced adhesion of monocytes to endothelial cells and their transformation into tissue-specific cells. Adiponectin significantly reduces the activity of phagocytes and the synthesis of TNF in response to lipopolysaccharide (LPS) stimulation, decreases the expression of receptors in macrophages and monocytes and can induce their apoptosis (4,18,19). Adiponectin inhibits the synthesis of TNF induced by leptin. The modulation of the immune system and inflammatory activity is also attributed to resistin.

Resistin induces TNF-α and IL-6 secretion by human blood leukocytes and, in turn, resistin expression is induced by IL-1, TNF-α and IL-6, suggesting a potential feed-forward loop of pro-inflammatory cytokines. Resistin RNA is expressed at higher levels in visceral fat than in non-abdominal subcutaneous fat and serum resistin levels are higher in obese subjects than in lean subjects (4,20,21).

Chemerin, a leukocyte chemotactic factor produced from the Tazarotene-induced gene 2 as an inactive precursor, prochemerin, by a number of tissues, with the liver and adipose tissues as the main sources. Chemerin, whose levels increase with obesity, may be responsible for the recruitment of NK cells, macrophages and other leukocytes to adipose tissue. Adipocyte chemerin synthesis is elevated both by TNF-α and IL-1β, suggesting a possible feed-forward loop of leukocyte recruitment and inflammatory cytokine production, leading to greater leukocyte recruitment (21,22).

Visfatin upregulates pro-inflammatory cytokine expression in monocytes, including IL-1β, TNF-α and IL-6. Visfatin also induces monocyte cell surface ligands for stimulatory lymphocyte receptors, including CD80 (B7-1), CD40 and CD54 (ICAM-1), increases macrophage phagocytosis and prevents neutrophil apoptosis It is produced by a number of tissues, including adipose tissue and skeletal muscle (21).

Other adipokines, such as vaspin, adipsin, omentin, cartonectin may be involved in metabolic and immunologic pathways; however, their role is less documented.

In the case of a chronic excess of calories, low levels of ghrelin are also observed for unknown reasons. Ghrelin is a neurohormone (orexigenic) which stimulates appetite, and thus promotes the conservation of body fat resources and inhibits the inflammatory response of the immune system. Increased levels of leptin and reduced ghrelin and adiponectin sustain chronic inflammation (1,23). It should be noted that the excessive pro-inflammatory activity of the immune system is retained in the 'vicious circle' mechanism. It has been demonstrated *in vitro* that the production of TNF and IL-6 in adipose tissue significantly increases during obesity, and this inhibits the synthesis of adiponectin, which acts in an opposite manner (i.e., anti-inflammatory) in adipose tissue. This fact is confirmed by the reduced levels of adiponectin observed in obese subjects with metabolic syndrome and type two diabetes. Hypoadiponectinemia is an independent risk factor for predicting mortality from cardiovascular disease (24). Other studies have shown that obese patients with type two diabetes, when compared with healthy individuals, possess lower levels of ghrelin. Therefore hypoghrelinemia may be considered as a new independent predictor of the development of insulin resistance and type two diabetes (25).

Thus, it is obvious that the positive energy balance is associated with changes in the functioning of the immune system, including chronic inflammation, which is clearly an unfavorable phenomenon. This does not facilitate the healing of the damaged tissue and compromises the ability to fight germs. Immune dysfunction accompanying obesity can exacerbate oxidative stress in addition to the already mentioned increase in the risk of the cardiovascular diseases and cancer, as well as premature aging and a significant increase in mortality (9).

4. Excessive caloric intake, obesity and the dysregulation of molecular pathways

There is ongoing research aimed at understanding the molecular pathways responsible for chronic inflammation accompanying obesity. The main point of interest is an enzyme belonging to the serine-threonine kinases, 5-adenosinemonophosphate (AMP)-activated kinase (AMPK). It is a highly conserved protein present in all eukaryotes, and is the central enzyme regulating cell metabolism (26). It regulates the transport of glucose and fatty acid oxidation and plays a key role in maintaining the energy homeostasis of the organism. AMPK activity is closely linked to the state of energy in cells. Enzyme activation depends on a low AMP/adenosine triphosphate (ATP) ratio, which is observed in an energy deficient state. Consequently, this is followed by an increase in food intake and ATP biosynthesis i.e., uptake and utilization of glucose and the oxidation of fatty acids. During the last few years, research has demonstrated that AMPK activity depends not only on the AMP/ATP ratio, but is also modulated by hormones and cytokines involved in the regulation of the energy balance of the body. AMPK has been found to be crucial in the mechanism of neuroendocrine feedback control in the hypothalamus, where the centers of hunger and satiety are located. Orexigenic neuropeptides, such as ghrelin, neuropeptide Y (NPY), agouti protein and adiponectin activate the enzyme (27-29), while operating anorexigenic leptin and melanocortin-3 and -4 receptor agonists and pro-inflammatory cytokines (TNF, IL-6) inhibit AMPK activity (30,31).

Thus, ghrelin and leptin, two essential hormones of counterbalanced activity, regulate AMPK activity in the hypothalamus. The activation of this kinase is crucial to maintain the feeling of hunger in the event of a negative energy balance (32).

With this feedback, our ancestors could survive in an environment deficient in food. It can be said that the regulation of food intake, which evolved during the hypocaloric diet, is in accordance with the principle that a lack of hunger leads to death and excessive appetite 'only' to obesity (33,34).

The list of transcription factors and enzymes that are affected by the activation of AMPK or lack of thereof is very long and still open to discussion (29). It has been shown that the activation of AMPK induces anti-inflammatory and immunosuppressive effects in many cell types and in experimental models of inflammatory and autoimmune diseases (35,36). The fact that AMPK activation increases the rate of glucose transport into skeletal muscle irrespective of the action of insulin, raises the hope of developing an effective treatment for metabolic disorders, including obesity and insulin resistance and type two diabetes. The study by Hatori *et al* showed that metformin, which has been used for >40 years in the treatment of type two diabetes, increases the activity of AMPK (37). Thiazolidinediones possibly operate in a similar manner. It has been suggested that metformin inhibits inflammation and reduces C-reactive protein (CRP) levels by affecting the transcription factor, nuclear factor (NF)-κB (37). The activation of AMPK and consequently, the increase in insulin-regulated glucose transporter 4 (GLUT4) expression and the phosphorylation of insulin receptor substrate 1 (IRS1) are possibly responsible for the beneficial effects of regular physical activity, improving insulin sensitivity (38,39). AMPK is possibly also a potent inhibitor of cell proliferation and a modulator of angiogenesis, aging and programmed cell death. It may also be involved in the inhibition of tumor growth (29).

It is known that the activation of AMPK mediates the anti-inflammatory effects of adiponectin. The anti-inflammatory effect of ghrelin is also possibly achieved by the activation of AMPK. It has been shown by Dixit *et al* that pro-inflammatory cytokine production in monocytes and T-lymphocytes is negatively affected by ghrelin through the NF-κB system. The authors suggested that the ATP-dependent phosphorylation of IκB inhibitor protein IκB kinase (IKK) increases the AMP/ATP ratio. In this way, the activation of AMPK may occur, which inhibits the activation of NF-κB, preventing the development of excessive inflammatory response (9,40). It is highly likely that this mechanism does not function well in the state of chronic calory excess and the permanent inhibition of AMPK is not able to prevent the development of chronic inflammation.

5. mTOR pathway

Another molecular pathway which can be affected by AMPK is the mammalian target of rapamycin (mTOR)/S6K1 signaling pathway. mTOR kinase and its effector kinase, S6K1, regulate protein synthesis, cell growth and proliferation, as well as

several other processes of gene transcription and protein translation. Therefore, mTOR pathway dysregulation may lead to the development of cancer. The proteins of the mTOR complex are activated by an excess of fatty acids, glucose and amino acids. It is known that in the case of overfeeding, prolonged mTOR/S6K1 pathway activation results in the development of obesity and insulin resistance (41). Anorexigenic neurohormones, such as leptin, activate mTOR and inhibit the expression of AMPK in the hypothalamus (30,42). Thus both enzymes, AMPK and mTOR, function as the sensors of the cell resources, where mTOR is a sign of excess, and AMPK, a shortage of energy (43).

Rapamycin, the mTOR inhibitor, which was isolated from the bacteria present in a soil sample found on Easter Island (Rapa Nui) is already registered as a drug due to its immunosuppressive and antiproliferative properties. It has been demonstrated that rapamycin can also block the path of TNF and IL-6 and prevent hepatic insulin resistance (44). It is therefore possible that the cellular sensors of the energy balance play a key role in the pro-inflammatory response, and AMPK and mTOR pathways are the molecular controllers in the strong association between metabolism and the immune system. It was experimentally proven that the inhibition of the mTOR pathway by rapamycin extends the life of mice (45). This report is supplemented with the observation that the only natural life extending interventions in mammals, including monkeys, is a low-calorie diet (CR, caloric restriction). It is believed that CR has beneficial effects not only on mortality and morbidity, but may be causative of slower aging of the immune system (46). Messaoudi *et al* observed that a hypocaloric diet in monkeys improved T-cell function and reduced the production of pro-inflammatory cytokines by memory T-cells (47). It has suggested been that a hypocaloric diet helps maintain the adequate population of T-cell precursors in the thymus despite aging (49). Perhaps the slower aging of the immune system in a state of caloric restriction is mediated by ghrelin. Yang *et al* and Dixit *et al* showed that ghrelin can reverse the age-related involution of the thymus (48,49).

As regards the asssociation between body fat and the immune system, one cannot ignore the fact that adipocytes and immunocompetent cells can interact directly, in a paracrine manner. This happens in a microenvironment of many tissues and organs, particularly in the aforementioned thymus, bone marrow and adipose tissue. In extreme obesity, adipose tissue becomes one of the largest organs in the human body and constitutes up to 50% of total body mass. The excessive production of pro-inflammatory cytokines by expanded macrophage populations within adipose tissue can, consequently, induce insulin resistance. Recent studies have found increased T-cell infiltration in adipose tissue in an obese state (49,50). Emerging evidence suggests that the activation of these lymphocyte populations in adipose tissue may contribute toward obesity-associated insulin resistance and metabolic syndrome (50). It is possible that the, so called, adipose-resident T-cells (ARTs) obtained from obese mice differ in their properties from the population of ARTs in lean mice (49).

It has been concluded that in the future, adipose tissue immunocompetent cell targeting approaches may help to reduce adipose inflammation and to dispose of the consequences of obesity (50).

6. Toll-like receptors

In the context of the association between obesity, metabolic disorders and the immune system, toll-like receptors (TLRs) should also be mentioned. They play an important role in the regulation of the innate and acquired immune responses. Their stimulation, and consequently, NF-κB complex activation leads to the production of multiple pro-inflammatory cytokines.

It has been shown that the expression of TLRs in preadipocytes depends on leptin and resistin. Previously, it was found that adiponectin inhibits TLR-induced NF-κB activation in epithelial and immunocompetent cells (51) and therefore, hypoadinectinemia accompanied by obesity is connected with excessive pro-inflammatory reactions. TLR1 to TLR9 have been found in mature adipocytes (52). TLR4, the most characterized TLR, which is a receptor for bacterial LPS, may contribute to the pathogenesis of insulin resistance. It has been demonstrated both *in vitro* and *in vivo* that nutritional free fatty acids (FFAs) can act through TLR4 in macrophages and adipocytes to induce inflammatory reactions and suppress insulin signaling (53). Moreover, TLR4 signaling appears to be crucial for a component of insulin resistance induced by FFAs following lipid infusion and high-fat diets (53). Thus, TLRs are another example of a molecular mechanism linking innate immunity, obesity and insulin resistance.

7. Conclusion

The abovementioned studies on the links between obesity, the immune system and lifestyle (limited or excessive calorie intake) provoke changes in the current therapeutic course. There is no doubt that the positive energy balance of the body affects the immune cells, and consequently, the changes intracellular pathways, leading to the disruption of their function. Research suggests that metformin, a drug long used to treat diabetes, and an alternative remedy in the treatment of obesity, increases the activity of AMPK. Thus, consequently, this review comes to the conclusion that alongside traditional methods, such as reducing calorie intake and increasing the energy expenditure of the body, the implementation of drugs affecting the activity of AMPK may improve the therapeutic outcome. In the future, other new therapeutic options may be available. The targeting of receptors or immunocompetent cells residing in adipose tissue may help to reduce the effects of obesity.

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