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Immune Response in Obesity and Type 2 Diabetes

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Abstract

Abstract. Obesity is a widespread chronic inflammatory disease that can lead to increased health risks and subsequent development of prediabetes and type 2 diabetes. The World Obesity Federation (WOF) predicts that the global number of obese adults will reach 1 billion by 2030. The World Obesity Federation (WOF) identifies Kazakhstan as a high-risk country for obesity. By 2030, obesity rates in Kazakhstan are expected to rise to 25.7% in men, 29% in women, and 9.5% in children aged 5 to 19. Kazakhstan's National Center for Public Health has observed a significant increase in overweight and obesity rates, particularly among children. Epidemiological data indicate that boys have a higher obesity rate than girls. Specifically, 23.6% of boys were classified as overweight, including obesity, compared to 17.6% of girls. Recent studies highlight the role of immune cell function in obesity-related inflammation providing a potential new target for treating obesity-linked inflammatory diseases. This review article discusses the role of immune cells in regulating obesity-related diseases, including diabetes.

Keywords: obesity, inflammation, type 2 diabetes, immune response, cytokines, T cells, B cells.

Introduction

Obesity is a multifaceted, complex illness that impairs health as excess body fat builds up. Chronic adipose tissue inflammation and the abnormal accumulation of fat deposits in the adipose tissue, liver, muscle, and pancreas triggers metabolic disorders that lead to an increased risk of diseases such as cardiovascular diseases, cancer, and type 2 diabetes mellitus (T2D). According to the World Obesity Federation (WOF), the prevalence of obese individuals in the world will increase to 1 billion adults by 2030. The WOF includes Kazakhstan as a high-risk country for obesity. In 2030 obesity in Kazakhstan is predicted to reach 25.7% in men, 29% in women, and 9.5% in children aged 5-19. The National Center for Public Health of the Republic of Kazakhstan has reported a significant increase in the prevalence of overweight and obesity, particularly among children. According to the results of epidemiological monitoring, the rate of obesity among boys was notably higher than that among girls. Specifically, 23.6% of boys were classified as overweight, including obesity, compared to 17.6% of girls. Additionally, 8.7% of boys were classified as obese, compared to 4.6% of girls [1, 2].

T2D is a long-term metabolic condition that seriously damages tissues and vital organs such as the liver, kidneys, heart, eyes, and other organs. Hyperglycemia, hyperinsulinemia, impaired glucose-stimulated insulin secretion (GSIS), and insulin resistance are hallmarks of T2D in individuals. Numerous studies have shown a strong correlation between obesity and T2D. Obesity is associated with increased susceptibility to multiple diseases and is estimated to contribute to 80 – 85% of the risk of developing T2D. Several factors have a substantial impact on the onset of obesity and type 2 diabetes (T2D), including insulin resistance, inflammatory cytokines production, impaired endothelial function, disturbed metabolism of fatty acids, and cellular mechanisms like mitochondrial dysfunction and endoplasmic reticulum stress [3]. Another potential risk factor for obesity and diabetes is long-term consumption of an obesogenic diet. In their study, Glavas et al. demonstrated the early effects of obesity and a high-fat diet on the function of the ß-cell in mice. According to their study, early overnutrition was found to cause weight gain, hyperinsulinemia, and the development of diabetes, particularly in male pups. Early overnutrition might lead to reduced expression of

the crucial transcription factor PDX1, which is responsible for normal pancreas development. This reduced expression leads to dysfunctional ß-cell and apoptosis [4]. Research has shown that the early effects of a high-calorie diet on beta-cell function in mice are associated with the pathophysiological conditions of being overweight and obese, along with insulin resistance [5].

Obesity is marked by the overproduction of pro-inflammatory cytokines, originating from impaired adipose tissue immune cells [6, 7]. Studies comparing adipose tissues in lean versus obese individuals have revealed variations in both the quantity and function of various immune cells. These include different types of macrophages (such as M1 and M2), subtypes of T cells (like T helper, CD8+, and T regulatory cells), natural killer (NK) cells, myeloid-derived suppressor cells (MDSCs), and B cells. In lean individuals, adipose tissue contains M2 macrophages, Th2, and T-regulatory cells that produce pro-inflammatory cytokines such as IL-10, IL-5, and interferon-γ. However, in obese individuals, adipose tissue is infiltrated with pro-inflammatory T cells and M1 macrophages, accumulating cytokines such as tumor necrosis factor α, IL-17, IL-6, and interleukin-1β (IL-1β). High cytokine production in obese individuals promotes adipose tissue remodeling, enhances energy expenditure, and impairs insulin sensitivity [8]. In their studies, Wu and Ballantyne classified inflammatory cells into two categories: Type 1 and 2. Type 1 inflammatory cells secrete interferon-gamma (IFN-γ), TNFα, IL-1β, IL-6, and IL-12 cytokines. Type 2 inflammatory cells include Th2 (T helper 2) cells, M2 macrophages, eosinophils, and innate lymphoid cells (ILC2) that release cytokines such as IL-4, IL-5, IL-10, IL-13, TGFβ [9]. McLaughlin et al. in their studies, show the connection between systemic inflammation and insulin resistance. In human obesity, an imbalance between Th-1 (pro-inflammatory) and Th-2 (anti-inflammatory) cells released from adipose tissues (visceral and subcutaneous) triggers systemic inflammation and leads to insulin resistance. High production of pro-inflammatory cytokines such as IL-6 and TNF-α in serum and tissues indicates pathologies (Figure 1). In obesity, increased levels of CRP, IL-6, TNFα and, IL-1β may serve as markers of pathological conditions [10, 11]. Here, we discuss immune cells' roles and behavior in regulating obesity and type 2 diabetes.

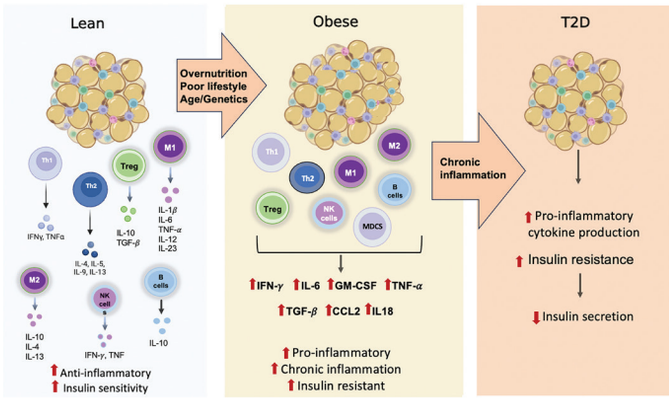

Figure 1 – Characteristics of immune cells in lean (normal), obese, and T2D conditions. In normal conditions, immune cells produce anti-inflammatory cytokines, while in obese and T2D they release more pro-inflammatory cytokines that lead to chronic inflammation, which causes insulin resistance. IL – interleukin, TGF – tumor growth factor, Th – T helper cells, Treg – regulatory T cells, IFN – interferon, TNF – tumor necrosis factor, M1/M2 – macrophages, NK – natural killer cells, MDSC – myeloid-derived suppressor cells.

Immunoregulatory cells in obesity and T2D

Macrophages

Macrophages are key components of the innate immune system that regulate immune response by releasing cytokines. Macrophages can develop unique functional traits through a process known as polarization, which is influenced by the surrounding microenvironment and the immunological context. Macrophages are divided into two distinct subtypes based on polarization: M1 macrophages (pro-inflammatory), which are classically activated, and M2 macrophages (anti-inflammatory), which are alternately activated. M1 macrophages have a strong cytotoxic ability and are immediately activated during the infection by producing pro-inflammatory cytokines. Increased levels of pro-inflammatory cytokines can result in inflammation and damage to tissues. M2 macrophages are activated to suppress inflammation by expressing anti-inflammatory cytokines and repairing tissue damage [12]. In pathological conditions, for instance, in infection and stress, the M1 macrophages produce interleukin-1β (IL-1β), IL-6, IL-12, IL-23 pro-inflammatory cytokines, nitric oxide, and tumor necrosis factor-alpha (TNF-α) as immune responses. The immunoregulatory M2 macrophages are activated release cytokines such as IL-10, and TGF-β during tissue remodeling and repair to maintain cell homeostasis. Increased levels of macrophages and accumulation in adipose tissues during obesity promote the progression of metabolic diseases including diabetes. Numerous studies reported that the pro-inflammatory macrophage accumulation in adipose tissues promotes metabolic dysfunction of cellular signaling [13]. The connection between obesity-associated inflammation and insulin resistance was made in 1993. The first well-established cytokine associated with inflammation and diabetes was TNF-α produced from the M1 macrophages [14]. Stavropoulos-Kalinoglou et al. showed regulation of inflammation using anti-TNF-α treatment increased sensitivity to insulin in rheumatoid arthritis patients with insulin resistance. The authors concluded that TNF-α can be a therapeutic target for the treatment of insulin resistance, obesity, and rheumatoid arthritis [15]. Butcher et al. found a connection between pro-inflammatory cytokine TNF-α, chemokine CCL2, and GSIS in type 2 diabetic human islets. The study found that high levels of TNF-α and CCL2 are linked to ß-cell dysfunction [16]. Thus the close connection between obesity-induced inflammation and diabetes is associated with both the failure of pancreatic ß-cells and insulin resistance in adipose and other tissues.

T Cells

T cells play a crucial role in inflammation and metabolic diseases. T cells begin their development in the bone marrow and differentiate into two distinct lineages (αβ and γδ-lineages). These lineages mature to different phenotypes of T cells that express diverse cytokines [17]. The imbalance of T cell subsets (T helper cells, cytotoxic T cells, and regulatory T cells,) in adipose and other tissues contributes to metabolic disorders [18]. Research has shown that in the case of inflammation caused by obesity, there is a significant buildup of T cells and macrophages in adipose tissue [19]. Each of the T cell subtypes expresses cytokines that regulate immune responses. During the initial phases of inflammation, pro-inflammatory cytokines like IFN-γ and TNF-α, released by various T cell subsets, such as Th1, Th17, and CD8+ cells, are essential for the disease progression.

T helper cells

T helper cells or CD4+ T cells are classified as Th1, Th2, Th17, and regulatory T cells (Treg) play a key role in regulating

the immune response. They express a wide range of cytokines for instance, Th1 produces IFN-γ, IL-4, IL-5, IL-13 from Th2, Th17 cells release IL-17, IL-21, IL-22 and IL-10 and TGFβ by Treg [20]. In metabolic syndrome and obese states, visceral adipose tissue expresses more pro-inflammatory cells, which indicates a typical shift towards a more Th1-dominated response, contributing to chronic inflammation [19, 20]. By differentiating into several subtypes, several cytokines by differentiating into several subtypes, which play a distinct role in inflammation and metabolic regulation. For instance, Th1 cells produce cytokines such as IFN-γ and TNF-α, which can exacerbate inflammation and insulin resistance [21]. Hotamisligil et al, in their study, first suggested that TNF-α is overexpressed in metabolic syndrome and obesity observing a positive correlation between insulin resistance and TNF-α level [22]. Thus, overexpression of TNF-α decreases insulin sensitivity, leading to elevated insulin levels. Uysal et al. also observed that neutralization of these cytokines can reverse insulin resistance and lower insulin levels [23].

Furthermore, it is essential to comprehend the role of CD4+ T cells in the development of insulin resistance. Recent studies have highlighted the important role of adipocytes as cells that present antigens within the immune system. Adipocytes were traditionally not considered part of the immune response; however, in obesity, they can release major histocompatibility complex (MHC) class II molecules. This expression enables them to present antigens to CD4+ T cells [24]. This capability suggests that adipocytes are not passive fat-storing cells but active participants in the immune dynamics of adipose tissue. They can modulate the activity of CD4+ T cells, potentially influencing the progression of inflammation and insulin resistance [22]. The interaction between adipocytes and CD4+ T cells highlights the complex feedback loops between metabolism and immunity in obese adipose tissue. For example, adipocytes can influence the differentiation and function of T cells through the secretion of adipokines and the presentation of antigens. This crosstalk is crucial for understanding how chronic inflammation is sustained in obesity and how it can be targeted therapeutically.

Cytotoxic T cells

CD8+ T cells are typically known for their role in cytotoxic immune responses against infected or malignant cells [25]. However, in the case of obesity, these cells accumulate in adipose tissue not in response to infection, but as part of an inflammatory reaction to excess nutrients and adipocyte hypertrophy [26]. This process is mediated by various chemokines and adhesion molecules expressed by adipose tissue under stressed conditions. The recruitment of CD8+ T cells is often preceded by changes in the adipose tissue environment, triggered by nutrient overload, which leads to adipocyte dysfunction and death. The presence of CD8+ T cells stimulates the polarization of macrophages to the M1 pro-inflammatory state [27]. This is critical as M1 adipose tissue macrophages are associated with the secretion of inflammatory cytokines, further contributing to the inflammatory environment within adipose tissue. Wang et al. highlighted that the number of CD8+ T cells is significantly elevated in the adipose tissue of both diet-induced and genetically obese mice [28, 29]. The study notes that CD8+ T cells are among the first immune cells to infiltrate the adipose tissue during the development of obesity. Their presence precedes that of macrophages, which are also key players in adipose tissue inflammation. Once in the adipose tissue, CD8+ T cells become activated and exert their effects by producing additional cytokines including IFN-γ and TNF-α, further exacerbating local inflammation. The depletion of CD8+ T cells in experimental interventions using neutralizing antibodies, have decreased adipose tissue macrophage infiltration, decreased inflammation in adipose tissue, and regenerated insulin sensitivity in obese models.

Interestingly, the study by Ahrendsen et al. reported a significantly higher presence of CD8+ T cells in the hypothalamic regions, specifically the median eminence/arcuate nucleus (ME/Arc) and the bed nucleus of the stria terminalis (BNST), of obese individuals compared to their non-obese counterparts. This was not observed in other brain regions or hypothalamic nuclei, indicating a targeted inflammatory response associated with metabolic regulatory centers. Along with the increased presence of CD8+ T cells, there was a notable rise in markers indicating cellular damage, such as activated caspase 3 and poly-ADP ribose, found in the ME/Arc of patients with obesity. This suggests that CD8+ T cells may not only be markers of inflammation but also active participants in causing neuronal damage within the hypothalamus, potentially disrupting crucial metabolic processes regulated by this area [30].

Regulatory T cells

Regulatory T cells (Treg) represent a specialized group of CD4+ T cells responsible for upholding peripheral tolerance and suppressing antigen-specific immune responses by producing TGF-β, IL-10, and IL-4 cytokines. Tregs, which are generally anti-inflammatory, are found in reduced numbers in obese conditions, further tipping the balance towards pro-inflammatory pathways. This imbalance not only perpetuates adipose tissue inflammation but also impairs insulin signaling in visceral adipose tissue and liver, promoting the progression of T2D. Treg cells represent a key type of immune cell found in visceral adipose tissue (VAT). Studies have shown that Treg cytokine production levels depend on physiological conditions. In normal conditions, the levels of Treg cells are elevated, while in diet-induced obesity, their reduction is found in VAT. The production of Treg cells in VAT is decreased by 80–90% in obese mice. Li et al. demonstrated that diet-induced obesity or long-term high-fat diet feeding inhibits the nuclear receptor PPARγ, which regulates Treg expression in VAT. Lack of PPARγ expression in mice causes a reduction in Treg cell expression that may lead to impaired anti-inflammatory activity. Reduced Treg levels have a positive effect on diabetes development and related complications. However, the exact molecular mechanisms explaining how Tregs protect against diabetes are not fully understood. The impairment of insulin production is closely linked to alterations in the immune system. The primary factors contributing to inadequate insulin release are the attack on ß-cells by Treg cells, CD8+ T cells and macrophages which release pro-inflammatory cytokines, as well as the assault on ß-cells by B cells and Th cells. In their meta-analysis, Qiao et al. found that elevated levels of pro-inflammatory cytokines (IL-6 and TNF-α) and reduced levels of the anti-inflammatory cytokine IL-10 in individuals with T2D may inhibit Tregs and the ratio of Tregs to Th1 and Th17 cells [31–34].

B cells

B cells are an important part of the adaptive immune system, primarily known for their roles in antibody production, antigen presentation, and cytokine secretion. These functions enable B cells to modulate other immune cells and influence inflammatory responses. In the context of obesity, B cells undergo significant changes that exacerbate the inflammatory environment. Such chronic immune activation is a hallmark of obesity and sets the stage for various complications, including insulin resistance and T2D. B cells accumulate in adipose tissue, particularly visceral fat surrounding internal organs. This accumulation is associated with several detrimental processes via

pro-inflammatory cytokine production, autoantibody production, and impact on T cell activation in adipose tissue. B cells in obese adipose tissue are known to produce pro-inflammatory cytokines such as TNF-α and IL-6. These cytokines contribute to the inflammatory milieu of obese adipose tissue, which can exacerbate insulin resistance, a precursor to T2D. Zhai et al. observed a B cell-mediated immune response in both obese non-diabetic and obese diabetic individuals. The results showed that B cells in both cases release pro-inflammatory cytokines such as IL-6 and TNF-α. However, the study found that obese diabetics experienced dysregulation of the immune suppression capacity of regulatory IL-10 cytokines, which is mediated by regulatory B cells [31, 35]. Moreover, B cells can produce autoantibodies that react with self-antigens in adipose tissue. This autoimmune-like response further fuels inflammation, which can impair the normal function of insulin, leading to insulin resistance and, eventually, diabetes. B cells also influence the function of T cells in adipose tissue by presenting antigens and secreting cytokines that promote T-cell activation, leading to a pro-inflammatory response. This T cell activation contributes to the systemic inflammation observed in obesity. Additionally, while B cells from obese subjects without diabetes were able to maintain some regulatory functions via IL-10 production, B cells from diabetic patients showed an impaired ability to produce this anti-inflammatory cytokine, even when stimulated. IL-10 is vital for controlling immune responses and its deficiency could lead to unchecked inflammation, further complicating metabolic dysregulation in diabetic patients [36]. One of the most critical findings from the studies conducted is the impaired antibody response to new antigens in obese diabetic patients. Despite an overall increase in antibody production, these individuals showed a reduced ability to generate antigen-specific antibodies. This was evident from their response to the influenza vaccine, where obese diabetic subjects had significantly lower increases in specific antibodies compared to non-diabetic obese subjects. This phenomenon suggests a defect in the adaptive immune response, where despite high overall B cell activation, the specificity of the immune response is compromised [36, 37]. This could potentially lead to an inadequate immune defense against new pathogens, while also contributing to chronic tissue inflammation seen in metabolic disorders.

Myeloid-Derived Suppressor Cells (MDSC)

Epidemiological studies have demonstrated that obesity changes some immune cell phenotypic and functional characteristics. Pathologically activated neutrophils and monocytes are called myeloid-derived suppressor cells (MDSCs) with strong immunosuppressive properties. The common myeloid progenitor (CMP) is a varied group of immature myeloid cells found in the bone, capable of differentiating into myeloid-derived suppressor cells (MDSCs). In mice, this process also occurs in the spleen. MDSC cells are classified into two groups, monocytic (M-MDSC) and polymorphonuclear/granulocytic (PMN-MDSC) that regulate immune response via different cellular mechanisms by producing immune suppressive cytokines. Accumulation of MDSC cells in obesity induces suppression of T-cell activation, preventing NK cell cytotoxicity, and polarizing macrophages toward a tumor-promoting phenotype. These types of cells are well-studied in tumor development and chronic inflammatory diseases in obese individuals [38–40]. Despite some advancements, our understanding of the roles and unique characteristics of these cells in individuals with T2D remains limited and requires further research.

Natural Killer (NK) Cells

Natural Killer (NK) cells are a type of innate lymphocyte that can quickly react to infected or altered cells without needing prior activation, releasing destructive substances like perforins or granzymes. They primarily kill target cells through cytotoxic activity, however, they contribute to immune regulation by releasing substantial levels of pro-inflammatory cytokines and chemokines, including TNF, IFN-γ, and granulocyte-macrophage colony-stimulating factor (GM-CSF). Moreover, these characteristics show their difference from T and B lymphocytes. Numerous studies demonstrate the frequencies of NK cells are decreased in individuals with excess weight, which relates to insulin resistance. However, some studies found that the frequencies of NK cells did not change during obesity [32, 41]. Therefore, the structural and functional properties of these cell groups in obesity are still unknown and need more studies.

Conclusion

Obesity and its health consequences are increasing global problems. The obesity phenomenon is characterized not only by an elevation in body mass due to high levels of fat deposits but also by a low-level chronic inflammatory response caused by the expression of inflammatory adipokines (for instance, leptin, MCP-1) from adipose tissue and molecular mediators of inflammation (e.g., IL-1β, IL-8, IFN-γ, and IL-17). The chronic, low-grade inflammatory process in excessive body mass triggers chronic damage/inflammation that systemically affects the entire body and stimulates an increase in immune cell density within the bloodstream, contributing to the development of many metabolic diseases, including T2D. The role of immune regulatory cells in the context of obesity, their phenotypic characteristics, and their underlying mechanisms of action still need further investigation. Research on immunoregulatory cells will enable a more profound comprehension of the cellular processes involved in disease progression and potentially provide for earlier diagnosis of obesity-related diseases.

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