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Chemokines: Small Molecules Participate in Diabetes

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Abstract

***Background*:** Chemokines are small protein molecules involved in cell signaling processes. They play a crucial role in many physiological and pathological processes. Chemokines are functionally classified into two categories; inflammatory/inducible and constitutive. Their biologic functional differences are the result of their receptors structural differences. Recently some studies were performed about the chemokines changes in diabetes. Inflammatory mechanisms have an important role in diabetes.

***Materials and Methods*:** In this review article we searched the keywords chemokines, diabetes, diabetes pathogenesis, and type 1 and 2 diabetes in Persian resources, PubMed and famous English-language websites through advanced search engines and found the newest studies about the role of chemokines in the pathogenesis of diabetes.

***Results*:** The results of the studies showed that diabetes and its disorders enhance the activation of immune cells and the expression of cytokines such as IL-1, IL-6, IL-8, IL-10, SDF-1, INF-γ, TGF-β, MCP-1, IP-10, TNF-α, and RANTES; most of them have impact on the pathogenesis of diabetes.

***Conclusion*:** Comparison and analysis of the results obtained from our research and the results of performed studies in the world and Iran shows that chemokines, like other protein molecules involved in the pathogenesis and etiology of diabetes, play a role in this process.

Introduction

Diabetes is a metabolic disorder which reduces the speed and ability of the body to use and metabolize the sugars,therefore leads to the increase of blood sugar.In fact, diabetes is a disease where the body is insulin deficient or do not use the produced insulin properly [1, 2]. Most types of diabetes can be diagnosed without early symptoms, and if there is some they are painless and hence undetectable [2]. Diabetics are prone to damages such as heart attacks, kidney problems, blindness, deafness, and burning feet syndrome. Diabetes may lead to esophagus dysfunction, stomach laziness, gallbladder and liver dysfunctions, and colon and small intestine impairments that each one in turn may cause specific symptoms [2]. More than 220 million people have diabetes worldwide and it is estimated to be doubled until 2030 [3]. At present, 11 percent of Iranians are suffering from diabetes. Due to lack of awareness of diabetes and its control methods, a person dies every 10 seconds and a person lose his/her feet every 30 seconds in the world. People inappropriate life style caused this disease to outspread [3].

Given the importance of diabetes from various aspects such as health, economic, and social issues and the role of immune system in the control and treatment of this disease, it has attracted a lot of views.

According to the mentioned introduction, in this study we decided to design a review article with the centrality of the roles of chemokines and their receptors in the pathogenesis of this disease which is somewhat derived from human technology, and provide at least partly and locally an appropriate response to the question that where did chemokines are located in this areas.

Materials and Methods

In this review article we searched the keywords chemokines, diabetes, diabetes pathogenesis, and type 1 and 2 diabetes in Persian resources such as SID, affiliated to University Jihad and IranMedex of Ministry of Health and Medical Education, as well as famous English-language websites like PubMed and various publishers such as Elsevier and Blackwell, through advanced search engines and found the newest studies about the role of chemokines in the pathogenesis of diabetes. Then we translated them and the source references of the authors in the field of chemokines and provided a review article.

Discussion

Chemokines: Chemokines are one of the components of the immune system that play numerous roles. They are the largest operational group of cytokines. Chemokine is a portmanteau word consisted from the first part of chemotactic (chemotaxis) and the last part of cytokine (chemotactic cytokines). Chemokines are a large family of low molecular weight secretory proteins that play crucial roles in physiological and pathological processes, such as hematopoiesis, angiogenesis, inflammation, atherosclerosis, allergy, infection, and immunologic diseases (Fig. 1) [4, 5]. Their primary function is the regulation of leukocyte migration when required, but chemokines also activate various cells in order to produce and secrete inflammatory mediators (ranging from histamine to cytokines).

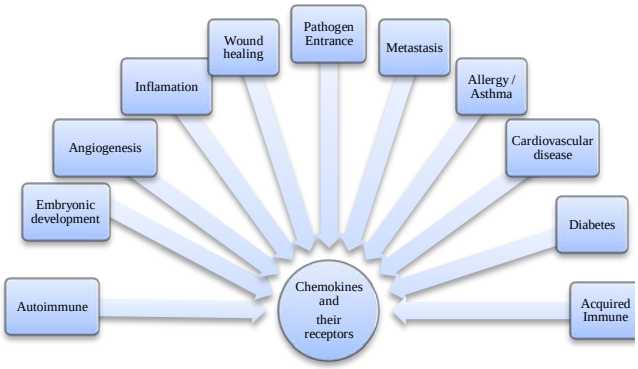

Figure 1. Physiologic and pathologic role of chemokines and their receptors

Research about chemokines is complicated because they usually bind to seven-transmembrane domain receptors, which are coupled with G-proteins. Some studies have been recently proposed the alterations of chemokines in diabetes [6]. Chemokines are functionally classified into 2 categories; inflammatory/inducible and constitutive. Inflammatory chemokines have a critical role in attraction of leukocytes to inflammation site and play a role in the innate immune system through the attraction of neutrophils, monocytes/macrophages, natural killer (NK), and dendritic cells. Their biologic functional differences are the result of their receptors structural differences (homo or heterodimerization), their natural changes; that is structural breaking and rejoining which produce different forms of chemokines, genetic polymorphisms and posttranslational changes of proteins [7, 8].

Diabetes: Inflammatory mechanisms have an important role in diabetes. Diabetes was classified into two types 1 and 2, in 1974 [9]. Both are characterized by defects and destruction of beta cells. In diabetes type 1, there is an autoimmune attack against beta cells that leads to their extensive death which in turn result to complete or nearly complete defect of insulin production. Type 1 diabetes can be considered as an inflammatory disease in which Langerhans cells die through apoptosis (programmed death process) and the interaction of beta cells and T type lymphocytes and inflammatory cytokines [1]. The pathogenesis of type 2 diabetes is more diverse and includes some degrees of beta cell defects and insulin resistance [2]. The risk of type 2 diabetes, known as adults diabetes, increases with age. It is believed that type 2 diabetes is an autoimmune disease, thus the study of the immune system differences of these patients with healthy individuals is one of the objectives of researchers in this field [10, 11]. Obesity and insulin secretion defect are proposed to be the major risk factors of type 2 diabetes [12]. An extensive reduction in efficiency of beta cells leads to glucose intolerance that is observed in type 2 diabete [13]. According to studies, it seems logical to say that dyslipidemia and sugar increment negatively affect beta-cells volume through enhancing apoptosis in type 2 diabetes; the mechanism through which increased sugar negatively affect the efficiency of beta cells is not known exactly.

Rodents' beta cells that were exposed to high glucose had changes in their phenotype, including changes in gene expression, and cell viability and growth; these changes can be caused by cytokines [14, 15]. Seventy to 80% of beta-cells volume decrease in type 1 diabetes (at diagnosis) [16]. In type 2 diabetes, 35-50% of beta cells destroy. Recent studies in diabetic patients have shown that there is a significant decrease in beta cells and three-fold increase in apoptosis. These observations suggest that beta-cells volume has decreased and apoptosis has increased in type 2 diabetes [17].

Chemokines changes in diabetes: As mentioned, apoptosis is the main form of beta cells death in both forms of the disease. The mechanism that leads to beta cells death includes the activation of interleukin-1 and NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) transcription factor. Macrophages are the most dominant immune cells that increase in type 1 diabetes. Increase of CD8+ and CD4+ lymphocytes (cluster of differentiation) and other cells such as NK and beta cells is common also in diabetes [18]. These immune cells are activated and enhance the expression of cytokines such as interleukin-1, TNF-α and INF-γ [19, 20]. Interleukin-1, TNF-α, and INF-γ induce apoptosis of beta cells. In-vitro exposure of beta cells with interleukin-1 and INF-γ cause a similar functional changes in diabetic patients [21, 22]. And early reduction of insulin secretion in response to glucose is mediated by interleukin-1 which leads to decrease in the merging of insulin granules with beta cells membranes. Extended contact with these cytokines induces cell death [1].

In general, interleukin-1 activates NF-κB that affects differentiation of beta cells, homeostasis of endoplasmic reticulum calcium, absorption and activation of immune cells, and beta cells apoptosis. Direct contact of human beta cells with interleukin-1 does not lead to apoptosis, but when combined with INF-γ it leads to apoptosis in 50% of these cells [1]. That means interleukin-1 and INF-γ have a synergistic effect. Increased glucose enhances production of interleukin-1 in beta cells in Langerhans

islets. In another study, it was found that in addition to IL-1, IL -8 level as well as the activity, expression, and secretion level of normal T cells were higher in diabetic patients than normal people, while IL-10 and eotaxin had little changes [23]. The results of a study showed that INF-γ increased in diabetic patients compared to the control group but no increase was seen in IL-4 [24].

Several other studies showed the relation of IL-8, IP-10, and MCP-1 expression and secretion with diabetes [25, 26].

IL-6 is another cytokine which plays a key role in immunologic and non-immunologic events in most cells and tissues [4]. Studies have proven the role and effect of IL-6 in type 1 and 2 diabetes, obesity and insulin resistance. These studies have demonstrated both protective and pathogenic effects of IL-6. IL -6 has an essential role in destruction of beta cells. Although it requires other cytokines for this effect [27]. But in some species it may have a protective effect. In addition to apoptosis enhancement, IL -6 inhibits the production and release of insulin that in turn gives rise to type 2diabetes [28, 29].

Risks of diabetes, atherosclerosis: As it was said, diabetes is a heterozygous disorder and atherosclerosis is its risk factor; it has been almost proved that inflammation has an important role in atherosclerosis. Leukocyte infiltration into the vessel wall is involved in all stages of this disease. Evidences show that chemokines such as IL-8 and MCP-1 have an important role in this process by attraction of monocytes inside the arterial wall [30]. Monocytes are the primary inflammatory cells which are found in atherosclerotic plaques [31, 32]. IL-8 mediates the binding of glucose-stimulated monocytes to the endothelium and it has been shown that it is involved in plaque formation of atherosclerosis disease. Therefore, the high incidence of heart disease and atherosclerosis in type 2 diabetic patients may be due to IL-8 [33]. Obesity is associated with increased expression of chemokines in adipose tissue that may leads to the increase of circulating IL-8 concentration. It is said that the expression of IL-8 in adipose tissue and endothelial cells is directly related to glucose and also it has been shown that glucose increases the binding of monocytes to endothelial cells in vitro [34].

SDF-1 is another chemokine; the most active one that affects the migration and trafficking of leukocytes. In type 2 diabetic patients who are genotypically heterozygous for SDF-1, the insulin movement from ancestral cells increases [35, 36]. It has been shown that SDF-1 induces platelet aggregation in patients with atherosclerosis. Previous studies have demonstrated the important role of SDF-1 in angiogenesis of ancestral cells in vascular injuries; this may help to reduce the harmful effects of diabetes [37]. SDF-1 genotype would be useful for detecting cardiovascular risks in diabetic patients.

Diabetic kidney: Another diabetic disorder is diabetic kidney. All studies have shown that the aggregation of macrophages in the kidney is associated with the development of diabetes and kidney damage [38, 39]. This belief has been proven in animal models in which the reduction of macrophages aggregation in the kidney leads to the suppression of diabetes expansion [40]. This point led the researchers to explore which macrophages has a role in this process, and they found that MCP-1 is the main factor in diabetic kidney which causes the aggregation of macrophages, and in fact in response to diabetes, the kidney tissue produces IL-1, MCP-1, and platelet-derived growth factors that induce interstitial fibroblast proliferation [39]. MCP-1 is the special chemokine to attract monocytes, which makes the involvement and activation of monocytes/macrophages in glomerular disease. Mesenchymal cells of humans and rodents can synthesize the MCP-1 in response to various factors related to the glomerular damage, such as IL-1, TNF-α, LDL (low density lipoprotein), interferon, thrombin, and immune complexes [41]. A recent study showed that there is an active MCP-1 in the urine of diabetic and nephropathic patients [42]. Epithelial cells of renal proximal tubules can produce MCP-1 as well, in response to cytokines and urinary proteins [43]. Also high sugar and glycated albumin increase MCP-1 expression by mesenchymal cells and podocytes cells; this increase can be suppressed by NF-κB activation inhibitors [44].

In addition, the use of anti-MCP-1 antibody leads to a decrease in urinary protein excretion, glomerulosclerosis, and glomerulopathy in mice. MCP-1 deficiency reduces tissue accumulation of interstitial myofibroblasts and reduces the deposition of interstitial and glomerular collagen type 4 [41]. However, sometimes MCP-1 levels in diabetics increase without any relation to urinary excretion of albumin or macrophages aggregation or nephropathy.

In other studies it have been shown that TGF-β (tumor growth factor) induces renal hypertrophy or renal fibrosis, and the cytokines such as TNF-α and RANTES (Regulated upon Activation, Normal T-cell Expressed, and Secreted) facilitate and mediate the infiltration of macrophages to the kidney. High expression levels of these chemokines also lead to the interstitial fibrosis and glomerulosclerosis [38, 40].

From the items listed above, one can deduce that inflammatory mechanisms play an important role in both diabetes and its disorders such as atherosclerosis, nephropathy, hypertrophy, and renal fibrosis.

Chemokines expression increases in inflammatory mechanisms and most of them are destructive for pancreatic beta cells; this increase in expression and secretion of chemokines probably leads to diabetes and its disorders.

Authors' Contributions

All authors had equal role in design, work, statistical analysis and manuscript writing.

Conflict of Interest

No conflict.

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