WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 7.421
Volume 7, Issue 12, 366-374 Review Article ISSN 2278 – 4357

INTERLEUKIN-10 GENE POLYMORPHISMS AND CORONARY ARTERY DISEASE- A REVIEW

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Article Received on
29 Sept. 2018,

Revised on 19 Oct. 2018,
Accepted on 09 Nov. 2018

DOI: 10.20959/wjpps201812-12725

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ABSTRACT

Inflammation plays a major role in the pathogenesis of atherosclerotic lesions of vascular walls. This concept, initially promoted by Ross, was confirmed by several lines of evidence in recent years. Components of the inflammatory system were found in the atheromatous plaque, a relation between lipid metabolism, endothelial damage and inflammation was pointed out, and progression or instability of cardiovascular disease is associated with a systemic inflammatory response. These findings directed attention towards interleukin (IL)-10 as one of the most important mediators that physiologically limits and down-regulates inflammation. Indeed, IL-10 proved to have several protective features acting against atherosclerotic disease. Interest in this cytokine was further strengthened by its role in patients with chronic renal failure, in whom a very high level of systemic inflammation is associated with an enormous burden of cardiovascular morbidity.

KEYWORDS: Interleukin-10, cardiovascular disease.

INTRODUCTION

Understanding of the pathophysiology of atherosclerosis has changed markedly over the past few decades. It is now widely accepted that inflammation plays a fundamental role in the genesis and development of atherosclerosis. Inflammatory mechanisms also appear to determine clinical presentation and disease outcome. Atherosclerotic lesions have high concentrations of inflammatory cells (T lymphocytes and activated macrophages) as well as an abundance of pro-inflammatory cytokines [interleukin (IL)-1, IL-6, IL-8, interferon-γ, tumor necrosis factor-α, etc.] that modulate local inflammatory responses. These may also alter plaque stability and facilitate the development of acute cardiovascular events. The role of anti-inflammatory cytokines in this context remains to be studied. IL-10 is an anti-inflammatory cytokine synthesised by T-lymphocytes and macrophages and has other anti-inflammatory effects. IL-10 expression within human atherosclerotic plaques has been demonstrated and animal experiments have shown that low levels of IL-10 lead to the development of extensive and unstable atherosclerotic lesions. Currently available evidence suggests a potential protective role for IL-10 in atherosclerosis.[1]

Coronary artery disease (CAD) is highly prevalent and one of the most important causes of morbidity and mortality in industrialized societies. The underlying process in CAD is atherosclerosis, and it is currently considered a chronic inflammatory disease of the arterial wall. The most severe clinical presentation of this process is an acute coronary syndrome (unstable angina and infarcts [AMI]),[6-8] which occurs secondary to the occlusion of the diseased arteries. Histological study of the atherosclerotic plaques reveals the presence of progressive infiltration and accumulation of lipids, inflammatory cells (monocytes/ macrophages, T-lymphocytes), smooth muscle cells (SMC), and an extracellular matrix in the arterial wall.[2] The identification of the inflammatory cells in the atherosclerotic lesions, as well as the complementary factors, immunoglobulins, cytokines,[3,9] and others, implicates the involvement of the immunological system in atherogenesis. During this inflammatory reaction, a great quantity of cytokines is produced by macrophages and activated T-cells present in the plaque,[3] charged with modulating inflammatory response. This process may alter plaque stability and favor the development of acute events.[3] Nevertheless, the manner in which this local or systemic, or both, immunological response is initiated and propagated to produce or favor the development of atherosclerotic lesions is still not completely clear.

Numerous studies of experimental animals fed with diets rich in cholesterol have shown that immunosuppression causes the development of more extensive and more severe atherosclerotic lesions as compared to controls.[4] In recent years, multiple scientific studies have emphasized the role of the immunological system cells (monocytes, lymphocytes, etc.) and pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, INF-γ, etc.)[5] in the development of atherosclerosis. Nevertheless, there is little evidence available on the potential role of antiinflammatory cytokines in this process. The aim of this article is to review the knowledge currently available concerning the potential protective role of anti-inflammatory cytokines, specifically interleukine 10 (IL-10), in the pathogenesis and development of atherosclerotic lesions.

PHYSIOPATHOLOGY OF ATHEROSCLEROSIS

The development of atherosclerotic lesions is a process that begins in the second or third decades in the life of an individual, and can be divided into various stages through which the composition of the atherosclerotic plaque changes progressively until it acquires the morphology of a mature plaque.[6]

Endothelial dysfunction

The first event in the development of atherosclerosis is the appearance of endothelial dysfunction (ED). The endothelium plays an important part in maintaining the equilibrium of vascular bed function. It has a regulatory role in vasomotor tone by the production of vasodilator substances, such as nitric oxide (NO) and prostacycline (PGI2), and also of vasoconstrictor substances such as endothelin 1 and angiotensin II. It also possesses anti-atherogenic (antiaggregate, anti-adhesive, anti-proliferative and antioxidant) and anti-inflammatory properties, segregating chemoattractant substances from monocytes and lymphocytes, as well as modulators of vascular growth. There are multiple causes of ED that favor the development of atherosclerosis including the presence of elevated modified LDL values (ox-LFL, MM-LDL); free radicals; immunoregulatory substances (TNF-α, IL-1β, LPS); infectious microorganisms (HSV, Chlamydia, CMV, etc.); genetic alterations; elevated serum homocysteine values, and classic risk factors (hypertension, diabetes, smoking). Endothelial dysfunction leads to a loss of the homeostatic functions of the endothelium, resulting in the adhesion of plaques and inflammatory cells (monocytes and lymphocytes to the vascular wall; an increase in endothelial permeability that allows the deposit of modified LDL at the intimal level; a liberation of cytokines and growth factors that produces the

proliferation of smooth muscle cells and the attraction of more inflammatory cells to the altered arterial wall. As a consequence, it also causes perturbation of the thrombolitic-thrombotic equilibrium in the endothelial bed that promotes the development of thrombotic phenomena, such as the abnormal regulation of vasomotor tone secondary to decreased bioavailability of NO, with the subsequent tendency to arterial vasoconstriction.[4,6,8]

Vulnerability of atherosclerotic plaque

Atheromas are dynamic structures where equilibrium exists between the destructive influence of the inflammatory cells and the stabilizing effect of SMC.[9] The latter are responsible for synthesizing extracellular matrix (ECM) proteins, the principal component of the fibrous cover of atherosclerotic plaques that gives the lesion stability.36 In atherosclerotic plaques there is a balance between the processes of synthesis and collagen degradation that are narrowly controlled by the inflammation mediators and regulate the contents of same in atherosclerotic lesions. The vulnerable plaque (that have a tendency to rupture) are characterized by a highly lipidic nucleus, an elevated infiltration of inflammatory cells (macrophages and T-lymphocytes), few SMC, and a thin fibrous cover. The plaque-activated T-lymphocytes produce INF-?, which inhibits the proliferation of SMC and their ability to synthesize collagen. The activated macrophages produce metalloproteinases (gelatinase, stromelysine, and interstitial collagenase) that degrade the ECM proteins, favoring the disruption of plaque, 46 and synthesizing the tissular factor (TF), of the principal activators of the coagulation cascade, which promotes thrombosis of the plaque. These macrophages also induce the apoptosis of the SMC, with a consequent decrease in collagen synthesis and weakening of the fibrous cap, destabilizing the plaque.[9] In addition to the monocytes, the T-lymphocytes are equally attracted to the dysfunctional arterial wall by chemoattractant substances, and they are activated at the wall, initiating the production of more cytokines such as INF-γ, TNF-α; interleukins (IL-1, IL-2, IL-6, IL-8) and growth factors such as GM-CSF that activate the monocytes present in the plaques and favor their proliferation, enabling a local inflammatory response.[8] The result of the interaction of these factors is a progression of the atherosclerotic lesion from its initial state of fat striae to complex atherosclerotic plaque.[9] The rupture or ulceration of the unstable plaque results in the exposure of the procoagulant and prothrombotic surfaces to the blood, causing the activation of platelets and the formation of thrombi, which can trigger clinical complications by occluding the vessel lumen or producing asymptomatic plaque growth. Therefore, in all the different developmental studies of atherosclerotic plaques, signs of chronic inflammation can be noted,

and various physiopathological mechanisms that influence the development, progression, and instability of atherosclerotic lesions have been described.[10]

THE ROLE OF IL-10 IN ATHEROSCLEROSIS

Among the anti-inflammatory cytokines, IL-10 is considered the anti-inflammatory interleukine par excelance. It was originally identified as the inhibitory factor in cytokine synthesis (CSIF), as it inhibits the production of cytokines by T-lymphocytes, particularly IFN-γ, by Th1 cells in the murine systems. Nevertheless, this inhibition is only seen when the macrophages act as antigen presenting cells (APC). Later studies revealed that IL-10 is in fact a cytokine with pleiotropic properties that acts on different types of cells, including thymocytes,81 cytotoxic Tcells, mastocytes, B84 cells, and monocytes-macrophages. 80 IL-10 is principally produced by a lymphocyte subtype CD4+ (Th2) and also in large quantities by macrophages. It is a cytokine with potent anti-inflammatory properties that is capable of inhibiting important functions of these 2 types of cells.76,79 Therefore, it has been described as inhibiting the production of proinflammatory cytokines by macrophages and T85cells, activated by various stimuli. IL-10 has been identified in early and advances atherosclerotic lesions,[11] principally located in the cytoplasm of the macrophages, although it is also located in SMC and the extracellular matrix.[12]

Inflammatory properties of IL-10: action mechanisms

One of the first properties attributed to IL-10 was its capacity to inhibit the synthesis of cytokines. There are many published studies supporting this affirmation. Waal Malefyt et al showed that both human IL10 or its viral recombinant form added to monocyte cultures activated by INF-γ or LPS, or both, as is produced endogenously in response to these stimuli, was capable of inhibiting the production of inflammatory cytokines, including IL-1α, IL-1β, IL-6, IL-8, TNF-α, INF-γ, GM-CSF and G-CSF by the monocytes. Added to these effects, endogenous IL-10 has an auto regulatory effect on it own production, reducing the synthesis of mRNA IL-10 by the activated monocytes. Wang et al 85 showed that it could also act on T-cells, inhibiting the production of IL-2, TNF-β, INF-γ and GMCSF. It also decreased the expression of major histocompatability complex class II molecules (MCH II) by the monocytes/macrophages, and the capacity of these to act as antigen presenting cells, ultimately limiting the specific proliferative antigen response of T-lymphocytes[13] and, therefore, the inflammatory response. Various mechanisms have been proposed for the manner in which IL-10 inhibits the synthesis of pro-inflammatory cytokines. One of the most

studied is the inhibition of the nuclear transcription factor NF-κβ by IL-10 in monocytes and T-cells by the intervention of secondary oxygen free radical messengers.[14] This results in a reduction in the synthesis of pro-inflammatory interleukins, adhesion molecules, growth factors, and chemoattractants of immunological system cells that limit the local inflammatory response in the plaque. This IL-10 action mechanism differs from that of IL-4, another anti-inflammatory interleukine that also inhibits the synthesis of pro-inflammatory factors, but by a process that does not involve NF-κβ but secondary to an increase in mRNA degradation of said molecule.[15] O´Farrel et al proposed as another possible mechanism to explain the anti-inflammatory effects of IL-10 the inhibition of interferon production via the activation of STAT group transcription factors.[16] In a parallel manner, it has been demonstrated that IL-10 can inhibit the expression of pro-inflammatory genes that present areas rich in AU (ARE), such as TNF-α, IL-1α, IL-1β, βGM-CSF, IL-8, and others, destabilizing its mRNA by acting on these ARE mofits. In addition, it has been shown that IL-10 is capable of inhibiting monocyte response mediated by CD40.[17]

CD40L interaction, which appears play relevant role in atherosclerosis.67 Mach et al demonstrated that the in vivo block of this interaction by antibodies in mice subjected to an atherogenic diet limited the size of the atherosclerotic plaques, reduced it lipidic content, T-cells and macrophages, and decreased the expression of adhesion molecules (VCAM-1). Therefore, this experimentsl animal model demonstrates another mechanism by which IL-10 appears to play a protective role by limiting the development of atherosclerotic lesions.[18-22]

CONCLUSIONS

The current knowledge about the physiopathology of atherosclerosis has changed radically from that of the last decades. Today it is generally accepted that inflammation plays a fundamental role in the development and progression of atherosclerotic lesions, leading in the long or short term to the appearance of clinical signs. Nevertheless, the intrinsic mechanism by which this inflammatory response is triggered and develops continues to be clearly understood. The best knowledge of the physiopathological phenomenon underlying the process of atherogenesis will allow new investigative paths to be opened to combat the disease. From this point of view, various studies performed to study the relevance of IL-10 in atherosclerosis suggest that it has a protective role limiting the local inflammatory response, which favors the progression and instability of the atherosclerotic plaque, eventually leading to the development of acute coronary syndromes. This allows us to postulate the possible role

of IL-10 as a therapeutic agent whose exogenous administration restrains the development of lesions and confers stability, improving the clinical course of the patient. IL-10 could also be a new risk marker that allows us to predict plaque instability and its propensity toward complications.

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