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Mini Review

Inflammation and Atherosclerosis

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Abstract

There are many biochemical elements implicated with the inflammation mediators and markers and this review show their identities and their atherosclerotic effects. Cytokines identified as participants in the mechanisms of atherogenesis were first discovered as involved in the process of natural (or innate) and specific (or acquired) immunity, responsible for defending against foreign organisms such as viral or bacterial agents. They are protein hormones produced mainly by mononuclear phagocytes (monocins) in direct response to microbes, or originated from T lymphocytes (lymphocins) when stimulated by antigen, as part of specific immunity. T lymphocytes produce several cytokines that primarily serve to regulate the activation, growth and differentiation of the various lymphocyte populations. Other cytokines derived from the T lymphocyte work primarily in the activation and regulation of inflammatory cells, such as mononuclear phagocytes, neutrophils and eosinophils. Thus, cytokines derived from T lymphocyte are effector molecules of cell-mediated immunity, and are also responsible for communications between the cells of the immune and inflammatory systems.

Keywords: inflammation; atherosclerosis; interleukins; lipoproteins; citokynes

Introduction

Atherosclerotic disease is one of the most important morbidity and mortality in the western world. Its etiology is multifactorial and prophylaxis consists in the identification and control of a set of predisposing factors, called risk factors. Among the risk factors most addressed in the Update of the Brazilian Dyslipidemia Guideline and Prevention of Atherosclerosis-2017 [1] we found the age of the individual, high LDL-cholesterol, smoking, hypertension, diabetes mellitus, low HDL cholesterol and early family history of atherosclerosis in first-degree relatives. Age is considered a risk factor when above 45 years of age in males and 55 years in females, based on consistent epidemiological data on the incidence of coronary artery disease having earlier manifestation in men compared to women. This difference in the incidence of coronary artery disease in relation to sex leads to assumption about the possible role of circulating sex steroids and their influence on the mechanisms involved in the atherogenesis process.

The normal endothelium

Atherogenesis begins with a wide loss of protective functions of the endothelium. In healthy conditions, this layer of cells between the blood and the vascular wall presents selective permeability for macromolecules and lipoproteins, with orientation and stretching in the direction of laminar flow and several redundant mechanisms to maintain an anticoagulant surface [2-5]. The normal endothelium inhibits leukocyte aforeption and infiltration, limits the growth and migration of smooth muscle cells from the middle layer of the vessel and regulates the synthesis of the matrix in the intima in adequate amounts. The first observations of clinical and experimental studies showed that some of the protective mechanisms are easily lost when the endothelial cell layer is exposed to known risk factors for the development of coronary artery disease, resulting in progressive thickening of the intima called atherosclerosis [6-8].

Atheogenesis and inflammation

Numerous pathophysiological observations in humans and animals led to the formulation of the hypothesis of response to injury in the genesis of atherosclerosis, which initially proposed that endothelial denudation was the first step in atherosclerosis [9] and that even in the most recent scientific investigations occupy a prominent place [10,11].

The recent version of this hypothesis emphasizes endothelial dysfunction, more than denudation, as an early stage of atherogenesis. Each characteristic lesion of atherosclerosis represents a different stage of a chronic inflammatory process in the artery and if it is not slowed or becomes excessive, it will result in an advanced and complicated lesion. Possible causes of endothelial dysfunction leading to atherosclerosis include high and

modified LDL-cholesterol in oxidized form, free radicals caused by smoking, hypertension, diabetes mellitus, genetic changes, high concentrations of plasma homocysteine, infections by microorganisms such as chlamydia pneumoniae and combinations of these and other factors. Thus, the different forms of injury increase the adesivity of the endothelium in relation to leukocytes and platelets, as well as their permeability. The lesion also leads the endothelium to have procoagulant properties instead of anticoagulants and to foe vasoactive molecules, cytokines and growth factors (Figure 1).

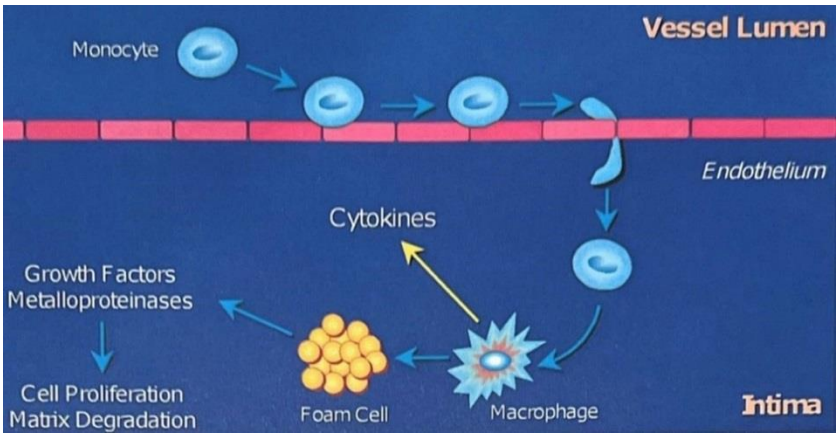

Figure 1: Atherosclerosis is an inflammatory disease.

Atherosclerosis involves endothelial infiltration monocytes and T lymphocytes. Monocytes interact with the endothelial surface, initially adhering lightly (bearing) and then firmly, followed by migration to the sub endothelial space. where they differ in macrophages. These cells release a variety of substances, including cytokines and capture LDL lipoprotein particles in oxidized form, forming into foamy cells. Macrophages and foamy cells secrete growth factors that lead to cell proliferation and matrix production, as well as metalloproteinases that lead to its degeneration. Thus, both macrophages and foamy cells stimulate the growth of the lesion and may contribute to thrombotic events instability (adapted from Ross R.[12]).

If the inflammatory response does not effectively neutralize or remove offending agents, it may continue indefinitely and stimulate the migration and proliferation of smooth muscle cells that become infiltrated in the area of inflammation to form the intermediate lesion [12]. The continuation of the process, if not attenuated, will result in thickening of the arterial wall, which may be associated with a remodeling with vessel dilation, remaining the light unchanged [13]. Considering inflammatory cells, granulocytes are rarely present in any phase of atherogenesis [14], In its place, the inflammatory response is mediated by macrophages originating from monocytes and by specific subtypes of T lymphocytes at each stage of the disease [15,16]. Continuous inflammation results in an increased number of macrophages and lymphocytes, both emigrating from the blood and multiplying within the lesion. The activation of these cells leads to the release of hydrolytic enzymes, cytokines, chemokines and growth factors [17,18]. Thus, cycles of mononuclear cell accumulation, migration and proliferation of smooth muscle cells and formation of fibrous tissue result in additional increase of the lesion that becomes covered by a fibrous capsule coating the lipid nucleus and necrotic tissue. At some point, vessel dilation can no longer compensate for the injury that can then bulge into the light and alter blood flow.

Certain branches, curvatures and arterial bifurcities cause characteristic changes in blood flow, including decreased shear stress and increased turbulence [19]. Considerable evidence suggests impairment of endogenous atheroprotective mechanisms in these sites, where endothelial cells are exposed to changes in blood flow [20]. For example, the absence of normal laminar "shear stress" can reduce local production of nitric oxide derived from the endothelium. This endogenous vasodilator molecule also has anti-inflammatory properties and may limit the expression of adhering molecules. Consequently, the decrease in nitric oxide formation results in loss of the natural protective mechanism and thus the change in flow can induce the increase of specific molecules responsible for the adhering of monocytes and T cells [21].

Cytokines identified as participants in the mechanisms of atherogenesis were first discovered as involved in the process of natural (or innate) and specific (or acquired) immunity, responsible for defending against foreign organisms such as viral or bacterial agents. They are protein hormones produced mainly by mononuclear phagocytes (monocins) in direct response to microbes, or originated from T lymphocytes (lymphocins) when stimulated by antigen, as part of specific immunity. T lymphocytes produce several cytokines that primarily serve to regulate the activation, growth and differentiation of the various lymphocyte populations. Other cytokines derived from the T lymphocyte work primarily in the activation and regulation of inflammatory cells, such as mononuclear phagocytes, neutrophils and eosinophils. Thus, cytokines derived from T lymphocyte are effector molecules of cell-mediated immunity, and are also responsible for communications between the cells of the immune and inflammatory systems. The discovery of certain cytokines in a first phase in the years 1950 to 1970, was associated with the investigation of infectious disease and about immune responses induced by antigens. The second phase of the research on cytokines covering basically the 1970s involved the partial purification and characterization of many individualized cytokines.

In this period, it was first appreciated that several effects mediated by cytokines, studied by different researchers, were often mediated by the same molecule. For example, interferon-gamma (IFN-y) was discovered by virologists as an antiviral protein derived from the T lymphocyte, and independently discovered by immunologists as an activator of macrophage functions. Similarly, interleukin-1 (IL-1) was discovered as an endogenous mediator of fever (a pyrogen) produced in response to bacterial infections, having been similarly discovered by immunologists as a co-stimulator of T lymphocyte activation. An important hypothesis generated at this time was that cytokines were synthesized mainly by leukocytes, and that they acted primarily on other leukocytes, and thus could be called interleukins. For example, a co-stimulator of T lymphocyte activity derived from macrophages was designated IL-1, and a growth factor of T lymphocytes was called interleukin-2 (IL-2). However, the cytokine preparations available at the time were often impure and many existing anticytokine antibodies were not exclusively specific to a cytokine. The golden period of cytokine research began in the 1980s, characterized by molecular cloning and expression of individual cytokine molecules, and by the production of absolutely specific, often monoclonal neutralizing antibodies. These reagents allowed a definitive identification of the structure and properties of

individualized cytokine molecules. The 1980s were more than a culmination of early work because, moreover, many new cytokines were discovered, and because many previously unexpected properties of known cytokines were revealed. As a result of these studies, there is currently [22] a large mass of information about the origins and biological activities of certain cytokines. Although they constitute a varied group of proteins, there are a number of properties shared by these molecules. In summary, in natural immunity, microbial products directly stimulate mononuclear phagocytes, so that they secrete their cytokines. In contrast, cytokines derived from T lymphocytes are produced primarily in response to the specific recognition of foreign antigens. However, these distinctions are not absolute, because cytokines produced by a cell type often regulate the synthesis of cytokines from other cells.

Cytokines, like other polypeptide hormones, initiate their action by binding to specific receptors on the surface of target cells. The target cells can be: the same cell that secretes cytokine (autocrinae action), a nearby cell (paracryna action), or a distant cell, acting in this case as authentic circulating hormones (endocrine action). For many target cells, cytokines act as regulators of cell division, that is, as growth factors.

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None.

Conflicts of interest

No conflict of interest.

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