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REVIEW ARTICLE

Atherosclerosis and Cancer; A Resemblance with Far-reaching Implications

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Atherosclerosis and cancer are chronic diseases considered two of the main causes of death all over the world. Taking into account that both diseases are multifactorial, they share not only several important molecular pathways but also many ethiological and mechanistical processes from the very early stages of development up to the advanced forms in both pathologies. Factors involved in their progression comprise genetic alterations, inflammatory processes, uncontrolled cell proliferation and oxidative stress, as the most important ones. The fact that external effectors such as an infective process or a chemical insult have been proposed to initiate the transformation of cells in the artery wall and the process of atherogenesis, emphasizes many similarities with the progression of the neoplastic process in cancer. Deregulation of cell proliferation and therefore cell cycle progression, changes in the synthesis of important transcription factors as well as adhesion molecules, an alteration in the control of angiogenesis and the molecular similarities that follow chronic inflammation, are just a few of the processes that become part of the phenomena that closely correlates atherosclerosis and cancer. The aim of the present study is therefore, to provide new evidence as well as to discuss new approaches that might promote the identification of closer molecular ties between these two pathologies that would permit the recognition of atherosclerosis as a pathological process with a very close resemblance to the way a neoplastic process develops, that might eventually lead to novel ways of treatment.

Key Words: Atherosclerosis, Cancer, Inflammation, Oxidative stress, Proliferation, Angiogenesis.

Introduction

Nowadays it is well established that although industrial development has represented a substantial progress for mankind, it has also promoted a notable increase in chronic pathologies including cardiovascular disease and cancer, both considered among the top causes of morbidity and mortality around the world (1–3). In this respect, atherosclerosis and cancer considered diseases that arise from multiple factors are consolidated along different stages in their development where different factors might be related to their origin, including; genetic, nutritional, psychosocial and environmental conditions (Figure 1). Cardiovascular diseases are primarily a result of complications promoted by atherosclerosis, defined as a chronic and progressive inflammatory state caused by and immune response correlated to an uncontrolled proliferation of vascular smooth muscle cells, endothelial cells and *in situ* macrophages (4,5). As an outcome, the progression along the different stages of the disease commonly ends in a thrombotic process that might lead to myocardial infarction or stroke (6–12). Interestingly, the development of cancer as a multifactorial disease also takes place through an alteration of molecular events catalyzed by the same factors previously mentioned for atherosclerosis and where their initiation and evolution could take years to develop (13). Therefore, although these two pathologies have been in the past considered to be unrelated, by performing a thorough analysis of the molecular manifestations in both diseases, important similarities have become clear showing evidence of a tight relationship (14,15). This analysis is particularly relevant when the identification of potential targets for therapeutic use comes into play.

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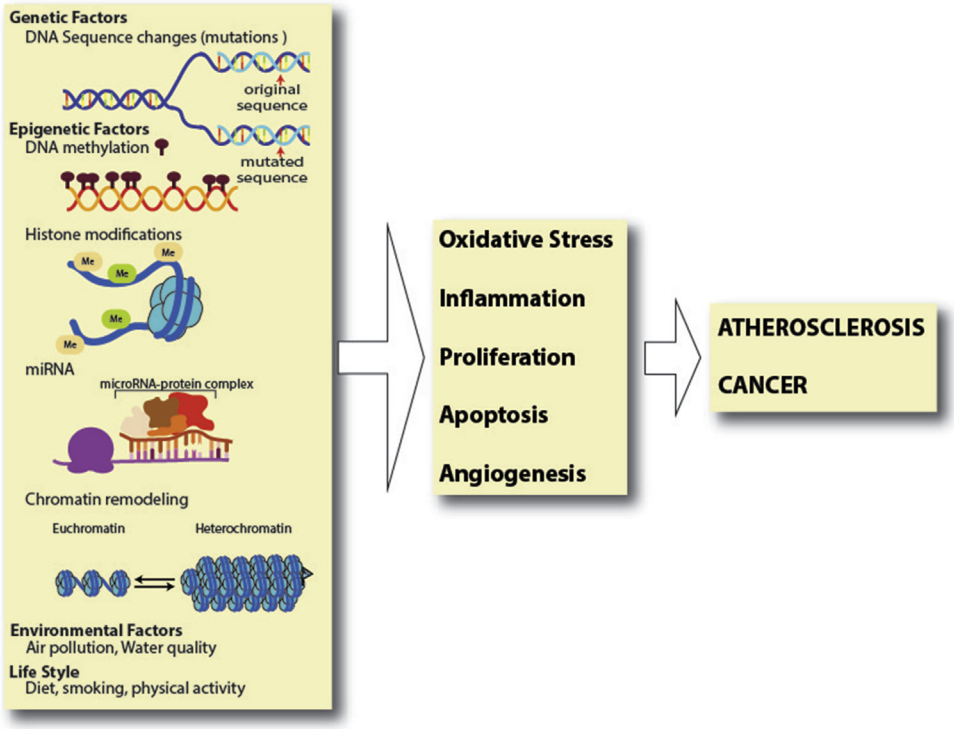

Figure 1. Factors involved in the early stages and development of atherosclerosis and cancer. Among the important similarities found in both multifactorial diseases, the identification of changes in the DNA sequence in close correlation to epigenetic modifications, can be transmitted across generations in relationship with key environmental factors. These external factors can by themselves start or potentiate anomalous processes evidenced in the long-term as oxidative stress, inflammation, aberrant apoptosis, uncontrolled cell proliferation and angiogenesis.

One of the most important characteristics in both diseases is uncontrolled cell proliferation favoring the establishment and severity of lesions in the later stages of both diseases (16,17). Deregulation of cell proliferation in many cases promoted by an oxidative stress condition, allows the development of the atherosclerotic plaque and also the establishment of different types of cancer (14,17,18). Other alterations that contribute to the development of both diseases are related to changes in cell adhesion molecules, an altered expression of proteases linked not only to the formation of plaque but also to tumor invasion, metastasis initiation (15) and the modulation of angiogenesis, an important process in both pathologies directly related to the expansion of the atherosclerotic plaque and tumor formation (17).

Inflammation

The process of inflammation is recognized as the initial response by cells to harmful stimuli and induced by the migration of leukocytes from the blood to a damaged tissue. The stimulus triggers a cascade of biochemical events that are propagated and enforce the inflammation response involving the local microvascular system, including the immune system, the connective tissue and parenchymal cells within the microenvironment of a damaged tissue (19–21). The inflammatory process during atherogenesis is mediated by monocyte migration to the vessel wall, a key event in the growth of an atherosclerotic lesion. Through differentiation, monocytes establish themselves as macrophages and eventually as lipid-rich foam cells (22,23). Macrophages derived from monocytes recognize and internalize oxidized lipoproteins via scavenger receptors where lipid-rich foam cells contribute to the development of the necrotic nucleus, a key element of the vulnerable atherosclerotic plaque. At a molecular level, the presence of cholesterol crystals also activates the inflammasome releasing IL-1β cytokines considered important mediators of inflammation (24–27) (Table 1) (Figure 2). On the other hand, monocyte-derived macrophages often found as host cells in tumors, operate as components of an inflammatory response that builds a supporting stroma (49) that takes part in tumor growth (27,50,51). These processes carried out by activated neutrophils, monocytes, endothelial cells and macrophages provide the pro-inflammatory response of damaged tissues (20,27,52).

In cancer, inflammation is manifested by tissue infiltration of inflammatory cells that include macrophages, B and T lymphocytes, natural killer cells, neutrophils, and