Inflammation in the molecular pathogenesis of cancer and atherosclerosis

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ABSTRACT

Chronic inflammation, atherosclerosis and cancer are leading causes of death in industrialized society. Epidemiological studies have shown that chronic inflammation predisposes individuals to certain cancers, while anti-inflammatory and anti-oxidant agents may protect against cancer development and metastasis. Inflammation supports the different phases of cancer development through the inflammatory molecules produced by infiltrating immune cells, resident stromal cells and even cancer cells. Although atherosclerosis has been considered to be multi-factorial disease, in which genetic and environmental factors have been implicated, inflammation also significantly contributes to plaque formation and progression, and to stenosis of atherosclerotic lesions. Major nuclear transcription factors and molecular mediators of inflammation that induce altered cell expression of adhesion molecules, proteases, and growth factors are common factors in the microenvironment leading to disease development and progression of both atherosclerosis and cancer. Important pathogenic pathways on atherosclerosis and cancer follow endothelial cell dysfunction and the activation of the hemostatic system and angiogenesis via inflammation-dependent mechanisms represent important features of this dysfunction. Therefore, novel target-oriented therapies affecting altered mechanisms of inflammation, angiogenesis and tissue proliferation may similarly inhibit atherosclerosis and cancer. Main treatment strategies include reducing oxidative stress; inhibiting chemokine, cytokine, and growth factor cell signal transitivity; down-regulating excess matrix digestion; inactivating nuclear factor-kappa B signal pathway, and interfering with cell cycle regulation.

RESÚMEN

Las enfermedades inflamatorias crónicas, la arteriosclerosis y el cáncer están entre las primeras causas de muerte en la sociedad industrializada. Estudios epidemiológicos han demostrado que las enfermedades inflamatorias crónicas predisponen a la aparición de ciertos cánceres, mientras que algunos agentes antiinflamatorios y antioxidantes protegen frente al desarrollo del cáncer y su metástasis. La inflamación facilita diferentes fases del desarrollo del cáncer, a través de moléculas producidas por células del sistema inmunitario infiltrantes de los tumores, por células del estroma tumoral e, incluso, por las propias células tumorales. Aunque la arteriosclerosis se ha considerado como una enfermedad de etiología multifactorial, en la que están implicados factores genéticos y ambientales, la inflamación también contribuye a la formación y el desarrollo de la placa e, incluso, la estenosis vascular en las propias lesiones arterioescleróticas. Los principales factores nucleares de transcripción y mediadores moleculares de la inflamación que alteran la expresión de moléculas de adhesión, proteasas y factores de crecimiento, son factores habituales del microambiente que conduce al desarrollo de la arteriosclerosis y el cáncer. De hecho, sus rutas patogénicas más importantes dependen de alteraciones del endotelio vascular y la activación del sistema hemostático y la angiogénesis a través de mecanismos inflamatorios. Por consiguiente, los nuevos tratamientos orientados a dianas moleculares específicas, que afectan a mecanismos alterados de inflamación, angiogénesis y proliferación tisular, podrían inhibir igualmente la arteriosclerosis y el cáncer. Entre las principales estrategias a considerar están la disminución del estrés oxidativo, la inhibición de algunas quimiocinas, citocinas y transductores intracelulares de factores de crecimiento, la regulación negativa de la digestión de matriz extracellular, la inactivación del factor nuclear kappa B y la interferencia de reguladores del ciclo celular.

Chronic inflammation: tissue recovery versus disease progression

Chronic inflammation has been implicated in the pathogenesis of autoimmunity, atherosclerosis, and cancer. Inflammation is the initial response of the body to harmful stimuli and is achieved by the increased movement of plasma and leukocytes from the blood into the injured tissues. A cascade of biochemical events propagates and strengthens the inflammatory response, involving the local microvascular system, the immune system, the connective tissue and parenchymal cells within the microenvironment of injured tissue. The recovery of the acute phase of inflamed.Inflamación en la patogenia molecular del cáncer y la arteriosclerosis

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There is a poorly understood, but longstanding, observation and epidemiologic link between inflammation and cancer. It was in 1863 when Rudolf Virchow reported for the first time leukocytes in neoplastic tissues and made a connection between inflammation and cancer. He suggested that the “lymphoreticular infiltrate” reflected the origin of cancer at sites of chronic inflammation. Recent estimates suggest that about 20% of all human cancers are caused by chronic infection or chronic inflammatory states. Prominent examples for this phenomenon are the strong associations between chronic gastritis, hepatitis, prostatitis and colitis and increased risk of primary carcinoma in the corresponding organ. Almost 30% of people who suffer from inflammatory bowel disease will develop colorectal cancer, and around 18% of people who suffer from inflammation of the prostate will develop prostate cancer. Similar numbers exist for the development of liver cancer from hepatitis. Therefore, the development of cancer cells from chronic inflamed tissues is a major problem in the world.

It has been suggested that chronic inflammation supports the different phases of tumor development, i.e. initiation, promotion and progression. Inflammatory molecules that are produced by resident tissue cells and infiltrating defense cells, including macrophages, lymphocytes, natural killer cells, neutrophils, dendritic cells and eosinophils, in part provide this support. For instance, Helicobacter pylori-induced gastritis is associated with gastric carcinoma and gastric B-cell lymphoma. Chemokines induced by H. pylori attract B-cells to the mucosa where they become targets for the carcinogenic process that can occur during the chronic inflammatory process. However, biochemical processes in chronic inflamed tissues that are responsible for the development of cancer are still unclear. The transformation of chronic inflamed tissue into cancerous tissue is a process comprising of at least three stages. The first stage is the
Inflammation in atherosclerosis

Atherosclerosis has been viewed to reflect the deposition of lipids within the vessel wall of medium-sized and large arteries. Despite the fact that the association between LDL cholesterol and atherosclerosis has been evident for at least three decades, our understanding of exactly how LDL precipitates atherosclerosis is still unclear. Now this concept has changed and it is assumed that a complex endothelial dysfunction induced by elevated and modified low-density lipoproteins, free radicals, infectious microorganisms, shear stress, hypertension, toxins after smoking, or combinations of these and other factors, can lead to a compensatory inflammatory response. Endothelial dysfunction is characterized by decreased nitric oxide synthesis, local oxidation of circulating lipoproteins and their entry into the vessel wall. Intracellular ROS, similarly induced by the multiple atherosclerosis risk factors, lead to enhanced oxidative stress in vascular cells and further activate intracellular signaling molecules involved in gene expression. Upregulation of cell adhesion molecules facilitates adherence of leukocytes to the dysfunctional endothelium and their subsequent transmigration into the vessel wall. The evolving inflammatory reaction is instrumental in the initiation of atherosclerotic plaques and their destabilization, and, therefore, inflammation is considered to play an important role in the progression of atherosclerosis and artery plaque destabilization, converting a chronic process into an acute disorder with ensuing thrombo-embolism.

During atherosclerosis, T cells and macrophages infiltrate the vessel wall triggered by endothelial dysfunction, and locally interact in a synergistic manner. Auto-reactive T cells recognize oxLDL, heat shock proteins and share microbial antigens by molecular mimicry and release proinflammatory cytokines. Macrophages on stimulation by T-cell-derived cytokines and transformation into foam cells after uptake of oxLDL, also secrete matrix metalloproteases predisposing the plaques to subsequent rupture. Plaque-associated macrophages, moreover, are an important cellular source of tissue factor. Finally, on plaque rupture, tissue factor-rich plaque material gets in contact with the circulation and activates the extrinsic coagulation pathway.

The fact that proinflammatory cytokines are instrumental in the progression of atherosclerosis, as revealed by numerous animal studies and suggested by their expression in atherosclerotic human plaques, opens the therapeutic prospect of targeting cytokine expression and cytokine-signaling proteins. In experimental settings, blockade of IFN-gamma and TNFalpha ameliorates atherosclerosis development. Pentoxifylline—a TNF antagonist—inhibits plaque formation in apoE−/− mice by shifting T cells toward T-helper-2 differentiation, characterized by increased production of immune suppressant cytokine IL-10. As another approach, inhibitors of matrix metalloprotease activity and suppressors of cytokine signaling proteins can also ameliorate cytokine-induced chronic inflammation in the vessel wall. Current therapeutics effective in preventing atherosclerosis and stroke
such as statins, acetylsalicylic acid and renin-angiotensin system inhibitors may also exert part of their effects by modulating inflammatory responses in the vessel wall.

**Inflammation in the pathogenic intersection between atherosclerosis and cancer**

Atherosclerosis and cancer are the most important source of morbidity and mortality in the developed world. Both chronic diseases appear to be multi-staged in their progression, with genetic, nutritional, psycho-social, environmental and viral factors influencing their appearances. However, major molecular inflammatory pathways and their nuclear transcription factors, such as NFκB, have a significant role in the pathogenesis and progression of both atherosclerosis and cancer. For example, alteration of cytokine-dependent cell adhesion molecules, such as integrins and cadherins, have been linked to plaque formation and thrombosis, as well as to cancer invasion and metastasis. Altered expression of proteases associated with thrombolysis has also been implicated in atherosclerotic plaque expansion and hemorrhage, and in the pathogenic process of cancer invasion and metastasis. Ligand-growth factor receptor interactions (tyrosine kinases) have been associated with early atherosclerotic lesions, as well as with cancer development and spread. Moreover, pro-angiogenic inflammatory factors have recently been linked to plaque expansion and restenosis of atherosclerotic lesions as well as cancer cell spread from primary tumors and metastatic tumor growth.\(^{15-17}\) On this basis, as we move forward in our understanding of these diseases, efforts are increasingly focused on the inflammatory mechanisms underlying disease activation, that precipitate major clinical manifestations of both atherosclerosis—heart attack and stroke—, and cancer,—primary tumor invasion and distant metastasis—. Moreover, novel target-oriented therapies affecting altered mechanisms of inflammation, angiogenesis, matrix remodeling and tissue proliferation have similarly inhibited atherosclerosis and cancer. Main treatment strategies in clinical development include reducing oxidative stress; inhibiting chemokine, cytokine, and growth factor cell signal transmit; down-regulating excess matrix digestion; inactivating nuclear factor-kappa B signal pathway, and interfering cell cycle regulation.

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