Should atherosclerosis be considered a cancer of the vascular wall?

Jian-Jun Li*, Run-Lin Gao

Department of Cardiology, Fu Wai Hospital, Chinese Academy of Medical Science, Peking Union Medical College, 167 Bei Li Shi Road, Beijing 100037, PR China

Received 3 November 2004; accepted 5 November 2004

Summary Atherosclerosis and cancer are the leading causes of death in industrialized society. Although atherosclerosis has been considered to be multi-factorial disease in which genetic, environmental, and other factors have been implicated, the gaps remain in our knowledge of the etiopathogenesis as well as features of atherosclerosis. However, Numerous data suggested that the some characteristics of atherosclerosis were similar as a cancer. Should atherosclerosis be considered a cancer of the vascular wall?

A large number of data have showed that both cancer and atherosclerosis are characterized by a local increase in tissue mass that may be hard to control, and appears that the disease state of atherosclerosis and cancer might share a common etiology. More recently, a series of molecular markers and gene-regulating pathways have been associated with disease development and progression common in both atherosclerosis and cancer. These chronic diseases appear to be multi-staged in their progression, with genetic, nutritional, psycho-social, environmental and viral factors influencing their appearances. In addition, the experimental and clinical studies on atherosclerosis and cancer have also showed common pathogenic mechanisms of clotting system.

Furthermore, emerging novel therapeutic strategies have similarly targeted both atherosclerosis and cancer, including reducing oxidative stress; inhibiting chemokine, cytokine, and growth factor cell signal transmit; down-regulating excess matrix digestion; inactivating nuclear factor-kappa B (NF-κB) signal pathway, interfering cell cycle regulation, applying radiation treatment for controlling expansion and invasion of both atherosclerosis and cancer.

Based on those previous observations, a hypothesis has been proposed that atherosclerosis and cancer may represent variants of a common disease entity. In the other word, atherosclerosis may be just a cancer of vascular wall. In the future, it is likely that the shared features of atherosclerosis and cancer will not only become clinically significant but also stimulate therapeutic strategies for clinical applications.

© 2004 Elsevier Ltd. All rights reserved.

Introduction

Cardiovascular diseases are the leading cause of morbidity and mortality in industrialized coun-
tries. Most cardiovascular disease result from complications of atherosclerosis, which is a chronic and progression inflammatory condition characterized by excessive cellular proliferation of vascular smooth muscle cells, endothelial cells and inflammatory cells leading to occlusive vascular disease, such as myocardial infarction and
stroke. Cardiovascular diseases derived from the complications of atherosclerosis account for nearly one million deaths each year in the United States [1]. Although atherosclerosis has been recognized as a multi-factorial trait resulting from the effect of a combination of environmental and genetic factors, the gaps remain in our knowledge of the etiopathogenesis as well as features of atherosclerosis [2].

Cancer is the second leading cause of death in the United States, with more than one half million Americans dying from this disease annually [3]. A most important feature of cancer is excessive cellular proliferation that is hard to control. However, atherosclerosis and cancer were considered, for many years, to have completely unrelated pathogenesis and disease progression features characterized by separate therapeutic strategies. Therefore, defining the etiology of these diseases, through clinical, epidemiological, metabolic, animal and cellular studies have long-term been the major focus of the researches and physicians.

Pathogenesis

In fact, the atherosclerosis and cancer are the consequences of complex interactions between genetic and environmental factors, and are the leading causes of death in westernized society. As early as 1980s, a tumorigeneic theory of atherosclerosis or a mutation theory hypothesis was proposed, indicating that the disease state of atherosclerosis and cancer might share a common etiology, and these chronic diseases appear to be multi-staged in their progression, with genetic, nutritional, psycho-social, environmental and viral factors influencing their appearances [4–6].

It is well-known that advanced stages of both cancer and atherosclerosis are characterized by a local increase in tissue mass that may be hard to control. Actually, excessive cell proliferation contributes to the pathology of human disease with a high health and socio-economic impact, including cancer and vascular occlusive disease, such as atherosclerosis, in-stent restenosis, transplanted vasculopathy, vessel bypass graft failure. This increase in tissue mass can be attributed to oxidation-sensitive modification of cell cycle-related events, including cellular proliferation, differentiation, and apoptosis, which could be secondary to alteration in the activity of tumor suppressor gene and oncogene products [7]. Recent advances in the understanding of the molecular networks governing the hyperplastic growth of tumors and vascular obstructive neointimal lesions have provided perspectives for preventive and therapeutic strategies against these disorders [8]. As the cell cycle-related events is a final common pathway in cell proliferation, the inhibition of the cell cycle have emerged as logical targets for the treatment and prevention of excessive cell proliferation including atherosclerosis and cancer.

Mammalian cell proliferation requires the activation of several cyclin-dependent protein kinases (CDKs). Posttranslational activation of CKDs is a complex process that involves their association with regulatory subunits called cyclins [8,9]. The activity of CDK/cyclin holoenzymes is negatively regulated through their interaction with members of the CDK family of inhibitory proteins (CKIs). Moreover, over 50 low molecular weight pharmacological CDK inhibitors that target the ATP-binding pocket of the catalytic site of CDKs have been identified. Tissue remodelling in the cardiovascular system is a regulated balance between pro- and anti-proliferative molecules, and this balance becomes derailed in cardiovascular pathology [8]. Therefore, usefulness of the pharmacological and gene therapy strategies against CDK/cyclins in animal models and clinical trials of cancer and cardiovascular disease has been demonstrated to be a promising approach.

Recently, a large number of published data have suggested that atherosclerosis and cancer similarly develop from a clone proliferation of altered cells at the sight of local tissue injury, inflammation and genomic instability [10,11]. A series of molecular pathway have in common a significant role in the pathogenesis and progression of atherosclerosis and cancer. Shared mechanisms implicated for both disease including oxidative stress and the cellular damage that results from it, toxic metabolites produced by cigarette smoking, and increase dietary intake. Atherosclerosis may begin when an injury or infection mutates or transforms a single arterial smooth muscle cell in the progenitor of a proliferative clone, similar to the most widely held carcinogenesis theory [12,13]. Cell proliferation regulatory pathway has also been associated with plaque progression, stenosis, and restenosis after angioplasty and with cancer progression [10,13,14]. Alterations in adhesion molecules have been linked to plaque formation and thrombosis and to tumor invasion and metastasis. Altered expression of proteases associated with thrombolyis has been implicated in atherosclerotic plaque expansion and hemorrhage and in the invasion and metastasis of malignant neoplasmas [11]. Ligand–growth factor interactions have been associated with early atherosclerotic lesions and with cancer
development and spread. Nuclear transcription factors have been associated with progression of both diseases [14]. Angiogenesis modulators have been linked to plaque expansion, restenosis of atherosclerotic lesions and to local metastatic tumor expansion.

In addition, the experimental and clinical data on atherosclerosis and cancer have showed common pathogenic mechanisms of hemostatic/clotting system [15]. It is suggested that common pathway follow dysfunction of the vascular endothelium. The activation of the hemostatic system and the overexpression of cytokines and adhesion molecules by the endothelial cells represent important features of this dysfunction. These mechanisms can be responsible for progression of both diseases and explain the higher incidence of thromboembolic events in cancer patients, the occurrence of similar laboratory findings and the effect of many drugs on the course of the two diseases [9,15]. Those data confirmed that atherosclerosis and cancer share common mechanisms, and might stimulate further clinical trials on the use of drugs active on the hemostatic system in both atherosclerosis and cancer patients.

Thus, atherosclerosis and cancer may represent variants of a common disease entity, sharing a common etiopathogenesis.

**Therapeutic strategies**

Moreover, emerging novel therapeutic strategies have similarly targeted both conditions, including reducing oxidative stress by eliminating cigarette smoking, reducing dietary fat intake and administering antioxidant therapeutics [16], using anti-inflammatory agents to reduce chemokine, cytokine, and growth factor cell signalling [17], employing anti-proliferative drugs targeting growth factor receptors to reduce cell proliferation [18], for example, postangioplasty restenosis in coronary and carotid atherosclerosis, reducing excess matrix digestion caused by excessive metalloprotease stromal digestion; reducing nuclear factor-kappa B (NF-κB) signalling with proteasome inhibitors, interfering cell cycle regulation [19–21], and anti-angiogenesis strategies designed to delay atherosclerotic plaque expansion and cancer invasion and metastasis. In addition, radiation treatment was also introduced to prevent restenosis after angioplasty and stent placement, although early published reports indicate that efficacy of this approach has been needed to be proven for long-term. Interestingly, radiation treatment can also cause atherosclerosis in irradiated vessels similar to the development of second malignance in sites of irradiation for previous tumors and benign condition.

In addition, the increased biological understanding of the participation of cell cycle events and targeting these events may enable to attenuate or prevent some of the complication of atherosclerosis and cancer. Antioxidant strategies, RNA synthesis inhibitors such as mithramycin, and gene therapeutic approaches with anti-sense oligonucleotides against candidate targets such as cyclin-dependent kinase/cyclin holoenzymes, members of the cyclin-dependent kinase family of inhibitory proteins, tumor suppressors, growth factors and transcription factors that control cell cycle progression are some of the promising strategies [7].

**Arguments**

*Should atherosclerosis be considered a cancer of the vascular wall or a variant of cancer?* Evidence in support of the hypothesis included the disease process, the following biomarkers, predicative factors, and pathogenic pathways; genetic predisposition plays a significant role; oxidative stress is a major cause of disease development; sex hormone levels appear to modify the disease risk; cigarette smoking, tobacco products, and possibly high dietary intake increase disease incidence; disease has a predilection for sites of predisposed tissue injury; chronic inflammation is a disease mediator; local DNA microsatellite instability predisposes to disease development; cell proliferation and clonal expansion of the lesion are a shared feature; the tumor growth factor-β signalling pathway plays a major role as does signalling from other peptide growth factors; cell adhesion molecules and the Wnt-β–catenin signalling pathway are important contributors; matrix digestion and clotting system disturbances are common to both conditions [9,10]; the NF-B signalling pathway is activated in both conditions; angiogenesis plays a pivotal role in disease development and progression; and novel therapeutic strategies including growth factor and/or receptor, cell cyclin-dependent kinases, transcription factors inhibitors, and anti-angiogenesis drugs or biological approaches may prove efficacious for treating both diseases [22].

However, many factors that may be not in agreement with a unified disease hypothesis that
Atherosclerosis is just a cancer of vascular wall. For example, the lake of a proven impact on cancer incidence for the typical atherosclerosis risk factors such as hypertension, diabetes, and hyperlipidemia; the desirable impact of angiogenesis on progression of both conditions; the lack of proof that infections, a major cause of cancer development, are similarly causative for atherosclerosis; and the many differences in clinical presentation, physical findings, laboratory and radiological studies, and response to therapy for the two disorders.

Clinical implications

Despite these obvious differences, however, modern research using molecular technique has now revealed irrefutable major similarities in the pathways of development and progression for atherosclerosis and cancer. This has led several investigators to conclude that they may represent variants of a single disease entity [9,10].

In general, the increased biological understanding of the participation of cell cycle events and targeting these events may enable to attenuate or prevent some of the complication of atherosclerosis and cancer. In the future, it is likely that the shared features of atherosclerosis and cancer will only become clinically significant if emerging therapeutic strategies such as the new anti-inflammatory agents, proteasome inhibitors, and cell cycle and angiogenesis regulators prove simultaneously successful in blocking the development and progression of the both diseases.

Conclusion

Atherosclerosis and cancer are the leading causes of all deaths in industrialized society. Numerous data suggested that the features of atherosclerosis were similar as a cancer including a feature of local increase in tissue mass, hard to control, a common etiology, especially in expression of molecular markers and activation gene-regulating pathways, pathogenic mechanisms of clotting system. Moreover, emerging novel therapeutic strategies have similarly targeted both atherosclerosis and cancer, including reducing oxidative stress; inhibiting chemokine, cytokine, and growth factor cell signal; down-regulating excess matrix digestion; inactivating nuclear NF-κB signal pathway, interfering cell cycle regulation, applying radiation or gene therapy treatment for controlling expansion and invasion of both atherosclerosis and cancer. Therefore, atherosclerosis may be just a cancer. In the future, it is likely that the shared features of atherosclerosis and cancer will not only become clinically significant but also stimulate therapeutic strategies for clinical applications.

References


