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Transforming Growth Factor-β Expression as Biomarker of Atheroma Development: A Mini Review

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Abstract

Atherosclerosis is a disease of the arterial wall that is modulated by the inflammatory balance. Transforming growth factor [TGF] type β1, β2, and β3 are cytokines with broad activities on cells and tissues in the cardiovascular system and have been proposed to play a role in the pathogenesis of atherosclerosis. This cytokine is a major orchestrator of the fibroproliferative response to tissue damage. In fact, besides its effects on cell cycle regulation and survival/apoptosis in many cell types including endothelial and smooth muscle cells, TGF-β is an important anti-inflammatory cytokine. Although we might be tempted to label TGF-β as either an "atheroprotective" or "atherogenic" factor, TGF-β is more likely to play a central role in both normal and pathological vascular repair.

Keywords: Transforming growth factor-β; Atherosclerosis

Introduction

Atherosclerosis has been designed as an inflammatory disease of the arterial wall [1]. In fact, endothelial activation by oxidized lipoproteins plays an important role in the initiation of the atherosclerotic lesion through increased adhesion of mononuclear cells and their recruitment into the vascular wall [1]. It was demonstrated that the recruited inflammatory cells induce inflammatory cytokines and chemokines expression, enhancing lesion progression. Therefore, accumulation of lipids and inflammatory cells and production of extracellular matrix by the vascular smooth muscle cells [VSMC] participate in the formation of advanced lesions. The inflammatory response also determines plaque composition and, as a result, strongly contributes to the occurrence of plaque complications that are responsible for clinically severe acute ischemic syndromes [2]. Moreover, many results suggest that anti-inflammatory cytokines with deactivating properties on macrophages and/or T cells are produced within the atherosclerotic lesion [3-6]. Among the most potent known anti-inflammatory factors is transforming growth factor-beta [TGF-β], which suppresses inflammation in a variety of cell types. In VSMC, TGF-β suppresses inflammatory markers such as inducible nitric-oxide synthase and interleukin 6 via the SMAD3 pathway [7]. The role of TGF-β and SMAD signalling in atherogenesis and vascular inflammation has previously been reviewed by Feinberg and Jain [8]. In adult human VSMC, TGF-β potently inhibits migration and proliferation of VSMC [9]. In addition, reduced TGF-β activity/signalling is a feature of atherosclerosis, as evidenced by low TGF-β activity in vessel walls and low levels of circulating TGF-β in the plasma of affected patients.

Transforming Growth Factor-β and Atherosclerosis

In this mini-review, we have as objective to examine the role of TGF-β in the pathogenesis of atherosclerosis. In fact, besides its effects on cell cycle regulation and survival/apoptosis in many cell types including endothelial and smooth muscle cells [9], TGF-β plays a relevant role in local inflammatory reaction [10]. According to the literature, TGF-β was first reported to be a deactivating factor of macrophages and also has potent anti-inflammatory effects in vitro on vascular cells reducing cytokine-induced expression of chemokines and adhesion molecules [11-13]. Additionally, atherosclerotic lesions of anti-TGF-β-treated mice showed increased infiltration of inflammatory cells, particularly macrophages, and decreased collagen content compared with the lesions of control mice, suggesting a switch toward an unstable plaque phenotype. These plaque features are compatible with the deactivating properties of TGF-β on inflammatory and vascular cells [10] and with the role of TGF-β in matrix remodeling [14]. On the other hand, TGF-β signaling is generally lower in patients with atherosclerosis [15]. This idea has led to a "protective cytokine" theory of atherosclerosis, a proposal that emphasizes the role of reduced TGF-β bioactivity in generating a pro-atherosclerotic environment [16]. Although we might be tempted to label TGF-β as either an "atheroprotective" or "atherogenic" factor, TGF-β is more likely to play a central role in both normal and pathological vascular repair. In fact, it is clear that there is no direct causal relationship between TGF-β activity and atherosclerosis was established [17]. On the other hand, TGF-β effects have been proposed to favour matrix deposition and to increase lipoprotein trapping in the arterial intima [18], potentially leading to plaque formation and progression. Thus, an understanding of the molecular mechanisms that regulate vascular repair, including TGF-β signalling, is crucial for the development of treatments for occlusive vascular disease. This cytokine is a major orchestrator of the fibroproliferative response to tissue damage. It was proposed that TGF-β effects are context-dependent and is heavily determined by the nature of the vascular injury. In the early stages of repair, TGF-β is released from platelets and activated from matrix reservoirs; it then stimulates the chemotaxis of repair cells, modulates immunity and inflammation and induces matrix production. At later stages, it negatively regulates fibrosis through its strong antiproliferative and apoptotic effects on fibrotic cells. In advanced lesions, TGF-β might be important in arterial calcification [19].

Recently, more and more studies are interested by endoglin (CD 105, TGF-β receptor III). For example the extensive article of Nachtigalet al., [20] showed that the increased levels of soluble endoglin was related to the plaque neoangiogenesis, production of collagen, hypercholesterolemia and acute myocardial infarction. The authors propose that measurement of soluble endoglin might give information about progression of the atherosclerotic process or the efficacy of therapeutic interventions, which is the task that must be answered in clinical trials. In an attempt to shed more light on the possible role of this cytokine in the onset and progression atheroma plaque, we compared its expression at mRNA levels in atheroma plaque compared to nearby macrospically intact tissue by microarray analysis. Gene microarray technology can be used to investigate global mRNA expression to identify mRNA populations that exhibit differential regulation in disease processes, thus providing important clues to the underlying molecular pathology. mRNA gene expression was measured by an AffymetrixGeneChip Human Gene 1.0 ST arrays (Affymetrix, Santa Clara, CA, USA) using RNA prepared from 68 specimens of endarteriectomy from 34 patients. We studied by microarray analysis whether intact vascular tissue and carotid plaque from the same patient differ in TGF-β transcriptional profiling in response to atheroma formation. These results showed that atheroma formation coincided with TGF-β2 and 3 decrease expression. In addition, TGF-β2 was decreased more than 0.6 fold (p=2.18E-06) and TGF-β3 was downexpressed than 0.7 fold (p=3.21E-07). We conclude that atheroma formation coincided with TGF-β decrease expression (unpublished data).

The potential effect of this decrease on inflammatory drive is interesting and important. For instance, pathway analysis might reveal that reduced TGF-β ligand levels are correlated with reduced levels of elements of the TGF-β intracellular signalling cascade. Function classification and pathway analysis might indicate a correlation between the reduced TGF-β ligand levels and inflammation-related cascades and transcripts. We will pursue our investigations vigorously until we find additional information and fully understand TGF-β role in atheroma development. For that purpose correlations between TGF-β mRNA levels and clinical status of the patients will be done. Adding these data may strengthen our data and will be the task for the future. Previous studies was performed in mouse models, so although a detailed molecular analysis was provided, this may not be analogous to the clinical setting. Our study therefore adds important data regarding the link between atherosclerotic patients and TGF-β expression.

Conclusion

Considering the need for updated reviews on specific role of TGF-β signalling in atherogenesis, plaque growth and its complications, in this paper we review the controversial role of this cytokine in plaque development. Many relevant additional data are provided by the present review and we attempted to state the functional role of TGF-β signalling pathway in experimental and human atheroma and propose a hypothetical model for its effects.

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