Smooth Muscle Cell
A Key Cell for Plaque Vulnerability Regulation?

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The concept that the atheromatous plaque undergoes a complex inflammatory and fibroproliferative process, which is likely responsible for the onset of complications, and the notion of vulnerable plaque have acquired wide acceptance during the last years. The crucial participation in these events of inflammatory and immunocompetent cells has been demonstrated, however the mechanisms through which these cells exert their noxious activities still remain a matter of investigation. Changes of the extracellular matrix have also been suggested to be at the origin of plaque vulnerability, mainly because of local production of proteolytic enzymes. Much less studied are plaque changes involving: (1) the modulation of smooth muscle cells (SMCs) toward the myofibroblastic phenotype and (2) the remodeling of extracellular matrix including tissue deformations typical of granulation tissue; these changes are a landmark of chronic inflammation in various organs undergoing fibrotic changes, where myofibroblasts represent a large proportion of the cellular population. Myofibroblasts become capable of generating contractile forces thanks to the neogenesis of α-smooth muscle (SM) actin, the actin isoform typical of vascular SMCs; in addition they produce collagen and proteolytic enzymes. In general myofibroblasts originate from local fibroblasts; their more sporadic derivation from local SMCs, local epithelial cells (through epithelial/mesenchymal transition), or circulating mononuclear cells has been recently documented during several pathological settings. Fibroblast/myofibroblast modulation is essentially regulated, in addition to mechanical forces, by transforming growth factor-β1 (TGF-β1) produced locally by macrophages and eventually fibroblastic cells; TGF-β1 has been shown to stimulate the synthesis of α-SM actin and collagen type I by fibroblastic cells.

The possible modulation of SMCs toward a myofibroblastic phenotype within the human plaque has been suggested for a long time but has only recently been documented. This observation reinforces the notion that the plaque undergoes chronic inflammatory phenomena, but leaves open the question concerning possible mediators. Obviously the mechanisms regulating this process must be different compared with those regulating fibroblast/myofibroblast transition. In particular they should bring about a decreased expression of α-SM actin and of collagen, both highly expressed by vascular SMC: hence TGF-β1 can be excluded as possible mediator.

γ-Interferon, a cytokine secreted by T-lymphocytes and macrophages, is abundant in the atheromatous plaque; it has also been shown to stimulate the expression by SMCs of major histocompatibility class II (MHC II) antigens and to reduce the expression of both collagen type I and α-SM actin. Hence it represents a candidate for mediating SMC/myofibroblast transition in vivo. The presence of MCH II molecules within the plaque is likely responsible for the chronic stimulation of inflammatory phenomena.

In the current issue of Circulation Research, Buttice et al. based on previous work of their laboratory and of other laboratories, present new important data unveiling the mechanism through which collagen type I and MHC II genes are regulated by γ-interferon in human SMCs. They first show that 2 major isoforms (III and IV) of the MHC II transcription regulatory protein CIITA are induced by γ-interferon in SMCs. They further show that CIITA plays a crucial role in both γ-interferon–induced repression of collagen type I synthesis and increase of MHC II expression. Simvastatin also lowers collagen type I expression by SMCs but with a mechanism that is independent of CIITA activation.

These data strongly support the view that CIITA is responsible for at least 2 major γ-interferon activities at the plaque level: (1) perpetuation of the inflammatory response mediated by an increase of MHC II molecules produced by SMCs, and (2) impaired stabilization of the extracellular matrix within the plaque, mediated by a decrease of collagen type I expression. It would be of interest to verify the possibility that CIITA mediates also the decrease of α-SM actin expression induced by γ-interferon in SMCs. This finding would definitively support the view that the γ-interferon control of SMC/myofibroblast transition depends on CIITA.

In any event this work underlines again the participation of SMCs to the complex process of atheromatous plaque evolution; moreover, by establishing the key role of CIITA in γ-interferon–induced SMC modulation, it opens a new line of research toward the understanding of plaque remodeling mechanisms and toward the planning of strategies aiming at influencing plaque vulnerability.

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References


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