Transforming Growth Factor-\(\beta\) (TGF-\(\beta\)) and Vascular Disease

CARP as a Putative TGF-\(\beta\) Target Gene in the Vessel Wall

James N. Topper

The transforming growth factor-\(\beta\) (TGF-\(\beta\)) superfamily of growth factors and cytokines consists of multiple isoforms of TGF-\(\beta\), bone morphogenetic proteins (BMPs), activins, and many other structurally related proteins in vertebrates. Through the work of many investigators, there is increasing evidence to support a role for members of this family in a broad range of biological processes, including the pathogenesis of chronic vascular diseases. For example, TGF-\(\beta\), is a powerful and essential immune regulator in the vascular system, capable of modulating inflammatory events. This is most dramatically illustrated by the phenotype of mice that lack the gene for the TGF-\(\beta\) isoform and die in utero or in the perinatal period because of widespread, uncontrolled inflammation, an effect that can be reversed by the systemic administration of active soluble TGF-\(\beta\). Conversely, the dysregulated actions of TGF-\(\beta\) (such as in the presence of excessive amounts of active TGF-\(\beta\), ligand) are reproducibly associated with the pathological accumulation of excessive extracellular matrix, and this phenomenon has been proposed to play a central role in the pathogenesis of disorders such as hypertensive vascular diseases and diabetic renal disease. TGF-\(\beta\) is a potent regulator of the cell cycle in many cell types, including vascular smooth muscle cells (VSMCs) and endothelial cells, and, as a result, this growth factor has been postulated to play an important, although largely undefined, role in vascular proliferative disorders. Alterations in the levels (either circulating or within the vessel wall) of active TGF-\(\beta\), a soluble form of endoglin (a cell-surface molecule that is thought to modulate signaling through the TGF-\(\beta\) receptor) as well as a recently described BMP isoform, termed BMP6, have been implicated as important contributors to the pathogenesis of atherosclerotic vascular disease in both experimental animals and humans. Finally, the targeted deletion of the Smad6 gene in mice (a regulator of TGF-\(\beta\) superfamily signaling) results in a variety of developmental and homeostatic abnormalities in the cardiovascular system. Thus, both dysregulated ligand expression (eg, TGF-\(\beta\) and BMPs) and alterations in the signaling pathways used by this superfamily of cytokines may contribute to human vascular disease, and the modulation of the expression or actions of this family of cytokines has been proposed as a potential site of therapeutic intervention.

Because of their importance in many diseases, the basic signaling mechanisms used by the TGF-\(\beta\) superfamily of growth factors have been an active area of investigation. In the case of TGF-\(\beta\), its cellular effects seem to be transduced via at least 3 types of cell-surface receptors (types I, II, and III), 2 of which are serine/threonine kinases. The active form of soluble TGF-\(\beta\) binds to the type II receptor at the cell surface, and this complex subsequently interacts with and transphosphorylates the cytoplasmic domain of the type I receptor. This phosphorylation event activates the type I receptor–kinase domain, which then propagates downstream signals within the cell. This process can be modulated by the presence of a type III receptor, such as betaglycan, a membrane-bound proteoglycan. Once activated, the type I receptor can transiently interact with a specific set of intraacellular signaling molecules known as Smad proteins and activate them by serine phosphorylation. This results in their translocating to the nucleus, where they modulate gene expression. On the basis of their structures and functional roles, the mammalian Smad proteins seem to fall into at least 3 classes. Proteins in the first class, typified by Smads 1, 2, 3, 5, and, more recently, 8 and 9, seem to be capable of interacting with the activated type 1 receptors corresponding to a particular TGF-\(\beta\) superfamily ligand (eg, TGF-\(\beta\)-s, BMPs, and activins), undergo receptor-mediated phosphorylation, and subsequently translocate to the nucleus. As part of this process, these signaling (also known as receptor-associated or pathway-restricted) Smads bind to a distinct Smad, Smad4, that can synergize with certain signaling Smads and act as a transcriptional activator. Thus, Smad4 seems to define a second class of Smad protein that does not interact directly with receptors but is required for signaling (termed a co-Smad). Although both the signaling and co-Smads have transcriptional activation domains and, in some cases, can bind to DNA in promoters directly, the specificity of these processes is limited. Thus, Smads likely function as specific transcriptional effectors by interacting with a variety of other sequence-specific DNA-binding transcription factors, such as AP-1, TFE3, and certain Forkhead proteins. In addition, like many other regulated transcriptional effectors, Smads specifically interact with a class of proteins known as transcriptional coactivators, a process that is critical to their ability to regulate gene expression. Members of a third class of Smad proteins (Smad6 and Smad7) are capable of inhibiting TGF-\(\beta\) signaling. In contrast to the other classes of Smads, these inhibitory Smads demonstrate inducibility in response to a variety of stimuli, such as TGF-\(\beta\) itself, or biomechanical stimuli such as shear stress.
All 3 classes of Smad proteins are also subject to regulation by or interaction with a variety of other (non–TGF-β) signaling pathways such as the mitogen-activated and stress-activated kinase cascades and certain receptor tyrosine kinases. Thus, both the particular mix of Smad proteins present and the nature and relative activity of the signaling pathways present (ie, the molecular context) will determine the nature of TGF-β–stimulated responses in a particular cell type. These types of mechanisms likely account for the pleiotropic and context-specific effects that characterize this class of growth factors.

In this issue of Circulation Research, Kanai et al report the identification of a novel TGF-β-responsive target gene in cultured VSMCs. They have identified the cardiac ankyrin repeat protein (CARP) as a gene that is upregulated at the transcriptional level in response to exogenous TGF-β, but not in response to a variety of other growth factors. In addition, they demonstrate that this gene is upregulated in the media of arteries after balloon injury in an animal model, an in vivo setting where it resides in the nucleus and putatively regulates gene expression. This is the first report that this protein can be induced in vascular smooth muscle cells and the first report to implicate the actions of this protein in the regulation of the cell cycle. This observation may be particularly important, because TGF-β is a potent regulator of the cell cycle in VSMCs, and alterations in this response are thought to be important in vascular disease pathogenesis. For example, defects in the ability to respond to TGF-β (such as in the presence of somatic mutations in the type II receptor for TGF-β), have been implicated in the dysregulated smooth muscle cell hypertrophy/hyperplasia that is a hallmark of arteries after balloon injury in an animal model, an in vivo setting where it resides in the nucleus and putatively regulates gene expression.

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