Transforming Growth Factor-β (TGF-β) and Vascular Disease

CARP as a Putative TGF-β Target Gene in the Vessel Wall

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Because of their importance in many diseases, the basic signaling mechanisms used by the TGF-β superfamily of growth factors have been an active area of investigation. In the case of TGF-β, 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-β 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 intracellular 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-β superfamily ligand (eg, TGF-βs, 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-β signaling. In contrast to the other classes of Smads, these inhibitory Smads demonstrate inducibility in response to a variety of stimuli, such as TGF-β 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.6 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 al8 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 context in which the induction of TGF-β has been well documented. They have extended this intriguing observation by demonstrating that the transcriptional activation of the CARP promoter is dependent on the action of Smad proteins and that overexpression of CARP in VSMCs can inhibit DNA synthesis. Although the results as reported are insufficient to conclusively link the induction of CARP to the ability of TGF-β to regulate the cell cycle, they do identify a new TGF-β target gene within the vasculature and point to a potentially novel role for CARP. CARP was originally identified as a cytokine-inducible gene in cultured microvascular endothelial cells.9 Subsequently, this protein has been reported to be expressed in a pattern restricted to the heart, where it resides in the nucleus and putatively regulates gene expression.10 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 neointimal formation or restenosis after vascular injury.11 Thus, the study by Kanai et al8 raises the intriguing possibility that CARP may be an important effector of the actions of TGF-β that is restricted to VSMCs (and possibly myocytes).

As such, this protein (and the other constituents of this signaling pathway, should they exist) may represent a very attractive target for the development of therapeutics, which could selectively modulate the actions of TGF-β in the cardiovascular system. To pursue this hypothesis, future studies should be focused on demonstrating robustly that CARP is in fact an important effector of the actions of TGF-β in VSMCs. This will require the ability to selectively manipulate the level of expression or actions of CARP in response to TGF-β. In addition, because the actions of TGF-β and related growth factors (such as the BMPs) can vary dramatically depending on the particular cellular context, it will be critically important to examine the relationship between TGF-β and CARP expression in a variety of VSMC contexts both in vitro and in vivo.

The TGF-β superfamily is among the most important and complex families of signaling molecules. However, recent advances in our understanding of the molecular mechanisms by which this family of factors operate are providing unprecedented opportunities to define their roles in particular disease contexts. Kanai et al8 have identified a novel target gene for TGF-β in VSMCs and, in so doing, have potentially identified a novel effector of the actions of this growth factor that may be restricted to the cardiovascular system. These kinds of cell-type selective-effector pathways may ultimately provide the most attractive opportunities for the therapeutic modulation of the pathological actions of TGF-β in the cardiovascular system.

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References


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