The Pleiotropic Nature of the Vascular PPAR Gene Regulatory Pathway

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The peroxisome proliferator-activated receptors (PPARs) are a family of ligand-activated transcription factors within the broad nuclear receptor superfamily. Recent evidence indicates that the PPARs play critical regulatory roles in a variety of biologic processes relevant to the heart and vasculature including lipid and energy metabolism, inflammation, and cellular differentiation (reviewed in Desvergne and Wahli1). The PPAR family includes three members encoded by distinct genes: α, β (also known as δ or Nuc1), and γ. The three PPARs are distinguished by tissue- and developmental-specific patterns of expression and by the distinct, albeit overlapping, nature of lipid and eicosanoid ligands capable of activating each receptor. For instance, the expression of PPARγ is highly adipose-enriched, whereas PPARα is expressed in tissues with high rates of mitochondrial fatty acid oxidation, such as heart and liver. Ligand activation of PPAR leads to obligate heterodimerization with members of the retinoid X receptor (RXR) subfamily and subsequent binding to cognate DNA response elements within target gene promoter regions. The true endogenous PPAR ligands have not been defined with certainty. Long-chain fatty acids activate each of the PPARs to varying degrees suggesting that lipid species serve as cell-specific PPAR ligands. A number of pharmacologically active, PPAR-specific compounds have been identified leading to a rapidly growing interest in this family of nuclear receptors as targets for drug development. For example, the PPARα activators clofibrate and gemfibrozil have been developed as hypolipidemic agents. Thiazolidinediones (eg, troglitazone, rosiglitazone) are PPARγ-specific activators with potent insulin-sensitizing action.

The activity of the PPAR/RXR complex is controlled by an exquisite array of regulatory mechanisms (Figure; reviewed in Barger and Kelly2). The remarkably pleiotropic nature of this regulation allows for the dynamic modulation of PPAR target gene expression across a wide response range in a cell-specific manner. First, the nuclear levels of specific PPARs, RXRs, and their cognate ligands determine the amount of heterodimer available for binding to target DNA element sequences. The availability of the RXR ligand 9-cis retinoic acid (RA) also contributes to the degree of PPAR/RXR activation. Second, the engagement of PPAR ligand leads to the recruitment of a coactivator complex containing proteins such as SRC-1, CBP/p300, PBP/TRAP220, and PGC-1. The coactivator complex possesses histone acetyltransferase activity leading to chromatin remodeling and increased transcription of the target gene. Although most of the coactivator proteins are ubiquitously expressed, certain coactivators such as PPARγ coactivator 1 (PGC-1) are inducible providing another means of boosting the activity of the PPAR complex in response to physiologic stimuli.3,4 Third, recent studies have shown that the activity of PPARγ and PPARα can be regulated by phosphorylation events. Specifically, phosphorylation by extracellular signal-regulated kinase mitogen-activated protein kinase (ERK-MAPK) inhibits the activities of PPARα and γ.5,6 In contrast, phosphorylation by protein kinase A or p38 MAPK activates PPARα.7,8 This differential regulation of PPAR activity by signal transduction events provides a mechanism for rapid, cell-specific control of PPAR target gene expression by extracellular stimuli (Figure).

Evidence is emerging that the PPAR regulatory pathway plays a critical role in the regulation of diverse biologic processes within the cardiovascular system.2 PPARα activates the expression of genes involved in the cellular fatty acid utilization pathway in the normal heart.2 In contrast to PPARα, PPARγ is not enriched in the normal adult mammalian heart but has the potential to regulate cardiac metabolism indirectly via its influence on circulating lipid and glucose levels. The biologic function of the PPAR regulatory pathway in the vessel wall is a focus of active investigation. The results of recent studies indicate that PPARs are active in multiple vascular cell types. PPARα and PPARγ are expressed in smooth muscle, macrophages, foam cells, and endothelial cells of normal and atherosclerotic vessels in several species including humans.9–14 Vascular PPARβ expression has not been extensively characterized to date. Evidence is emerging that PPAR signaling influences the development and severity of vascular disease states such as atherosclerosis and response to injury. Two general strategies have been used to investigate the functional role of PPARs in vascular biology: (1) systemic administration of PPAR activators (activator studies) and (2) evaluation of the vascular phenotype of mice with genetic ablation of PPARα or PPARγ genes (loss-of-function studies). Administration of PPARγ activators leads to a reduction in the extent of atherosclerosis in murine models of atherosclerosis such as the apolipoprotein E-deficient mouse.15 PPARγ activators have also been shown to reduce the neointimal response to injury.14,16,17 The mechanisms involved in these protective effects are unknown, but possible mechanisms include the...
Questions about the role of PPAR signaling as “protector” versus “bad player” in vascular disease. Given that PDGF is generally considered to serve as an upstream trigger of pathologic vascular smooth muscle proliferation, is it possible that under certain circumstances PPARγ mediates pathologic responses of the vessel? This conclusion would be premature. Caution must be used in extrapolating the results of cell culture studies to the in vivo scenario. As noted above, previous studies have demonstrated that systemic administration of PPARγ agonists is capable of inhibiting vascular intimal hyperplasia. Moreover, the results of activator and loss-of-function studies to date indicate that PPARγ serves to reduce the formation of foam cells and atherogenesis in vivo. This seemingly paradoxical collection of results underscores the importance of using multiple complementary experimental strategies to unravel the vascular PPAR regulatory pathway. Systemic administration of PPAR agonists provides information about the in vivo response and the potential for a therapeutic success. However, elucidation of the direct effects of the PPARs on specific vascular cell types will require loss-of-function studies in mice and isolated cell studies. Cell culture studies, such as that reported by Fu et al., will continue to serve an important role in the investigation of cell-specific effects and to identify upstream regulatory events relevant to the control of PPAR activity. The molecular dissection of the upstream and downstream components of the vascular PPAR gene regulatory pathway should ultimately lead to the development of novel therapeutic approaches aimed at the inhibition of common disease processes such as atherogenesis and the hyperproliferative response of the vessel wall to injury. Moreover, identification of relevant vascular PPAR target genes should provide insight into genetically determined factors that predispose to common cardiovascular diseases.

References


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