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**Review**

# Regulation of endothelial prostacyclin synthesis by Protease-activated receptors: mechanisms and significance

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**Abstract:**

The cellular actions of serine proteases are mediated through activation of a novel family of four G protein-coupled receptors known as protease-activated receptors (PARs). PARs are emerging as important modulators of diverse biological functions and there is evidence supporting roles for these receptors in both physiological and pathological settings in the cardiovascular system. Endothelial cells express all four known PARs but their specific roles as modulators of endothelial cell function are not well understood. One physiologically important response of the endothelium to PAR stimulation is the generation of prostacyclin (PGI<sub>2</sub>) through cyclooxygenase (COX)-dependent pathways. Our studies have used selective PAR-activating peptides, endogenous PAR agonists, and pharmacological and molecular approaches to identify the mechanisms coupling PARs activation with endothelial PGI<sub>2</sub> synthesis and release. These mechanisms are differentially recruited by individual PARs but activation of the ERK1/2 and p38 families of mitogen-activated protein kinases (MAPK), as well as the nuclear factor kappa-B (NF-κB) pathway, play significant roles in controlling PAR-induced prostanoid formation through regulation of COX-2 induction and cytosolic phospholipase A<sub>2</sub>α (cPLA<sub>2</sub>α) activation. PAR agonists also modulate PAR expression by mechanisms that require p38<sup>mapk</sup> as well as NF-κB. The defensive actions of PGI<sub>2</sub> in the vascular wall are well-established, and the ability of PARs to drive acute and chronic synthesis of this mediator suggests a potential role for these receptors in vascular protection. Our findings therefore have important implications for defining the vascular effects of current and future therapeutic agents that target COXs, PARs, and the signalling elements controlling their expression.

**Key words:**

endothelial cell, prostacyclin, protease-activated receptors, cyclooxygenases

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