Osteopontin: A Protective Mediator of Cardiac Fibrosis?

Kristof Graf, Philipp Stawowy

Osteopontin (OP) is a multifunctional cytokine and adhesion protein that contains an RGD (arginine-glycin-aspartate) binding sequence that enables it to interact with several integrins, CD44 variants, and other adhesion receptors. OP receptor binding then directly or indirectly activates intracellular signaling pathways, mediating its effects on cell–matrix and cell–cell interactions. OP is increased in response to pro-inflammatory cytokines and mechanical strain in various cell types, and the function of its secreted protein can be altered by proteases, including thrombin. Thus, OP can exist as an immobilized matrix molecule (e.g., in bone, atherosclerotic plaques, or calcified heart valves) or as soluble cytokine.

Cell signaling by OP is predominantly mediated through integrin engagement. Cleavage of OP by thrombin exposes integrin binding sites (e.g., for \( \alpha_v \beta_3 \)), which are important for OP-mediated adhesion/migration. OP is chemotactic for various cell types, most notably monocytes/macrophages, which are attracted to sites of injury and inflammation. The best-characterized OP-induced signal pathway is the integrin-dependent FAK-Src-Rho pathway in osteoclasts. However, identification and dissection of signal transduction pathways are complicated by the fact that OP potentially binds to several cell surface receptors.

**OP and the Heart**

Proper organization of the extracellular matrix is required to maintain the integrity and organization of cardiac cells. Adaptive remodeling of the myocardium, caused by either increased workload or injury, requires mediators for the communication of cardiac cells with their surrounding extracellular matrix. This makes OP an ideal candidate. Various stimuli have been found to induce OP in cardiac cells, including fibroblasts, cardiomyocytes, macrophages, endothelial cells, and vascular smooth muscle cells. Angiotensin II (Ang II) is a potent inducer of OP expression in cardiac fibroblasts, in which OP mediates a number of Ang II-dependent cellular functions via binding to \( \beta_1 \) and \( \alpha_v \beta_3 \) integrins. In vivo OP expression is observed predominantly in cardiomyocytes in experimental models of Ang II-dependent myocardial hypertrophy.

Increased cardiac OP expression, either in fibroblasts and/or cardiomyocytes, has been reported with the onset of heart failure, after myocardial infarction, and in patients with progressive heart failure. This suggests that OP is involved in mechanisms regulating the cardiac response to pressure or volume load or myocardial injury.

Consequently, studies with OP \(^{+/−}\) mice have been performed to elucidate its role in cardiac remodeling. Generally, OP \(^{+/−}\) mice demonstrate a normally developed cardiovascular system but display impaired wound healing after skin injuries. However, Trueblood et al reported an impairment of collagen synthesis and increased left ventricular dilatation after myocardial infarction in OP \(^{+/−}\) mice. The same group demonstrated that OP inhibits IL-1β-induced matrix metalloproteinase activity in cardiac fibroblasts, indicating that OP deficiency impairs the balance between extracellular matrix synthesis and degradation. In this issue of Hypertension, Xie et al demonstrate that the loss of OP is responsible for the blunted hypertrophic response leading to early systolic impairment in a model of aortic banding. Their present study confirms findings of a previous report, which observed an impairment of systolic function and onset of left ventricular dilatation in OP \(^{+/−}\) mice after chronic Ang II infusion to induce myocardial hypertrophy.

Interestingly, cardiac hypertrophy measured as heart/body weight ratio was not affected in either of the studies. So far, these publications stress the importance of OP as modulator of the compensatory fibrotic and hypertrophic response. They indicate that the loss of OP hampers the function of the cardiomyocyte compartment, resulting in a reduced cardiac performance. Xie et al further demonstrate in their present study that OP deficiency impairs the intracellular activation of the Akt/GSK3-β, JNK, and p38 kinase pathways, signaling pathways important to myocardial hypertrophy. This findings imply that OP is important for the signal pathways controlling the adequate physiological response after pressure overload in both cell types, fibroblasts, and cardiomyocytes.

Collins et al investigated the role of OP in Ang II-induced hypertension and myocardial hypertrophy using OP \(^{+/−}\) mice. Their study revealed that OP deficiency did not change the blood pressure response to Ang II-infusion but significantly decreased cardiac fibrosis induced by Ang II. This corresponds to findings of Matsui et al, who found a decrease in cardiac fibrosis in Ang II-induced hypertrophy. Moreover, the effect of OP deficiency on fibrosis was comparable to the treatment of wild-type mice with the aldosterone antagonist eplerenone, which significantly reduced the amount of fibrosis induced by Ang II. Therefore, the authors concluded that part of the eplerenone effect could be mediated by inhibition of OP. Surprisingly, in their present study, Xie et al did not observe any effect on fibrosis in OP \(^{+/−}\) mice after 4 weeks.
of aortic banding, which suggests different mechanisms how OP interchanges with cardiac cells, beside its profibrotic effects. Most likely, both inhibition of fibrosis and modulation of signaling pathways might explain that the loss of OP leads to a decreased cardiac performance in cardiac remodeling.

Which cellular mechanisms are then involved? Collins et al.\(^1\) reported that the growth and adhesive properties of cardiac fibroblasts from OP\(^{−/−}\) mice are significantly reduced after chronic Ang II treatment. The effects of OP on cardiomyocyte function are unknown. OP is a well-characterized after chronic Ang II treatment. The effects of OP on cardiofibroblasts from OP

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