Endothelial Progenitor Cells and Angiogenesis Join the PPARty

Federico Biscetti, Roberto Pola

 Peroxisome proliferator-activated receptors (PPARs) are ligand-inducible transcription factors that belong to the nuclear hormone receptor superfamily. In mammals, the PPAR family consists of 3 subtypes of proteins encoded by separate genes: PPARα (NR1C1), PPARγ (NR1C3), and PPARδ (also known as β or NR1C2). They act as heterodimers with the retinoid X receptor and regulate gene transcription by binding to specific response elements in the promoter of the target genes. The classical biological activity of PPARα is the regulation of the rate of fatty acid uptake and their esterification into triglyceride or oxidation, whereas PPARγ is classically involved in adipocyte differentiation, regulation of fat storage, and maintenance of glucose homeostasis. The physiological functions of PPARδ are instead still unclear, although it is known that this receptor contributes to an inflammatory switch through its association and disassociation with transcriptional repressors. The clinical importance of PPARs originates with fibrates and thiazolidinediones (TZDs), which respectively act on PPARα and PPARγ and are used to ameliorate hyperlipidemia and hyperglycemia in subjects with type 2 diabetes mellitus (T2DM). Fibrates, such as gemfibrozil, clofibrate, fenofibrate, and bezofibrate, are drugs that effectively reduce triglycerides (TG) and free fatty acids (FFA) and increase high-density lipoproteins-cholesterol. Fibrates also improve glucose tolerance in T2DM patients, although this activity might be attributable to the fact that some of these compounds also have potential PPARγ activity. TZDs, such as rosiglitazone, pioglitazone, troglitazone, and ciglitazone, are insulin-sensitizing drugs and have constituted a major advance in the recent therapeutic management of T2DM. In addition to improving insulin sensitivity, TZDs have also effects on TG, FFA, and ketone body level in several animal models of T2DM. The role of PPARδ remained unclear for almost a decade after its cloning in 1992. Its near-ubiquitous tissue expression raised early speculation that it may serve a “general housekeeping role.” More recently, receptor knockouts revealed multiple developmental and homeostatic abnormalities in PPARδ-null mice, including placental defects causing embryonic lethality, decreased adipose mass, myelination defects, altered skin inflammatory response, and impaired wound healing.

In recent years, there has been increasing appreciation of the fact that, in addition to the classical biological activities mentioned above, PPARs have several other pleiotropic functions. For instance, they provide a fundamental contribution to the regulation of certain physiological activities of the prostacyclin (PGI2) system in cardiovascular tissues. Indeed, PGI2, which is the most abundant product of arachidonic acid in vascular tissues, acts through a dual signaling pathway, that includes both G protein–coupled cell surface receptors named IP and PPARs. In this respect, it has been recently demonstrated that the angiogenic abilities of stable analogues of PGI2 depend on their capacity to act on PPARs. Additional evidence also suggests that selective activation of PPARα and PPARγ promotes a robust angiogenic process in vitro and in vivo, through a mechanism that depends on the stimulation of the prototypical angiogenic agent vascular endothelial growth factor (VEGF). Other data from our group also demonstrate that the ability of PGI1 analogues to induce angiogenesis depends on the presence and proper function of the PPARα gene.

In an article published in this issue of Circulation Research, He et al shed new light on the functional relationships existing between the PGI1 system, angiogenesis, and the PPAR signaling pathway. In particular, they demonstrate that endothelial progenitor cells (EPCs), a population of bone marrow–derived cells committed toward the endothelial lineage, express cyclooxygenase (COX)-1 and PGI2 and that activation of COX isoforms and high production of PGI2 is important for the regenerative function of EPCs. In addition, by using stable PGI1 analogues with different affinity for IP receptors and PPARs, the authors provide the elegant demonstration that activation of PPARs is fundamental for the angiogenic effects of PGI2 in EPCs. They also identify PPARδ as the gene responsible for the regulation of PGI2-induced proliferation, in vitro tube formation, and in vivo capillary formation of EPCs.

This study adds substantially to the field. First of all, it demonstrates the importance of arachidonic acid metabolism and biosynthesis of PGI2 in the mediation of the angiogenic effects of human EPCs. Second, it strengthens the role of PPARs in angiogenesis. Third, it supports the notion that PPARs are also involved in EPC biology and function. Finally, it identifies a new biological activity for PPARδ, a gene whose function in vascular biology is unclear and under intensive investigation. Particularly interesting is the demonstration that the angiogenic effects of EPCs are controlled by PPARδ.

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by PGI₂ via a PPAR-dependent pathway (Figure). This concept is consistent with the findings of several recent reports that have demonstrated the ability of PPARγ to stimulate proliferation, differentiation, and therapeutic activity of EPCs in vitro and in vivo. However, the study by He et al is novel also in this respect, because it provides the first demonstration of PPARδ being involved in the regulation of EPC biological activities. So far, the only existing link between PPARδ and angiogenesis was the demonstration that the activation of this nuclear receptor induces proliferation of mature endothelial cells.

The intersection between the PGI₂ system, PPARs, and angiogenesis is intriguing and deserves further investigation. PPAR pleiotropy is another interesting field of research that might potentially improve our future understanding of the clinical effects of drugs that stimulate PPARs and are currently used in the clinic, with potentially important unexpected implications for the management of subjects with diabetes, hyperlipidemia, and ischemic cardiovascular diseases.

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