Endothelial Progenitor Cells and Angiogenesis Join the PPARβ

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. 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. 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. 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. 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.

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

Correspondence to Roberto Pola, MD, PhD, Department of Anatomy and Cell Biology, Tufts University School of Medicine, 36 Harrison Avenue, 02111 Boston, MA 02155. E-mail roberito.pola@tufts.edu

© 2008 American Heart Association, Inc.

Circulation Research is available at http://circres.ahajournals.org
DOI: 10.1161/CIRCRESAHA.108.180224
Hyperpolarization, vasodilatation, proliferation, etc.

**Figure.** A schematic representation of PGI₂ activity on EPCs. The IP signaling mediates several effects, such as hyperpolarization, vasodilatation, and proliferation, but the PPAR signaling is crucial for angiogenic process.

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.52–55 However, the study by He et al is novel also in this respect, because it provides the first demonstration of PPARβ being involved in the regulation of EPC biological activities. So far, the only existing link between PPARα and angiogenesis was the demonstration that the activation of this nuclear receptor induces proliferation of mature endothelial cells.36

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.

**Sources of Funding**

The authors’ work is supported by a grant provided by the Catholic University School of Medicine, Rome, Italy.

**Disclosures**

None.

**References**

27. Barger PM. Has angiogenesis been invited to the PPARty? *J Mol Cell Cardiol.* 2002;34:713–716.


Key Words: endothelial progenitor cells □ angiogenesis □ prostacyclin □ PPARs
Endothelial Progenitor Cells and Angiogenesis Join the PPARty
Federico Biscetti and Roberto Pola

Circ Res. 2008;103:7-9
doi: 10.1161/CIRCRESAHA.108.180224

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/103/1/7

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org//subscriptions/