Vascular Remodeling in Diabetes
Don’t Leave Without Your STAT5

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Diabetes mellitus is associated with increased risk of cardiovascular disease. A widespread endothelial dysfunction, altered production of vasoactive substances and superoxide and modification of the basement membranes, is believed to play a decisive role in the vascular complications observed in diabetes. More importantly perhaps, in diabetic patients collateral vessel development after vascular occlusion is impaired. It seems that in these patients, arteriogenesis, the growing of preexisting arteriolar connections into collateral to restore the blood supply to the ischemic area, is severely affected. This process of active vascular remodeling involves the recruitment of circulating monocytes-macrophage subsets that have a strong angiogenic response. Although these circulating angiogenic cells (CAC) do not adopt a typical endothelial phenotype in vitro, they are capable of enhancing neovascularization in a paracrine manner in vivo and are critical regulators of wound healing and tissue regeneration. Extensive studies have shown that the numbers of circulating angiogenic cells are significantly lower in type II diabetes, and their angiogenic potential is also dramatically diminished. These cells display defective adhesion to the endothelium, reduced proliferation rate, and impaired ability to create new vascular structures. Thus, to pursue any therapeutic application it is necessary to identify the signaling pathways and treatments that promote the proliferation and improve the functional capacity of circulating angiogenic cells in diabetes.

See accompanying article on page 114

In this issue of *Atherosclerosis, Thrombosis, and Vascular Biology*, Dentelli et al delineate the molecular mechanisms involved in interleukin (IL)–3–induced angiogenic cell expansion. Previous studies by the same group have revealed that this angiogenic mediator released by activated T cells can provide a permissive environment that enables angiogenic cells to expand and directly contribute to neovascularization. In their present work, they demonstrate that IL–3 induces the formation of a STAT5/PPARγ transcriptional complex that controls cyclin D1 expression and can partially rescue diabetic angiogenic cell bioavailability. The regulatory mechanism that they uncover is remarkable. On stimulation of CAC with IL–3, STAT5 transcription factors are activated. The phosphorylated STAT5s form homo- and heterodimeric complexes and translocate to the nucleus where they bind to specific DNA binding sites on PPARγ promoter and initiate transcription. This upregulation of PPARγ expression is a necessary step to promote entry into the cell cycle as knockdown of PPARγ expression ablates this response. Interestingly, activation of PPARγ signaling using specific endogenous ligands or synthetic agonists fails to mimic the response to IL–3, indicating that phosphorylation of STAT5 plays a pivotal role and acts as an upstream signal for activation of PPARγ in a ligand-independent manner. STAT5 and PPARγ will subsequently form a complex on the cyclin D1 promoter and induce cyclin D1 expression (Figure).

These findings are rather intriguing given the nature of the transcription factors that are involved. STAT5 is activated in response to various hematopoietic cytokines. The STAT5ab−/− knockout mice are characterized by fetal anemia and increased apoptosis of fetal liver erythroid progenitors. Surprisingly, peripheral hematopoiesis of the STAT5ab−/− mice is not dramatically altered, although reductions in the numbers of IL–3 and GM-colony stimulating factor (CSF) responsive progenitors and IL–7 responsive B-lymphoid progenitors have been reported. Competitive repopulation assays demonstrated that bone marrow and fetal liver cells of STAT5ab−/− mice have a decreased repopulating activity in granulocyte, macrophage, erythroid, and B-lymphocytes populations, with no detectable engraftment of T lymphocytes, suggesting that STAT5 is required to sustain a hematopoietic reserve.

PPARγ on the other hand belongs to a family of nuclear receptors. After ligand binding, it heterodimerizes with the retinoid X receptor, binds to responsive DNA elements, and induces gene expression. Several reports have implicated PPARγ in the control of cell cycle, apoptosis, and biological events such as adipogenesis and bone homeostasis. In vitro studies using PPARγ agonists have suggested that it mediates the beneficial effects of statins and bone homeostasis. In diabetes, PPARγ synthetic ligands such as thiazolidinedione drugs (TZD) are commonly used to improve insulin sensitivity and exert antiatherosclerotic and antiinflammatory effects.

Interestingly, bidirectional crosstalk between STAT5 and PPAR signaling seems to control the response to growth hormone (GH). Both inhibition of PPARα transcriptional activity mediated by STAT5b and downregulation of STAT5b transcriptional activity by PPARα and PPARγ have been reported. The findings presented in this study further add to the complexity of STAT5 and PPAR partnership, as a
novel direct physical interaction of the two factors in a transcriptional complex is demonstrated. The formation of this heterodimer seems to act as a switch, which either allows the expansion of circulating angiogenic cells or suspends it. As identifying ways of increasing the numbers of circulating angiogenic cells in diabetic patients is extremely important, it would be critical to define the other regulators that are involved in this interaction and that could potentially serve as targets for novel therapeutic interventions. Monitoring the effect of IL-3 treatment on other members of the PPAR family would also provide valuable insights into the biology of circulating angiogenic cells in diabetic patients. In conclusion, the present work brought forward a new concept that could stimulate further research and could lead to the design of novel more effective approaches capable of improving vascular function.

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References
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