



activate and escort YopJ/P to the signaling complex, where it would silence critical SUMO-1 conjugated proteins. This would in turn prevent phosphorylation of MKKs and IKK β . This hypothesis finds some support in the observation that activation of MAPK coincides with a redistribution of YopJ/P in the cell¹².

Last but not least, YopJ/P also induces apoptosis in macrophages^{13,14} by inactivation of NF- κ B. Given the observation that YopJ/P functions as a protease¹, revisiting the hypothesis of a direct action of YopJ/P on the apoptotic cascade seems to be worthwhile. All in all, microbes have still not finished astonishing us!

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Progress in cardiovascular biology: PPAR for the course

Studies on mice lacking the peroxisome proliferator-activated receptor (PPAR) suggest that PPAR ligands reduce lipid accumulation in foamy macrophages, and may target other receptors. These findings warrant an in-depth investigation into the gene regulatory mechanisms of PPAR ligands, which are currently being developed as drugs to treat atherosclerosis and diabetes. (pages 41–47)

Peroxisome proliferator-activated receptors (PPARs) are a group of lipid-activated nuclear receptors which regulate genes involved in lipid and glucose metabolism. PPAR- α is highly expressed in liver, heart, muscle and kidney, as well as in cells of the arterial wall, while PPAR- γ is expressed at high levels in white adipose tissue, where it activates adipocyte differentiation¹. The discovery that PPAR- γ is also highly expressed in foam cells (activated macrophages that play a major role in the pathogenesis of atherosclerosis) raised many questions about the roles of PPAR- γ and its ligands in cardiovascular disease^{2,3}. Three papers in this issue by Moore *et al.*⁴, Chawla *et al.*⁵ and Chinetti *et al.*⁶ provide support for an anti-atherogenic role of PPAR- γ . The papers also provide new models to improve our understanding of the biological mechanisms of PPAR-s.

Not surprisingly, interest in PPAR- γ research has recently increased. High affinity PPAR- γ ligands known as thiazolidinediones (TZDs) have been discovered to be an exciting new class of anti-diabetic drugs⁷. The explosion of new information has led to controversy about the identity of PPAR- 'natural' ligands, the tissues they target and the role of PPAR- γ in the development of colon carcinoma^{7,8}. There is

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even controversy over how to pronounce PPAR—some say “pee-par-gamma” whereas others, including this author, prefer to pronounce each letter.

A debate of tremendous clinical importance also concerns the role of PPAR- γ in cardiovascular disease. Previous work using a pre-macrophage cell line demonstrated that activation of PPAR- γ signaling enhanced macrophage differentiation, inducing expression of CD36, one of the cell's 'scavenger' receptors for the atherogenic low-density lipoprotein (LDL) (Fig. 1). According to the model, increased CD36 expression leads to an intracellular accumulation of cholesterol and production of natural PPAR- γ ligands. This leads to further activation of PPAR- γ , creating a vicious cycle of ever-increasing lipid accumulation and conversion of macrophages into atherogenic foam cells^{3,9}. However, PPAR- γ ligands have also been shown to reduce inflammatory cytokine production by macrophages, an effect which should be anti-atherogenic^{2,10}. Indeed, atherosclerosis is reduced, not increased, in rodents as well as patients treated with PPAR- γ ligands¹¹.

So, what is the role of PPAR- γ in athero-

sclerosis? Chinetti *et al.*⁶ show that neither PPAR- α nor PPAR- γ activation induces foam-cell formation from human monocyte-derived macrophages. Moreover, Chawla *et al.*⁵ and Moore *et al.*⁴ created PPAR- γ -null embryonic stem cells to demonstrate that the nuclear receptor is not required for development of the macrophage lineage *in vivo* or *in vitro*. Why, then, has it been observed that PPAR- γ activation induces expression of CD36, leading to the vicious cycle of lipid accumulation in foam cells and increased PPAR- γ activity?

The answer seems to be that this cycle is broken by opposing effects of PPAR- γ ligands (Fig. 1). Moore *et al.*⁴ report that PPAR- γ ligands have an opposite effect on a second low-density lipoprotein scavenger receptor, SR-A, causing its downregulation in mouse macrophages. Additionally, Chinetti *et al.*⁶ found that expression of ABCA1, a protein involved in cholesterol export, is activated by the LXR nuclear receptor, which is induced by PPAR- γ ligands. Thus, PPAR- γ ligands have multiple effects on influx and efflux of cholesterol and oxidized lipids, countering their potentially atherosclerotic effect of CD36 induction.

PPAR- γ ligands also have inhibitory effects on macrophage cytokine production. These anti-inflammatory effects are consis-

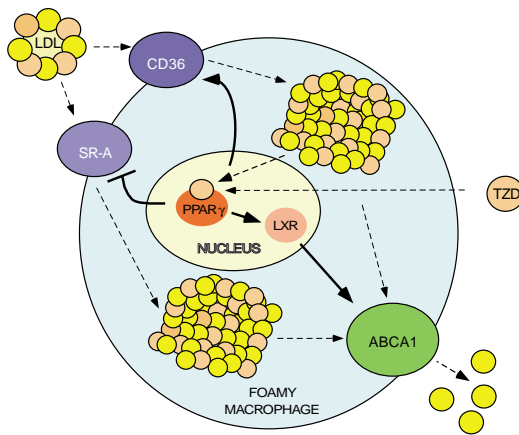


Fig. 1 Activation of PPAR- γ in foamy macrophages increases net lipid efflux. Lipids, including cholesterol (yellow), are transported in serum by low-density lipoprotein (LDL). The scavenger receptors SR-A and CD36, expressed on the surface of macrophages, bind to and internalize these lipids, causing the conversion of macrophages to pro-atherogenic foam cells. Oxidized lipids and antidiabetic thiazolidinediones (TZD) activate the nuclear receptor PPAR- γ , leading to increased expression of CD36. By itself, this effect increases foam cell lipid and might lead to atherosclerosis. However, three papers in this issue⁴⁻⁶ show that this is countered by reduced expression of SR-A and increased expression of another nuclear receptor, LXR, which induce the reverse cholesterol transporter ABCA1. The net effect of activation of PPAR- γ is thus anti-atherogenic in foam cells.

tent with the anti-atherogenic effects of these drugs. The anti-inflammatory efficacy of different PPAR- γ ligands, however, does not mirror their binding affinity^{2,10}, suggesting an alternative mechanism¹².

Moore *et al.*⁴ show that loss of PPAR- γ expression by macrophages does not alter basal or stimulated cytokine secretion. TZDs have been shown to inhibit the secretion of inflammatory cytokines, such as TNF- α and IL-6, in wild-type macrophages.

Scientists must be especially cautious in making conclusions about the functional mechanisms of PPAR- γ ligands, especially that of the prostaglandin 15-deoxy- $\Delta(12,14)$ PGJ₂. This molecule was originally thought to be a selective PPAR- γ ligand but turns out to have other biological effects¹². However, these new insights into the role of PPAR- γ in foamy macrophage formation and inflammation keep us on course to gain better insight of the function of PPAR

Remarkably, Chawla *et al.*⁵ observed that TZD's affect on cytokine gene expression and secretion was not altered in macrophages taken from PPAR- γ null mice. These findings suggest that PPAR- γ expression is not required for PPAR- γ ligands to exert their anti-inflammatory effects. Whatever the alternative signaling pathway is, it remains to be determined whether it is normally active or, rather, a compensatory mechanism for the lack of PPAR- γ in this model.

It is possible that another PPAR-related receptor, such as PPAR- α , mediates the anti-inflammatory effects of TZDs in the PPAR- γ null macrophages. Indeed, PPAR- α expression is activated by high concentrations of TZDs and Chinetti *et al.*⁶ demonstrated its ability to regulate transcription of some of the same macrophage genes as PPAR- γ . PPAR- γ ligands could also signal through a different nuclear receptor or by a completely distinct pathway.

receptors and their ligands in health and disease.

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Hitting the reset button for immune tolerance

Migratory cells can lead both to rejection and tolerance following organ transplantation, suggesting a direction for pro-tolerant immunomodulatory therapies. (pages 80-87)

When organs are transplanted between genetically non-identical individuals they are invariably destroyed through an immune-mediated phenomenon known as rejection. Immunosuppressive therapy generally prevents rejection, but must be continued for life. In rare instances however, the recipient can be treated with immune modulatory agents for only a short amount of time and become 'tolerant' of the new organ, meaning that the host immune system will no longer attack the graft, and the graft recipient will not require continuous immunosuppression.

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It has become clear that tolerance induction involves as much active participation of the immune response as rejection does, and is equally steeped in the complexities of physiological immune regulation. The exact factors, however, that govern the balance between immunity and tolerance remain a mystery, and the available mechanistic model has been insufficient to allow for a consistent induction of tolerance in clinical situations. In this issue of *Nature*

Medicine, Anderson and Matzinger¹ present a series of mouse experiments showing how cells from the transplanted organ can contribute to either induction of tolerance or rejection, and in doing so, provide some direction for this field of research.

These studies¹ address the issue of microchimerism, a phenomenon in which donor hematopoietic cells migrate from the transplanted organ and establish residence in other parts of the host's body—most importantly the primary and secondary lymphoid tissues such as thymus, bone marrow, lymph nodes and