Cardiovascular disease is the leading cause of morbidity and mortality in Western countries. Previous studies have highlighted the beneficial effects of PPAR agonists on cardiovascular disease; however, the role of other PPAR family members in atherosclerosis is less clear. A report in this issue of the JCI expands our understanding of PPARs in vascular biology and highlights the potential use of multiple PPAR agonists to limit lipid accumulation in macrophages (see the related article beginning on page 1564).

PPARs and atherosclerosis: nuclear receptor action in the artery wall
Atherosclerosis is a chronic inflammatory disease as well as a disorder of lipid metabolism (1). The accumulation of cholesterol-rich lipoproteins in the artery wall results in the recruitment of circulating monocytes, their adhesion to the endothelium, and their differentiation into tissue macrophages. Lipid-loaded macrophages play an important role in the production of chemokines, cytokines, and reactive oxygen species in the early stages of lesion formation. Therefore mechanisms that limit macrophage cholesterol accumulation and/or prevent the production of inflammatory mediators all have the potential to inhibit lesion development.

The PPAR family is comprised of 3 different proteins: PPARα, PPARβ (also referred to as δ), and PPARγ (2). Natural ligands for these receptors include fatty acids and oxidized fatty acids. The relevance of PPAR pathways to metabolic disease is underscored by the use of the fibrates (PPARα agonists) and thiazolidinediones (PPARγ agonists) to treat hyperlipidemia and type 2 diabetes, respectively. The expression of PPARs in cells of the artery wall has prompted a number of investigations into the effects of PPAR agonists on atherosclerosis in mice (3). Studies on PPARγ are in general agreement that activation of this receptor in the artery wall is beneficial (4–6). However, studies using PPARα- and PPARβ-knockout mice have yielded more complex results. Transplantation of bone marrow lacking PPARβ has been reported to reduce atherosclerosis in apoE−/− mice (7). Similarly, mice lacking both PPARα and apoE were shown to develop fewer lesions (8). On the other hand, intervention studies using PPARα agonists have suggested antiatherogenic effects in mice (9), and the Veterans Affairs High-Density Lipoprotein Intervention Trial showed a clear reduction in cardiovascular events in patients taking gemfibrozil (10). The impact of PPARβ agonists on atherosclerosis is unknown, although GW1516 was shown to have beneficial effects on plasma lipid profiles in obese rhesus monkeys (11).

PPARs are known to influence pathways for both lipid uptake and efflux in macrophages. PPARγ promotes CD36 expression (12), and both PPARα and PPARγ induce expression of liver X receptor α (LXRα) and ABCA1 (4, 13) (Figure 1). However, the ability of PPARs to control LXRα expression is much more prominent in human cells than in murine cells, raising the possibility that additional pathways are involved in the beneficial effects of PPARs observed in murine models. In addition to their effects on lipid metabolism, PPAR activators also inhibit inflammatory gene expression in cultured macrophages (14). Glass and colleagues have further shown that treatment of LDL receptor-deficient (LDLR−/−) mice with PPARγ agonists reduced the expression of inflammatory mediators (5). Thus inhibition of inflammation represents a second mechanism by which PPAR activation might influence atherogenesis.

Differential effects of PPAR family members on the development of atherosclerosis in mice
In the current issue of the JCI, Li et al. (15) compare the effects of PPARγ, PPARα, and PPARβ ligands on the development of atherosclerosis in LDLR−/− mice. They observed profound atheroprotective effects of the PPARα ligand GW7647, comparable to that previously observed for the PPARγ agonists rosiglitazone and GW7845 (5). In contrast, no change in lesion development was observed in mice treated with PPARβ ligand. Beneficial metabolic effects of PPARα ligand included reduced weight gain, reduced insulin levels, and decreased levels of VLDL and LDL fractions. No significant changes were observed with PPARβ ligand. This shows that the ability to improve plasma lipid profiles and increase insulin sensitivity are likely to be major factors in the effects of PPARα and γ agonists on atherosclerosis observed in diabetic patients and hypercholesterolemic mice.

Li et al. (15) further explored the effects of PPARα and PPARγ agonists on gene expression in atherosclerotic mice. Each of the PPAR ligands was found to repress the expression of inflammatory markers in the artery wall even though PPARβ did not reduce lesion formation. PPARγ ligand increased the expression of CD36, LXRα, and ABCA1 and promoted cholesterol efflux in cultured macrophages. However, at the end of the study, ABCA1 expression was not induced by either ligand, and LXRα expression was induced only by the PPARα ligand. PPARγ did activate LXRx and ABCA1 at earlier stages. Thus, neither anti-inflammatory activity nor the ability to regulate LXR correlated well with the anti-atherosclerotic effects.

Effects of PPAR family members on macrophage foam-cell formation
To further explore the mechanism of PPAR actions in atherogenesis, Li et al. (15) developed a novel approach for evaluating macrophage foam-cell formation in vivo. This approach involved the adoptive transfer of peritoneal macrophages from various PPAR null mice into the peritoneal cavity of LDLR−/− mice fed a cholesterol-rich diet. This innovative assay provides a new model for macrophage lipid uptake although further validation is needed to clarify whether the assay faithfully reflects the actions of artery wall macrophages during atherogenesis. Nevertheless, Li et al. found that PPARα and PPARγ ligands

Nonstandard abbreviations used: LDLR−/−, LDL receptor-deficient; LXR, liver X receptor.
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inhibited lipid accumulation in a receptor-dependent manner, pointing to direct protective mechanisms within the macrophage. PPARγ ligand also markedly reduced cholesterol esterification in macrophages. This newly appreciated activity may be a significant contributor to the atheroprotective effects of PPARγ agonists. The authors also investigated the potential role of LXRs in the antiatherogenic effects of PPAR ligands. LXR is a key transcriptional regulator of ABCA1 and ABCG1 expression and plays a major role in protection against cellular lipid overload, as deduced from studies using LXR-deficient macrophages and synthetic ligands (16–18). The results of Li et al. (15) suggest that the inhibition of foam-cell formation observed with PPARα ligands requires the expression of LXRs whereas inhibition by PPARγ ligands does not. Interestingly, the authors found that the ability of rosiglitazone to inhibit peritoneal foam-cell formation in WT and LXR null macrophages correlated with a modest increase in ABCG1 but not ABCA1 expression. Thus the ability of PPARγ to promote efflux independently of LXR may involve direct effects on efflux transporters (Figure 1). ABCG1 was recently shown to increase cholesterol efflux from macrophages to HDL, but not apoAI (19) and ex vivo macrophages from PPARγ ligand–treated mice showed increased cholesterol efflux to HDL, consistent with this mechanism. However, the definitive role of ABCG1 in lipid metabolism and atherosclerosis in vivo has not yet been established. Furthermore, the effects of PPAR agonists on ABCG1 expression in macrophages are small compared to those of LXR agonists (18), and the possibility that ABCG1 might be a direct target of PPARγ remains to be explored. In the future, it will be of interest to determine whether the atheroprotective effects of PPAR agonists are lost in mice lacking ABCG1.

Conclusions

The study by Li et al. (15) provides new insights into pathways regulating macrophage lipid accumulation and rounds out the family picture of PPARs in atherosclerosis (Figure 1). Both PPARα and PPARγ ligands were shown to protect against atherosclerosis in LDLR–/– mice and inhibit macrophage foam-cell formation. In contrast, the authors did not observe any effect from PPARβ activation. Given the discrepancies between PPARβ agonist effects in mice and primates, however, the possibility that PPARβ ligands may have beneficial effects on cardiovascular disease in humans is not excluded by the present study. Finally the work of Li et al. emphasizes that PPAR agonists are likely to exert their antiatherosclerotic properties by multiple mechanisms, including improving systemic lipid levels, improving insulin resistance, and inhibiting the accumulation of macrophage foam cells.

Address correspondence to: Peter Tonottonoz, Howard Hughes Medical Institute, UCLA, Box 951662, Los Angeles 90095-1662, California, USA. Phone: (310) 206-4546; Fax: (310) 267-0382; E-mail: ptonottonoz@mednet.ucla.edu.
commentaries


Fusion of bone marrow–derived stem cells with striated muscle may not be sufficient to activate muscle genes

Giulio Cossu

Stem Cell Research Institute, DIBIT, Milan, Italy.

Several studies have demonstrated the existence of pluripotent bone marrow–derived stem cells capable of homing to injured cardiac and skeletal muscle; however, there has been little evidence demonstrating the induction of tissue-specific endogenous genes in donor stem cells following engraftment. A new study in this issue reports an intriguing finding that raises additional concerns relating to stem cell plasticity and stem cell therapy in an already heated and controversial field. The study demonstrates that wild-type bone marrow–derived side population stem cells are indeed readily incorporated into both skeletal and cardiac muscle when transplanted into mice that lack δ-sarcoglycan—a model of cardiomyopathy and muscular dystrophy. However, these cells fail to express sarcoglycan and thus to repair the tissue, which suggests that this stem cell population has limited potential for cardiac and skeletal muscle regeneration (see the related article beginning on page 1577).

Bone marrow–derived side population (BM-SP) stem cells have the ability to repopulate the hematopoietic system (1) and to colonize, at low frequencies, many different tissues, including skeletal (2) and cardiac muscle (3). The δ-sarcoglycan–null mouse is a model of cardiomyopathy and muscular dystrophy (corresponding to a human limb-girdle myopathy) and develops microinfarcts in heart and skeletal muscle (4). Muscle cell death in this model is related to the lack of δ-sarcoglycan, which causes loss of the other sarcoglycans (ε, β, and γ) and in turn disassembly of the dystroglycan complex (Figure 1), which is composed of several proteins that link the cytoskeleton to the basal lamina and reduce membrane stress during contraction. Absence or reduction of the dystroglycan complex results in increased fragility of the membrane and increased chance of damage to the muscle cell. Resident cells capable of repairing injured skeletal muscle (satellite cells) are well characterized (5), and despite the long-held belief that heart cells cannot regenerate, evidence for the existence of cells with a similar reparative function in the heart has only begun to accumulate during the last 2 years (6, 7). This observation suggests that injured δ-sarcoglycan–deficient tissues should recruit both local and blood-born stem cells that may contribute to regeneration.

In this issue of the JCI, Lapidos et al. (8) transplanted BM-SP stem cells from wild-type male mice into female δ-sarcoglycan–null mice, and their results, consistent with those from previous studies of stem cell–mediated skeletal and cardiac muscle regeneration, demonstrated the presence of these donor cells, determined by the presence of a Y chromosome inside cardiac and skeletal muscle at the expected frequency. A fraction of the nuclei of these Y chromosome–positive donor cells was unequivocally shown to be present inside the cytoplasm of several differentiated car-