16.4.1 The Role of PPARs in Age-Related Inflammatory Diseases

16.4.1.1 Atherosclerosis and Cardiovascular Diseases

It has been suggested that chronic vascular inflammation underlies the pathogenesis of atherosclerosis.[71] Although atherosclerosis is traditionally viewed as a sole metabolic disease with abnormal lipids in systemic circulation, the inflammatory component of atherogenesis is increasingly being recognized.[72] It is now known that inflammation participates in all stages of atherosclerosis including initiation and progression of atherogenic dyslipidemia. Chronic low-grade inflammation also participates in cardiac hypertrophy and heart failure.[73] In this respect, PPARs are involved in the progression of atherosclerosis and other cardiovascular diseases and therefore they are promising targets for treatment of these diseases.

Roles for PPARα in the progression of atherosclerosis are well documented. PPARα agonists suppress the progression of atherosclerosis by inhibiting foam cell formation in a low-density lipoprotein receptor (LDLR)-deficient mice model.[74] Furthermore, PPARα expression in macrophages showed strong anti-atherogenic effects in an LDLR-deficient mice model *via* modulation of cell cholesterol trafficking and inflammation.[75] Interestingly, miRNA-21 induced by shear stress decreased PPARα expression and activated pro-inflammatory AP-1, demonstrating the anti-atherogenic role of PPARα.[76] PPARα also controls cardiac hypertrophy by reducing inflammation and regulating metabolism. A PPARα agonist inhibited hypertrophy of neonatal rat cardiac myocytes.[77] The role of PPARα in hypertrophy is also demonstrated using PPARα deficient mice in response to chronic pressure overload.[78] In addition, PPARα in association with NAD+-dependent deacetylase, SIRT1, reduces inflammation and cardiac hypertrophy.[79] PPARβ/δ also inhibits atherosclerosis and cardiac hypertrophy.[80] The synthetic PPARβ/δ agonists reduced atherosclerosis in LDLR-deficient mice by decreasing pro-inflammatory mediators.[81,82] Activation of anti-inflammatory mediator Bcl-6 seems to contribute to the anti-atherogenic role of PPARβ/δ.[82,83] Similarly, PPARβ/δ agonists normalize cardiac substrate metabolism and reduce cardiac hypertrophy.[84] Activated PPARβ/δ also dampens LPS-induced inflammatory signaling in cardiomyocytes, and it blocks lipid-induced inflammatory pathways in mouse heart and human cardiac cells.[85,86] PPARγ shows its anti-atherogenic activity in various cells, including endothelial cells, macrophages, and smooth muscle cells. The disruption of PPARγ in macrophages and smooth muscle cells increases atherosclerosis.[87,88] Endothelial PPARγ prevents the initiation of atherosclerosis by enhancing endothelial cell function.[89] There are conflicting outcomes on the role of PPARγ in cardiac physiology. Expression of PPARγ in macrophages attenuates progressive cardiac fibrosis occurring in diabetic cardiomyopathy.[90] However, cardiomyocyte expression of PPARγ can lead to cardiac dysfunction implying cell-specific functions for PPARγ.[90,91]