Changes in body composition account for the vast majority of declines in metabolic function. Increased visceral fat, which is commonly named as abdominal obesity, is a major contributor to IR and MS.[25] As it turns out, adipose tissue participates in many biological processes.[26] For example, adipose tissue is now recognized as an immune organ that secretes various adipokines and pro-inflammatory cytokines that contribute to the pathogenesis of IR and age-associated chronic diseases.[27] In addition, a decline in endocrine function also contributes to age-related metabolic dysregulation.

Age-related changes in growth hormone (GH), insulin-like growth factor-1 (IGF-1), and sex steroids are known to be linked to the aging process. GH/IGF-1 signaling pathways are particularly of interest because they elicit the same effect as insulin. GH/IGF-1 secretion markedly decreases with aging, and decreased levels of IGF-1 are associated with an increased risk of metabolic disorders.[28] Since nutrient sensing signaling is deregulated with aging, age-related decline of GH/IGF-1 signaling should also be considered important. Other changes including changes in energy sensing systems (mTOR, AMPK, and sirtuins), mitochondria dysfunction, and epigenetic modification also cause metabolic problems during aging.[9,10]

One recent study showed the importance of hyperthalamic inflammation (especially involved in NF-κB signaling) in aging.[23] Because study results show that the hypothalamus plays a pivotal role in the regulation of whole-body metabolism including appetite, glucose metabolism and lipid metabolism *via* endocrine system regulation, these findings suggest that uncontrolled inflammation in the hypothalamus may modulate systemic aging and metabolic disorders. Moreover, abnormal increases in several metabolites accompanying metabolic syndrome can directly influence inflammation. Among the numerous metabolites increased in metabolic diseases, saturated fatty acids (SFAs) and ceramides are potent inflammation inducers.[29] Collectively, these age-related alterations in inflammation and metabolism are active participants in a vicious cycle that can accelerate the aging process and onset of metabolic diseases.

16.3 Functions of PPARs in the Regulation of Metabolism and Inflammation

16.3.1 PPAR Signaling and Metabolism

PPARs are ligand-activated transcriptional factors belonging to the nuclear receptor superfamily.[30] PPARs are classified into three types: PPARα, PPARβ/δ, and PPARγ. By binding to PPAR-responsive regulatory elements (PPRE) with heterodimeric formation with retinoid X receptor (RXR), PPARs control the expression of networks of genes involved in a broad spectrum of biological processes including metabolism, inflammation, cellular proliferation, and tissue remodeling.[31] Although PPARs regulate various cellular processes, the most important role of PPARs is regulation of energy metabolism. Thus, PPARs agonists/antagonists are proposed to be promising therapeutic targets for the treatment of various metabolic diseases (Figure 16.1).[30]