mechanisms and beneficial effects of PPARβ/δ are not fully understood, recent studies have shed light on its physiological roles.[31]

PPARγ is a master regulator of adipogenesis.[42] It is most highly expressed in white adipose tissue (WAT) and brown adipose tissue (BAT), where it modulates whole-body lipid metabolism and insulin sensitivity. PPARγ exists as two isoforms, PPARγ1 and PPARγ2, because of alternative splicing and differential promoter usage.[43] The expression of PPARγ2 is restricted to adipose tissue under normal physiological condition, whereas PPARγ1 is expressed widely. Originally, PPARγ was described as a factor that permits differentiation of preadipocytes into adipocytes.[44] PPARγ null mice lacked adipose tissue, demonstrating that PPARγ is required for adipocyte differentiation.[45] Likewise, PPARγ directly induces many genes involved in adipocyte lipid storage. In addition to its role in regulation of adipose tissue differentiation and lipid metabolism, PPARγ also regulates glucose homeostasis.[46] PPARγ directly regulates the expression of glucose transporter type 4 (Glut4) and c-Cbl-associated protein (CAP), which is important for glucose homeostasis. PPARγ also controls the expression of numerous factors secreted from adipose tissue that influence insulin sensitivity. Therefore, PPARγ can play an important role in regulating metabolism and may be involved in achieving the insulin sensitizing effect.

16.3.2 PPARs and Inflammation

Although the main role of PPARs is regulating metabolic homeostasis in various pathophysiologic conditions, recent evidence has revealed a new role of PPARs as regulators of inflammation (Table 16.1).[47–49] This newly discovered anti-inflammatory feature of PPARs potentiated its role as an important metabolic regulator because many metabolic disorders are accompanied by pro-inflammatory states, as discussed in the previous section.

The well-characterized anti-inflammatory effects of all three PPAR isotypes are shown through the trans-repression of important transcription factors in inflammation. The most important regulators of inflammation, including NF-κB, activator protein-1 (AP-1), ATF family, and signal transducer and activator of transcription (STAT) family, are known to be regulated by PPARs through trans-repression mechanisms.[50,51] Activation of PPARs leads to repression of inflammatory cytokines and molecules through repression of these transcriptional factors. There are several proposed mechanisms for the possible interaction between PPARs and several transcription factors. First, the co-activator competition model proposes that NF-κB and PPARs use an overlapping set of co-activator proteins. In this scenario, PPARs compete with NF-κB for binding to the co-activators, thereby regulating its transcriptional activities.[50] The second model proposes direct interactions between PPARs and other transcriptional factors, resulting in the inhibition of transcriptional activity of one or both factors.[50,52,53] Lastly, the co-repressor-dependent model explains that PPAR ligands mediate the trans-repression of inflammatory genes by preventing the clearance of co-repressor complexes.[51]