between PPARγ and aging.[122] Interestingly, one recent study indicated PPARγ as an important longevity gene especially in white adipose tissue (WAT).[123] *In silico*, these authors found that both transcriptional signatures of the PPARγ signaling pathway and of the PPARγ agonist rosiglitazone overlapped in the subnetwork of their longevity-associated genes. Further *in vivo* experiments demonstrated the role of PPARγ in life span using WAT-specific PPARγ knockout mice.[123] These genetic approaches and other available biological evidence strongly suggest the very complicated involvement of PPARs in age-related diseases and aging processes.

16.5 Anti-Aging and Therapeutic Potentials of New PPAR Agonists

To date, many endogenous ligands and natural compounds have been discovered as PPARs activators, and new synthetic chemical compounds are being developed to activate PPARs.[124] Endogenous ligands, including polyunsaturated fatty acids and some eicosanoids like prostaglandins and leukotriene, are produced in the metabolic pathways of fatty acids and regulate an individual's metabolism.[125] In addition to endogenous PPARs ligands, many PPAR agonists are developed based on a ligand binding site. The hypolipidemic fibrate and antidiabetic thiazolidinedione (TZD) classes of drugs are two representative PPAR agonists that activate PPARα and PPARγ, respectively.[126]

As activation of PPARα is known to increase β-oxidation-associated gene expression, fibrates decrease high triglyceride-containing lipoproteins and improve overall lipid profiles. Fibrates also increase insulin sensitivity and reduce plasma glucose levels. TZD drugs are used in the treatment of type 2 diabetes mellitus as TZD increases insulin sensitivity. In particular, PPARγ activation by TZD prevents lipotoxicity by regulating adipose tissue lipid accumulation and protects non-adipose tissues (liver, skeletal muscle) against excessive lipid overload. Furthermore, activated PPARγ by TZD also permits adequate secretion of leptin and adiponectin, which are mediators of insulin action in peripheral tissues. Collectively, considering the wide range of actions of PPAR agonists, PPAR modulators are suggested to be promising agents for the treatment of metabolic disorders, including hyperlipidemia, hyperglycemia, and type 2 diabetes.

As mentioned earlier, the PPAR family has dynamic roles, including regulation of inflammation, immunity, cell proliferation, and tissue remodeling. As a consequence, some PPAR agonists have shown beneficial effects in various diseases, including atherosclerosis, cardiovascular diseases, Alzheimer's disease, inflammatory bowel diseases, and renal diseases.[126,127] Although the roles of PPAR activation in various disease models are fairly well demonstrated, their beneficial roles in the aging process are not fully verified. Recently, several studies have investigated the roles of PPAR agonists in pathophysiological changes during the aging process. Yang *et al.*