the anti-inflammatory effects of PPARα. PPARα, by directly increasing IκBα, can inhibit translocation of NF-κB to the nucleus and subsequently suppress transcriptional activity.[56] Furthermore, PPARα exerts its anti-inflammatory effect through regulation of leukotriene B_4 (LTB_4). LTB_4 is a potent pro-inflammatory lipid mediator that is increased in various forms of inflammation through lipoxygenase (LOX) activity. Since LTB_4 is a direct ligand for PPARα and since PPARα increases the expression of cytochrome P450 and β-oxidation enzymes responsible for the breakdown of LTB_4, PPARα can likely contribute to the resolution of inflammation through this mechanism.[57,58]

PPARγ also has several anti-inflammatory effects through trans-repression or other mechanisms. PPARγ agonists were shown to decrease inflammatory responses in several innate immune cells.[59,60] Pascual *et al.*[51] reported that PPARγ interacts with a protein inhibitor of the activated transcription factor (PIAS1), the physiological role of which is to facilitate the localization of PPARγ to the NCoR complexes on the promoters of inflammatory genes. Consequently, PPARγ inhibits NF-κB-mediated inflammatory gene expressions in a trans-repression manner. Furthermore, PPARγ is an important transcriptional factor for the alternative macrophage activation that shows anti-inflammatory properties needed for resolution of inflammation.[61] Although the Th2 cytokines (IL-4, IL-13) are needed for the alternative macrophage activation, the acquisition and maintenance of this phenotype require PPARγ activation.[61]

To understand the action of PPARβ/δ on inflammation, a description on Bcl6 is needed. The release of Bcl6 is known to contribute to several of the anti-inflammatory actions.[62] The dissociation of Bcl6 from activated PPARβ/δ renders this cofactor available for gene repression, such as MCP1 and IL-1β.[62] The inhibition of NF-κB signaling is another common mechanism for the anti-inflammatory actions of PPARβ/δ, although the clear mechanisms are not fully understood yet.[63,64] Induction of anti-inflammatory genes may also be another mechanism for the PPARβ/δ's anti-inflammatory actions. Some anti-oxidant genes and anti-apoptosis genes are induced by PPARβ/δ, which can indirectly suppress inflammation.[65,66] More directly, PPARβ/δ induces the well-known anti-inflammatory mediator TGFβ.[67]

16.4 Evidence for Involvement of PPARs in Age-Related Inflammatory Diseases and Aging

As mentioned above, aging is characterized by time-dependent changes in physiological functions accompanied by pathological diseases. Evidence from many recent studies has linked chronic inflammation to the progression of age-related diseases including arthritis, cardiovascular diseases, dementia, inflammatory bowel diseases, and metabolic syndrome. In this regard, it is evident that the ability of PPARs as regulators of inflammation and metabolism will retard age-associated diseases. Several reviews already cover a great deal of information regarding the role of PPARs in regulation of metabolism.[42,68–70]