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Review

Molecular mechanism of PPAR in the regulation of age-related inflammation

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Abstract

Evidence from many recent studies has linked uncontrolled inflammatory processes to aging and aging-related diseases. Decreased a nuclear receptor subfamily of transcription factors, peroxisome proliferator-activated receptors (PPARs) activity is closely associated with increased levels of inflammatory mediators during the aging process. The anti-inflammatory action of PPARs is substantiated by both in vitro and in vivo studies that signify the importance of PPARs as major players in the pathogenesis of many inflammatory diseases. In this review, we highlight the molecular mechanisms and roles of PPARα, γ in regulation of age-related inflammation. By understanding these current findings of PPARs, we open up the possibility of developing new therapeutic agents that modulate these nuclear receptors to control various inflammatory diseases such as atherosclerosis, vascular diseases, Alzheimer's disease, and cancer.

Keywords: PPARs; Aging; Inflammation; Inflammatory diseases

1. Introduction

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors belonging to the nuclear receptor superfamily. Originally, the involvement of PPAR activity was thought to be limited to lipid metabolism and glucose homeostasis. Later studies showed that PPAR activation regulates broader biological functions such as cell proliferation and differentiation as well as apoptosis (Houseknecht et al., 2002; Bishop-Bailey, 2002; Chinetti et al., 2003). To date, three PPAR isotypes have been characterized: PPARα, PPARβ/δ, and PPARγ. Intensive studies of PPARs during last few years have revealed their importance to both normal physiology and the pathology of various tissues. PPARα is expressed in liver, kidney, muscle, heart, and in cells from the vascular wall

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(Gervois et al., 2005). PPARγ is mainly expressed in adipose tissues where it plays a role in lipid metabolism (Ferre, 2004; Linford et al., 2007). PPARβ/δ is expressed in a wide range of tissues and is involved in regulation of lipid metabolism (Grimaldi, 2007).

More relevant to the main topic of this review is the involvement of PPARα and PPARγ in age-related inflammation, as a regulator of inflammatory responses (Genolet et al., 2004; Chawla et al., 2001). Several recent studies have revealed that PPARα and PPARγ inhibit the expression of inflammatory genes, such as cytokines, matrix metalloproteases (MMPs), and acute phase proteins (Jiang et al., 1998; Ricote et al., 1998). Interestingly, all available data indicate that the activation of PPARα and PPARγ modulates oxidative stress-sensitive pathways, redox-responsive nuclear factor-κB (NF-κB), activator protein-1 (AP-1), and signal transducers and activators of transcription (STAT) (Blanquart et al., 2003; Delerive et al., 1999). Findings such as these strongly indicate PPARα and PPARγ in controlling the inflammatory process and their potential as therapeutic target sites for age-related inflammatory diseases. The supplementation of the PPARα agonist, Wy 14,643 and dehydroepiandrosterone sulfate (DHEAS) suppressed the age-induced up-regulation of NF-κB activity and the expression of several NF-κB-regulated genes (Poynter and Daynes, 1998). Moreover, evidence shows an enhanced age-dependent rise of NF-κB activation in PPARα knockout mice and its retardation by PPAR agonists (Jones et al., 2002). In addition, PPARγ agonist also participates in the control of inflammation in modulating the production of inflammatory mediators, in part by inhibiting the activation of NF-κB (Jiang et al., 1998).

The key question regarding the involvement of PPAR in the aging process was recently addressed in a report by Howroyd et al. (2004). The authors showed that PPARα-null mice had decreased longevity compared with wild-type mice and presented data that the shortened life span may be related to various non-neoplastic spontaneous aging lesions, which occurred at a higher incidence and with shorter latency in the PPARα-null mice. In line with the involvement of PPARα in the aging process, PPARγ variants also were reported to have an important role in longevity, found in human with low insulin resistance (Capri et al., 2006; Paolisso et al., 2001). These results and other available evidence together suggest strongly the involvement of PPARs in age-related inflammation and aging processes.

In this review, a chronic inflammatory process in relation to aging is highlighted at first. Discussion describes the involvement of PPARα, γ in the aging process, focusing on age-related inflammation as well as the effects of naturally occurring PPAR agonists in inflammation and aging processes. Also, proposed molecular mechanisms of PPAR transrepression activity are described as a bridge between normal age-related changes and pathological expressions. Exemplifying aging-related conditions such as atherosclerosis, vascular diseases, Alzheimer's disease, and cancer will highlight arguments that PPARs are a regulator of pro-inflammatory responses and age-related inflammation-related signaling pathways.

2. Activation of inflammatory genes during aging

Our recent inflammation hypothesis of aging process presented evidence that the inflammatory process may play a major role in the aging process and aging-related diseases (Chung et al., 2002, 2006; Yu and Chung, 2007; Kim et al., 2002b). The basic tenet of the proposal is based on several lines of evidence: (1) a disrupted redox state and increased oxidative stress during aging; (2) the activation of many pro-inflammatory transcription factors exquisitely sensitive to redox changes due to increased oxidative stress during aging; (3) increased C-reactive protein (CRP), TNF-α, and IL-6 in aged animals and humans; (4) molecular data showing the up-regulation of IL-1β, IL-6, TNF-α, COX-2, and iNOS during aging; (5) enhanced susceptibility of aged animals to inflammatory stimuli, e.g., lipopolysaccharide (LPS). In line with these evidences, molecular examinations revealed that the redox-sensitive transcription factor, NF-κB plays a central role in regulating age-related inflammatory processes. NF-κB binds to defined DNA motifs (consensus: 5′-GGGPuNNPyPyCC-3′) to enhance the transcription activity of a variety of genes. In most cells, NF-κB engages in an early reaction that is characterized as a molecular inflammatory stage by activating the transcription of various pro-inflammatory genes encoding inflammatory cell adhesion molecules, cytokines, and chemokines (Chung et al., 2001; Baeuerle and Baltimore, 1996).

Our previous findings documented the role of NF-κB signaling in this inflammatory process by showing up-regulated levels of monocyte chemo-attractant protein (MCP)-1 in aged rats through the activation of NF-κB signaling (Kim et al., 2006). Others also reported that the expression of adhesion molecules such as aortic P-selectin, vascular cell adhesion molecule 1 (VCAM-1), and intracellular adhesion molecule-1 (ICAM-1) are up-regulated during aging by the activation of NF-κB signaling (Zou et al., 2004, 2006).

Under normal physiological conditions, NF-κB activation in response to pro-inflammatory signals is short-lived, and the reaction stops quickly once the signal is terminated. However, when the activation signal persists as in the aging process, a chronic inflammatory condition would have far reaching effects. Interestingly, some NF-κB-induced proteins are known to act as potent NF-κB activators, consequently synthesizing more inflammatory mediators (Yu and Chung, 2007). Consistent findings show that DNA binding activity and NF-κB transcriptional activity are enhanced in old rodents, as found in heart, liver, kidney, brain, and adipose tissues (Helenius et al., 1996; Kim et al., 2002b).

The regulation of NF-κB has been elucidated through the identification of its inhibitor kinase, IκB, which consists of the heterodimers IKKα and IKKβ, complexed with the regulatory subunit, IKKγ (Zandi et al., 1997). Phosphorylation by IKK of the IκB subunits of NF-κB leads to activation of NF-κB in the cytosolic compartment, thereby allowing the translocation of its subunits (p65 and p50) into the nucleus where the transcription of various pro-inflammatory genes takes place (Bruunsgaard et al., 2001). In a previous study, we provided supporting data showing that increased expressions of inflammatory genes are due to an age-related IκBα decrease and its increased dissociation from the complex in the cytosol, thereby allowing the nuclear translocation of NF-κB (Kim et al., 2002c; Chung et al., 2006).

Since the correlation between NF-κB signaling and inflammatory gene expression has become known, many researchers have been intensively studying the regulation of the NF-κB signaling cascade. Of the many modulators studied, PPARs have been shown to exert their anti-inflammatory effects by inhibiting the NF-κB signaling cascade at many different levels, including affecting upstream signaling molecules and blocking transcription in a process called transrepression (more discussion in later section). Therefore, these findings along with data from other investigations postulate that the NF-κB signaling cascade plays a key role in age-related inflammation and that its regulation by PPARs may have wide therapeutic applications for age-related inflammation.

3. Roles of PPARs in inflammation and aging

To date, many studies have focused on the involvement of PPARs in inflammation but few of these have investigated specific roles PPARs play in aging processes and age-related inflammation. Therefore, it is important to delineate the molecular characteristics of PPARs in age-related inflammation.

A wide involvement of nuclear receptor signaling in various physiological functions and diseases is now well appreciated (Carlberg and Dunlop, 2006). With regard to the aging process, Boylston et al. (2004) reported that the significantly increased expression of PPARγ in long-lived Snell dwarf mice relative to age-matched controls. Accumulated evidences show that PPARγ is decreased in the brains and spleens of old rodents compared with young ones (Sastre et al., 2006a; Gelinas and McLaurin, 2005). Our laboratory also found that mRNA levels, nuclear protein levels, and DNA binding activity of PPARα and PPARγ in rat kidney are decreased (Sung et al., 2004). Interestingly, the level of these PPARs decreased to greater extent in old rats than in young rats when they were challenged with inflammatory LPS (Sung et al., 2004).

As summarized in Table 1, many lines of evidence have indicated that the activation of PPARs can affect age-related inflammation by regulating NF-κB signaling and its target gene expression (Table 1). The supplementation of PPARα agonist, Wy-14,643 and DHEAS, for example, suppressed the age-induced up-regulation of NF-κB activity in spleen of aged mice (Poynter and Daynes, 1998). In support of evidence on the role of PPARα in the suppression of NF-κB activity, PPARα agonists also are shown to decrease production of pro-inflammatory mediators such as IL-6, IL-12, IL-1α, iNOS, and COX-2, which are associated with a decrease in NF-κB activation as found in kidney, heart, and brain of aged mice (Erol, 2005; Delerive et al., 2001; Spencer et al., 1997).

Recent findings from our laboratory when comparing kidneys of rats at ages 9 and 22 months provided strong evidence that the glucose-lowering, anti-diabetic, 2,4-thiazolidinedione (2,4-TZD), a well-known PPARγ activator, does exert anti-inflammatory effects on the aging process. This study revealed that the 2,4-TZD treatment brought about several major changes: decreased p65 translocation and NF-κB binding activity; and NF-κB-activated gene expressions, such as iNOS, COX-2, IL-1β, IL-6, adhesion molecules, VCAM-1, and P-selectin. Therefore, our results combined with others firmly established the inhibitory roles for PPARs on age-related inflammation (Sung et al., 2006).

Hallmarks of aging are the physiological changes that are characterized by fat re-distribution, obesity, and insulin resistance, for which PPARs may play a major role (Masternak and Bartke, 2007; Nunn et al., 2007; Cha et al., 2007).

Table 1
Alteration of inflammatory mediators during aging and suppression by PPAR

	Inflammatory process	Aging process	PPAR activity	References
Proinflammatory				
iNOS	↑	↑	↓	Erol (2005) and Delerive et al. (2001)
Enzymes				
COX-2	↑	↑	↓	
Proinflammatory				
IL-6	↑	↑	↓	Sung et al. (2006) and Poynter and Daynes (1998)
Cytokines				
IL-12	↑	↑	↓	
TNF-α	↑	↑	↓	
Adhesion molecules				
P-selectin	↑	↑	↓	Wang et al. (2002) and Pasceri et al. (2000)
VCAM-1	↑	↑	↓	
ICAM-1	↑	↑	↓	
Chemokines				
MCP-1	↑	↑	↓	Murao et al. (1999) and Pritts et al. (2003)
RANTES	↑	↑	↓	
NF-κB				
DNA binding activity	↑	↑	↓	Cabrero et al. (2002), Chung et al. (2000), and Castrillo et al. (2000)
IKK activation	↑	↑	↓	
Degradation of IκBα and IκBβ in cytoplasm	↑	↑	↓	
Phosphorylation of IκBα	↑	↑	↓	
Nuclear translocation of p50	↑	↑	↓	

↑, increased; ↓, decreased.

Several studies provided evidence that age-related inflammation in adipose tissue (AT) contributes to insulin resistance in type 2 diabetes (T2D) (Blanquart et al., 2003; Cock et al., 2004). Wu et al. (2007) showed that when compared to young mice, visceral AT from old C57BL mice had significantly higher mRNA expression of the pro-inflammatory cytokines IL-1β, IL-6, TNF-α, and COX-2 through NF-κB signaling and lower expression of anti-inflammatory PPARγ.

PPARs have been shown to be an effective modulator in a number of age-related inflammatory disease models by reversing increased inflammatory mediators during aging processes (Heikkinen et al., 2007). For instance, Giaginis et al. suggested that PPARs, especially the gamma isotype, could be targets in treatments for diverse bone diseases such as osteoporosis and osteopenia that are related to aging-associated inflammation (Giaginis et al., 2007). Several drugs of the TZD class and the natural ligand 15-deoxy-δ-12,14-prostaglandin J_2 (15d-PGJ_2) have been shown to inhibit age-related diseases such as type II diabetes and atherosclerosis by down-regulating inflammatory molecules (Argmann et al., 2005; Cock et al., 2004). It is interesting to note that the activation of PPARγ by non-steroid anti-inflammatory drugs (NSAIDSs) also was shown to suppress pro-inflammatory amyloid-β in an Alzheimer's disease animal model (Sastre et al., 2006a).

Some PPAR agonists also have been used as therapeutic drugs for the treatment of age-related inflammatory disorders such as arthrosclerosis and dyslipidemia, although these drugs are now suspended due to safety concerns. Nevertheless, it is obvious that PPAR ligands can be effective in controlling the inflammatory process during aging.

4. Effects of natural PPAR agonists on inflammation and aging

Recently, studies have been widely conducted on naturally occurring phytochemicals that up-regulate the functions of PPAR activation as pharmaceutical tools due to their safe and cost-effective properties (Huang et al., 2005). Epidemiological studies show that the consumption of vegetables, fruits, and tea is associated with a decreased risk of

inflammation-mediated diseases including cancer and cardiovascular diseases (Huang et al., 2005; Liang et al., 2001). In this regard, Liang et al. (2001) explored the PPAR agonist actions of several flavonoids, a diverse family of chemicals commonly found in fruits and vegetables. Of the compounds tested in their group, apigenin, chrysin, and kaempferol significantly stimulated PPARγ transcriptional activity. Importantly, these investigators found that these three flavonoids strongly enhanced the inhibition of pro-inflammatory mediators, iNOS and COX-2 promoter activities in part by inhibiting IKK activity in LPS-activated macrophages that contain the PPARγ expression plasmids.

Further evidence for the beneficial efficacy of natural phytochemicals on inflammation and aging comes from experiments with curcumin, the principal curcuminoid in the curry spice, turmeric, which exerts anti-inflammatory effects by up-regulating PPARs (Siddiqui et al., 2006). We showed recently that 3-methyl-1,2-cyclopentanedione (3-MCP), an ingredient of coffee extract, can suppress age-related inflammation by increasing PPAR activity. Our data showed that 3-MCP suppressed NF-κB signaling pathways and its target genes in the kidneys of aged animal rats, when comparing 6- and 21-month-old animals (Chung et al., 2007; Choi et al., 2007). In addition to this 3-MCP data, our most recent studies with other phytochemicals, zingerone and baicalein, also were shown to be efficacious against age-related inflammation in a similar magnitude to that observed with 3-MCP (data not published).

5. Proposed molecular mechanisms of PPAR transrepression activity

Studies exploring the molecular mechanisms of PPARs revealed that a much broader influence of PPARs on the inflammatory transcriptional activity other than NF-κB signaling pathway. For instance, PPARs also regulate transcription factors such as STAT family, AP1, ATF-1, 4 (Mendez and LaPointe, 2003; Subbaramaiah et al., 2001), and modulate the transcription of inflammatory molecules such as iNOS (Crosby et al., 2005) and COX-2 (Kim et al., 2002a).

Because PPARs participate in many diversified activities, it is difficult to define molecular mechanisms of PPAR activity. In the following, we describe three proposed models for the possible interaction between PPARs and NF-κB.

5.1. Co-activator competition model

The co-activator competition model proposes that NF-κB and PPARs use an overlapping set of co-activator proteins (Ricote and Glass, 2007; Yu and Reddy, 2007), and in this model, PPARs compete with NF-κB for binding to the co-activators. Under normal conditions, PPARs interact with a nuclear receptor co-repressor (NCoR) that serves to repress PPAR-mediated transcription. The switch from repression to activation needs the reduced affinity for co-repressor through a ligand-induced allosteric change in the C-terminal region of the ligand binding domain. In addition to the conformational change in ligands binding domain, ligand binding removes NCoR complexes from promoters of nuclear receptor target genes, increasing the affinity for co-activators (Li et al., 2000). However, a serious question was raised about this model because transrepression still occurs in the presence of excess co-activators (De Bosscher et al., 2000).

5.2. Direct interactions between PPARs and NF-κB

The second proposed model involves direct interactions between nuclear receptors and negatively regulated transcription factors, resulting in the inhibition of DNA-binding and/or transactivating activity of one or both factors (Ricote and Glass, 2007). For instance, in endothelial cell lines, PPARα inhibits the inflammatory response by direct protein–protein interaction with p65 (Poynter and Daynes, 1998). Similarly, PPARγ inhibits production of cytokines in LPS-stimulated macrophages by direct interaction with p65/p50 (Chung et al., 2000). PPARα ligands in smooth muscle cells and hepatocytes induce the expression of IκBα, leading to retention of the NF-κB subunits in the cytoplasm and consequently suppress their DNA binding activity (Delerive et al., 2000).

It is worth pointing out that PPARγ ligands besides promoting its interaction with NF-κB subunits, could have PPARγ independent actions. For instance, the PPARγ ligand, 15d-PGJ_2 inhibits the secretion of TNF-α and IL-6 in macrophages stimulated by LPS, and directly blocks activity of the IκB kinase complex in a PPARγ-independent way (Castrillo et al., 2000).

5.3. Co-repressor-dependent model

Recent studies have led to another model of co-repressor-dependent mechanism. According to this model, PPARγ ligands mediate the transrepression of inflammatory genes by preventing the signal-dependent clearance of co-repressor complexes. Pascual et al. (2005) reported that yeast two-hybrid screen assays showed that PPARγ interacts with the protein inhibitor of the activated transcription factor, STAT-1 (PIAS1). The physiological role of PIAS1 is to facilitate PPARγ to localize to the NCoR complexes on the promoter of inflammatory genes, including iNOS, in the presence of PPARγ ligands. Sumoylated PPARγ with the NCoR complex prevents subsequent recruitment of the ubiquitination machinery responsible for clearing the promoter of the repressive complex. Consequently, NF-κB mediated inflammatory gene expressions are down-regulated (Bailey and Ghosh, 2005).

6. Evidence for PPAR involvement in inflammatory diseases

Inflammation is a long-suspected, well-recognized risk factor underpinning many chronic inflammatory diseases, including arthritis, cardiovascular diseases, dementia, osteoporosis, metabolic syndrome, and diabetes (Chung et al., 2006; Yu and Chung, 2007). The following examples of atherosclerosis and vascular disease, Alzheimer's disease, and cancer, illustrate the intricate involvement of PPARs and their ability to modulate age-related, chronic diseases.

6.1. Atherosclerosis and vascular diseases

There is increasing recognition that chronic vascular inflammation plays a role in the pathogenesis of atherosclerosis, insulin resistance, and type II diabetes. In fact, instigation of inflammation is reported to be linked all phases of atherosclerosis, from the development of the fatty streak to processes that ultimately contribute to plaque rupture and atherosclerosis-associated disorders (Libby, 2002).

In the initial phase of atherosclerosis, endothelial-leukocyte adhesion molecules emerge as a particular candidate for the early adhesion of mononuclear leukocytes to the arterial endothelium at an atheroma initiation site of adhesion molecules. VCAM-1 is an interesting candidate as an atherogenic molecule due to its existence in nascent atheroma and because of its involvement in lesion formation (Cybulsky et al., 2001). Experiments using variants of VCAM-1 introduced into mice rendered susceptible to atherosclerosis show reduced lesion formation (Cybulsky et al., 2001). With respect to the aging process, transcriptional activation of the VCAM-1 gene is mediated in part by NF-κB in response to pro-inflammatory cytokines such as IL-1β or TNF-α (Zou et al., 2006).

Increased production of inflammatory mediators leads to endothelial cell death and stimulates the expression and activation of MMPs, specialized degrading components of the sub-endothelial basement membrane (Newby, 2005). In this way, inflammation can promote loss of endothelium, the hallmark of superficial erosion. According to a paper published by van Oostrom's group (van Oostrom et al., 2005), inflammation and MMP-9 levels slightly increased with age in plaques obtained from patients suffering from significant advanced atherosclerotic lesions.

It is worth noting that metabolic syndrome, insulin resistance and diabetes, have emerged as the main contributors in risks for atherosclerosis (McVeigh and Cohn, 2003). In metabolic syndrome, LDL levels often remain in the average range, although the particles may have qualitative alterations that render them small and dense, making them particularly prone to oxidation and hence evoking inflammation (Navab et al., 1998).

A series of well-designed clinical trials have recently established the utility of several different pharmacological strategies for preventing atherosclerosis and its related disorders by modulating inflammation. A well-known anti-diabetic drug and PPAR agonist, statins, for instance, shows possible pleiotropic effects including anti-inflammatory actions. The pharmacological effects of statins suppress inflammation in patients with atheroma as assessed by the reduced inflammatory biomarker, CRP (Ridker et al., 1998). Interestingly, data presented by Ridker et al. (1998) shows that the degree of lowering of CRP correlates poorly with a patient's drop in LDL, suggesting that some of its anti-inflammatory effect may not be derived simply from a lipid lowering action. In fact, statins interfere angiotensin II signaling, which is now known to be a part the pro-inflammatory process involved in eliciting VCAM-1, MCP-1, and IL-6 production (Libby, 2001). Moreover, the use of other PPAR agonists, TZDs in the treatment of type II diabetes also inhibits the development of atherosclerosis in part through anti-inflammatory actions in macrophages and other cells in the artery wall (Dandona and Aljada, 2002).

COX-2 is also reported to involve in the production of pro-inflammatory prostaglandins expressed in the macrophage foam cells of atherosclerotic lesions (Li and Glass, 2002). Bone marrow transplantation of ldlr$^{-/-}$ mice with liver progenitor cells deprived of COX-2 resulted in dramatically smaller lesion than those of ldlr$^{-/-}$ mice obtaining wild-type cells, thereby providing evidence for a pro-atherogenic function of COX-2 (Burleigh et al., 2005). Consistent with this observation, this study also found that the treatment of ldlr$^{-/-}$ mice with the PPAR agonists, NSAIDs (e.g., ibuprofen, indomethacin, naproxen) resulted in a decrease in lesion size. Therefore, clinical studies of patients taking statins, TZDs, and PPAR-agonist-NSAIDs indicate that further therapeutic advantage can be gained by exploring recently identified mechanisms that control inflammatory responses.

6.2. Alzheimer's disease

In Alzheimer's disease there is increasing evidence that neurotoxicity is mediated by CNS inflammatory processes (McGeer et al., 2006; Yu and Chung, 2007). One contributing factor inherent to age-related oxidative stress of the brain is the presence of microglial cells that are activated by amyloid-beta to produce pro-inflammatory cytokines like IL-1β, IL-6, and TNF-α. It is also worth noting that all synapses are encapsulated by cytokine generating glial cells and that cytokines are co-localized with senile plaques in Alzheimer's disease (McGeer et al., 2006; Sastre et al., 2006b). An epidemiological study suggests that Alzheimer's disease may be associated with the inflammatory process. Yaffe and his group examined 3,031 African-Americans and white men and women (mean age 74) who participated in the Health, Aging, and Body Composition Study, and found a correlation between higher concentrations of CRP, IL-6, and TNF-α, and greater cognitive declines (Yaffe et al., 2003).

Kitamura et al. (1999) revealed that in Alzheimer's disease brains, proinflammatory molecule, COX-2 was increased in particulate fraction, but not PPARγ level. Recent studies clearly showed the involvement of PPARγ gene in the pathogenesis of Alzheimer's disease (Scacchi et al., 2007; Koivisto et al., 2006), although the effects of PPARα gene on Alzheimer's disease are still not fully established (Sjölander et al., 2007; Brune et al., 2003).

In support of the involvement of PPARγ in Alzheimer's disease, people with long-term intake of PPARγ ligand, certain NSAIDs (e.g., ibuprofen, indomethacin, naproxen) exhibit reduced risk and manifest delayed development of Alzheimer's disease (Heneka and Landreth, 2007; McGeer and McGeer, 2004). Although the mechanisms by which these NSAIDs function are not fully accepted in consensus, the activation of the aforementioned anti-inflammatory transcription factor, PPARγ may be involved (Sastre et al., 2006a). Moreover, a TZD treatment also significantly reduced phosphorylation of tau at Ser202 and Ser396/404, which are residues of early and later stages of the neurofibrillary tangle accumulation observed in Alzheimer's disease and other neurodegenerative disorders (d'Abramo et al., 2006).

6.3. Cancer

Recently, the role of NF-κB activation in tumor development and progression has been demonstrated using various animal models (Karin and Greten, 2005). Several clinical trials have shown that natural compounds, such as ginseng extracts, flavonoids, and curcumin, which inhibit activation of the pro-inflammatory transcription factor NF-κB, reduce the incidence of lymphoma and cancer in various tissues (Karin and Greten, 2005). Because chronic inflammation is associated with constitutive activation of NF-κB with age, it has been proposed that NF-κB activation might link age-related inflammatory processes to tumor promotion and progression (Hagemann et al., 2007). For instance, environmental and endogenous factors are reported to induce NF-κB activation in cancer development mediated through expression of inflammatory cytokine genes, such as TNF-α, and that the expression pattern of these genes operates similarly in the aging process (Fujiki et al., 2002).

The possible implications of PPARs used in cancer prevention can be derived from the inverse association of PPAR activation with decreased inflammatory processes, cell cycle arrest and aging, both linked with tumorigenesis (Kopelovich et al., 2002; Everett et al., 2007). One distinct advantage in using PPAR ligands as IKKβ/NF-κB inhibitors as compared to other therapeutics is their ability to block NF-κB activation in infiltrating inflammatory cells, which are an important source of tumor growth and survival factors (Viatour et al., 2005). In agreement with the role of PPAR ligands in cancer, specific PPARγ ligand, GW 7845 as an example, significantly reduces tumor incidence, number, and weight in mammary tumors when fed to rats after carcinogen administration (Yin et al., 2005). The therapeutic use of PPARγ as the anti-neoplastic efficacy on various cancer cell lines, animal models, and clinical trials has been described (see review Grommes et al., 2004).

In contrast, there also is a report indicating that PPARα agonists inhibit hepatocellular apoptosis, perhaps leading to the formation of focal lesions in the aged liver (Youssef and Badr, 2005). Besides, the long-term use of PPAR ligands may present a certain amount of risk because of the critical role of NF-κB in the regulation of various innate and adaptive immune responses.

Additional research is needed to further characterize expression patterns of the various PPAR isoforms in cancerous and precancerous tissue and to determine their precise roles in the carcinogenic process. Confirming the crucial roles that PPARs play in tumorigenesis will foster the development of a novel class of cancer preventive drugs.

7. Conclusions

Our knowledge of the physiological roles of the PPAR nuclear receptors has progressed enormously in the last few years. More recently, data show that PPARs may play a major role in age-related inflammatory processes. Based on these data, this review highlights PPARs as key modulatory transcription factors responsible for the suppression of increased inflammatory processes during aging. In addition, by understanding the activation of PPARs by their ligands, we open up the possibility of developing new therapeutic agents that modulate these nuclear receptors to control various inflammatory diseases, including atherosclerosis, Alzheimer's disease, and cancer.

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