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REGULATION OF PPARγ FUNCTION BY TNF-α

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Abstract

The nuclear receptor PPARγ is a lipid sensor that regulates lipid metabolism through gene transcription. Inhibition of PPARγ activity by TNF-α is involved in pathogenesis of insulin resistance, atherosclerosis, inflammation, and cancer cachexia. PPARγ activity is regulated by TNF-α at pre-translational and post-translational levels. Activation of serine kinases including IKK, ERK, JNK and p38 may be involved in the TNF-regulation of PPARγ. Of the four kinases, IKK is a dominant signaling molecule in the TNF-regulation of PPARγ. IKK acts through at least two mechanisms: inhibition of PPARγ expression and activation of PPARγ corepressor. In this review article, literature is reviewed with a focus on the mechanisms of PPARγ inhibition by TNF-α.

The nuclear receptor PPARγ is a member of peroxisome proliferator-activated receptor (PPAR) family that includes PPARα, PPARγ, and PPARδ (PPARβ) (reviewed in (1;2). There are two isoforms in PPARγ, PPARγ1 and PPARγ2. PPARγ1 is expressed ubiquitously and PPARγ2 is mainly expressed in adipocytes. The biological activities of PPARγ are very broad, but it is generally accepted as a master transcriptional regulator of lipid and glucose metabolism (reviewed in (1-3). Inhibition of PPARγ function by inflammatory cytokines may contribute to pathogenesis of many diseases, such as insulin resistance, atherosclerosis, inflammation, and cancer cachexia. Disorder in lipid metabolism is a common feature in many diseases. Inhibition of PPARγ function by TNF-α may represent a molecular mechanism of the lipid and glucose disorders. TNF-α is known to inhibit the ligand-dependent transcriptional activity of PPARγ. However, the mechanism remains to be fully understood (4-9). In this review, the literature is reviewed on the possible mechanisms of PPARγ regulation by TNF-α.

Inhibition of PPARγ by TNF-α

The mechanisms of TNF-inhibition of PPARγ include three models according to experimental evidence. First, PPARγ expression is reduced at mRNA level by TNF-α (5;6). This is observed in 3T3-L1 adipocytes treated with TNF-α for 24 hours or longer. The mechanism is related to inhibition of C/EBPδ expression by TNF-α (10). C/EBPδ was shown to activate the PPARγ gene promoter through a direct protein-DNA interaction. When C/EBPδ expression is reduced by TNF-α, PPARγ gene transcription will be reduced. Second, PPARγ expression is not changed. This mechanism was demonstrated in cells transfected with a PPARγ expression vector (4;7;8). In the second model, the ligand-dependent transcriptional activity of PPARγ is reduced as a result of loss of DNA-binding activity of PPARγ. It was shown that the inhibition of DNA binding activity was dependent on association of NF-kB and PPARγ (7). Third, the

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transcriptional activity of PPARγ is inhibited by TNF-α through activation of nuclear corepressor (9). In this mechanism, the DNA-binding activity of PPARγ was not reduced by TNF-α. However, the DNA-bound PPARγ is inactivated by histone deacetylase 3 (HDAC3). All three mechanisms of inhibition are dependent on activation of IKK/NF-kB pathway as the TNF-α activity was abolished by the super repressor IkBα (Inhibitor kappa Bα) (6;9). The activities of both PPARγ1 and PPARγ2 are inhibited by TNF-α.

Signaling pathways of TNF-α

The intracellular signaling pathways of TNF-α are activated through cell membrane receptors. Engagement of the receptors by TNF-α leads activation of many signaling pathways, such as IKK/NF-kB, MAPK (JNK, ERK, and p38) and apoptosis pathway (11;12). NF-kB is a transcription factor that stays in the cytoplasm in the absence of activators. The inhibition is mediated by IkBα that inhibits NF-kB shuttling between the cytoplasm and nucleus (reviewed in (13)). IkBα degradation is controlled by a phosphorylation-mediated and proteasome-dependent mechanism that is initiated by activation of IKK2 (14). In the TNF-α signaling pathways, activation of IKK, ERK and JNK (c-JUN NH2 terminal kinase) were reported to inhibit the transcriptional activity of PPARγ (4;7;8;15-17), but p38 was reported to enhance the function of PPARγ (18-21).

IKK is a dominant kinase in TNF-regulation of PPARγ function

Although TNF-α activates several serine kinases that are able to regulate the ligand-dependent activity of PPARγ, IKK is a dominant kinase mediating the TNF-α activity in regulation of PPARγ function (7-9). The key evidence is that TNF-α activity is completely blocked by inactivation of IKK or its downstream event. The IKK/NF-kB signaling pathway is also required for IL-1 inhibition of PPARγ function (5;7;8;22).

The roles of MAPK (ERK, JNK and P38) in the regulation of PPARγ activity was known earlier than IKK. ERK and JNK was reported to inhibit PPARγ function by a direct phosphorylation of serine residues in PPARγ (4;15-17), such as Ser112 in PPARγ2 (4). The ERK-mediated inhibition is involved in prevention of diet-induced obesity in knockout mice of tyrosine kinases-1 (Dok1) (23). However, it is controversial for JNK in the regulation of PPARγ as a study suggests that JNK is involved in activation of PPARγ in foam cells (24). Since ERK and JNK are the major kinases in the signaling pathways of EGF (epidermal growth factor) and FGF (fibroblast growth factor) (25), these kinases may play an important role in the regulation of PPARγ activity by EGF and FGF (26-28). In addition to MAPK kinases (ERK, JNK and P38), PPARγ is also phosphorylated by Protein Kinase A and C (PKA, PKC), AMP Kinase (AMPK) and glycogen synthase kinase-3 (GSK3) (see reviewed (29)).

Coactivator and corepressor for PPARγ

The transcriptional activity of PPARγ is controlled by DNA-binding activity and nuclear receptor cofactors that include corepressors and coactivators. PPARγ is a heterodimer transcription factor composed of PPARγ and retinoid X receptor (RXR), which is activated by 9-cis retinoic acid (30). The heterodimer is associated with the nuclear receptor corepressor complex in the absence of PPARγ ligand. Upon activation by a ligand, the corepressor complex is replaced by coactivators leading to transcriptional initiation of target genes. The coactivators of PPARγ include the well-established cofactors such as p300/CBP, p160 and PGC-1 (PPARγ coactivator-1) (reviewed in (31), as well as the relative new coactivators TRAP220 (Thyroid hormone Receptor-Associated Protein 220 or PBP, PPARγ-Binding Protein) (32; 33), ARA70 (Androgen Receptor-Associated protein) (34) and PRIP (PPARγ-interacting protein, ASC-2/RAP250 /TRBP/NRC) (35-38). The coactivator p160 has three isoforms: SRC-1 (steroid receptor coactivator 1, NCoA-1), SRC-2 (NCoA-2/TIF2/GRIP1) and SRC-3

(NCoA-3/pCIP/AIB-1/ACTR/RAC-3/TRAM-1) (39). The corepressor for PPARγ is a protein complex containing HDAC3 (histone deacetylase 3) and SMRT (silencing mediator for retinoic and thyroid hormone receptors) or N-CoR (nuclear corepressor). RIP140 (receptor-interacting protein) may also be a component in the corepressor complex (40-43).

HDAC3 is required for IKK inhibition of ligand-dependent activity of PPARγ by TNF-α

TNF-α is able to inhibit PPARγ activity at two different levels (9). In the chronic (>16 hrs) treatment, TNF-α reduces expression of PPARγ in adipocytes. In the acute treatment, TNF-α inhibits the ligand-dependent activity without decreasing PPARγ expression or its DNA-binding activity. Both chronic and acute inhibition is dependent on the IKK/NF-kB pathway (6;8;9). Regarding the acute effect of TNF-α, NF-kB was reported to reduce the DNA-binding activity of PPARγ (7). Protein-protein interaction between NF-kB and PPARγ was proposed to mediate the inhibition, and PGC-2 was shown to be required for the NFkB-PPARγ interaction. Our data from ChIP and EMSA assays demonstrated that the DNA-binding activity of PPARγ was not changed by TNF-α in the acute treatment (9). The data is consistent in adipocytes and 293 cells. The only change induced by TNF-α was an increased association of PPARγ with HDAC3/SMRT. When this change was blocked by ssIkBα, TNF-α lost its inhibitory activity in PPARγ. These data suggest that the nuclear receptor corepressor is the target of TNF-α. Since TNF-α induces nuclear translocation of HDAC3, TNF-α may regulate the corepressor function through HDAC3. Recently, IKK has been shown to modify SMRT activity through direct phosphorylation of SMRT protein (44). If this IKK/SMRT interaction is involved in TNF-inhibition of PPARγ activity, it may not be a necessary step. The TNF-activity can be completely blocked by super suppressor IkBα (ssIkBα), which inhibits NF-kB activation without affecting of IKK activity. It is not clear if TNF-α can modify the phosphorylation status of HDAC3. If this does happen, nuclear translocation of HDAC3 is still necessary for the TNF-activity. The role of nuclear corepressor is also supported by our observation that the TNF-α inhibition was attenuated by overexpression of the nuclear receptor coactivators (Gao Z and Ye J, unpublished data). Overexpression of the coactivators is able to rescue PPARγ function from the TNF-α inhibition. The coactivator may act by antagonizing the deacetylase activity of the nuclear corepressor.

PPARγ inhibition by TNF-alpha requires nuclear translocation of HDAC3 (9)

In the HDAC3 protein, there are both nuclear export signal (180-313 aa in the central portion), and the nuclear localization signal (312-428 aa in the C-terminal) (45). HDAC3 shuttles between the cytoplasm and nucleus. The shuttling is regulated by IkBα (Fig. 1) (9). When IkBα is degraded, HDAC3 enters the nucleus. When newly-synthesized IkBα is available in the nucleus, HDAC3 is bound to IkBα and exported from nucleus. This molecular model is supported by four lines of evidence: (a) Nuclear translocation of HDAC3 is coupled with IkBα degradation; (b) HDAC3 is exclusively located in the nucleus in IkBα$^{-/-}$ cells; (c) ssIkBα retains HDAC3 in the cytoplasm and reduces the nuclear abundance of HDAC3; (d) IkBα associates with HDAC3 through the ankyrin repeat domain (46). Since HDAC3 regulates transcription of a variety of genes (47;48), the IkB-HDAC3 model provides a new mechanism for many phenomena observed for IkBα, such as death of newborn mice with IkBα knockout (IkBα$^{-/-}$) (49), inhibition of limb development by IkBα in drosophila (50), and enhancement of transcriptional activity of other transcription factors by IkBα (46;51). HDAC3 activity may also explain the inhibition of C/EBPδ expression by TNF-α (10).

HDAC3 was reported to inhibit NF-kB p65 activity by deacetylation of p65 protein (52-55). However, it is not clear what event mediates the protein-protein association of HDAC3-p65

(52;54). Since IkBα binds to both p65 and HDAC3, IkBα may mediate recruitment of HDAC3 by p65 (9).

In summary, there are three major mechanisms for TNF-α inhibition of PPARγ activity. One is dependent on inhibition of PPARγ gene expression. Two are related to suppression of the ligand-dependent transcriptional activity of PPARγ. The nuclear corepressor function may be required for all of the three mechanisms. TNF-α is able to enhance HDAC3 activity in the nucleus through a nuclear translocation mechanism. IkBα plays an important role in the regulation of HDAC3 shuttling between cytoplasm and nucleus. IkBα mediates IKK regulation of nuclear translocation of HDAC3. TNF-α inhibits activities of both PPARγ1 and PPARγ2.

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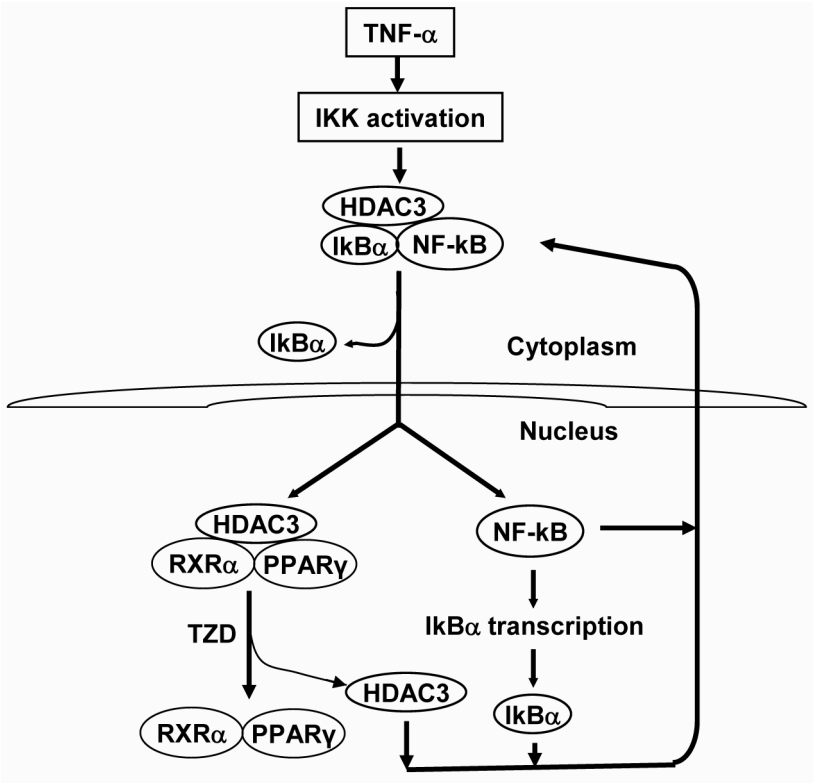

Fig. 1. Regulation of HDAC3 cytoplasm/nucleus shuttling by IkBa

HDAC3 is enriched in the nucleus after translocation of cytoplasmic HDAC3 into the nucleus. This change leads to inhibition of PPARγ function. The nuclear translocation of HDAC3 is initiated by degradation of IkBa, which is catalyzed by activation of IKK and required for NF-kB activation. NF-kB induces transcription and recovery of IkBa. IkBa then induces nuclear exclusion of HDAC3 and NF-kB through protein-protein association. This event leads to inhibition of NF-kB activity and reduction in HDAC3 protein abundance.