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Cross Talk on PPAR- γ and Nrf2 Against Cancer



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ABSTRACT

Cancer is a life-threatening ailment the combination of two defensive pathways nuclear erythroid 2p45-related factor 2 and PPAR- γ , stimulation of these 2 pathways by the pharmacological agents decrease mutation in the genes and acts as an anti-tumorigenic. NF-E2-related factor2(NRF2) is a master regulator for numerous cytoprotective genes. Under ordinary physiological conditions, Nrf2 is bound to cysteine-rich protein Keap1, further on moved into the core where it triggers cytoprotection of the cell by restricting along with little Maf proteins to the ARE in the administrative areas of target quality. PPAR- γ is stimulated within the oxidative stress response, an imbalance between antithetic pro oxidation and anti-oxidation forces that will lead the cell to apoptotic or necrotic death. PPAR- γ activation was shown to modulate numerous hallmarks of cancer through its pleiotropic effects on different cell types in the tumor microenvironment. As dimers, PPAR γ : RXR bind to PPAR response elements (PPREs) present on the promoter area of target genes. PPAR- γ inhibition of cell proliferation and induction of apoptosis, up-regulation of CDK inhibitors, downregulation of CDK and down-regulation of cyclin D1, up-regulation of Bax, and downregulation of Bcl-2. Nrf2 and PPAR- γ is connected by positive feedback loop regulate transcription factor. Both the ARES and PPREs are responsible for the simantenous stimulation of its transcription. The combinational activation of both Nrf2 and PPAR- γ by different pharmacological agonists can attain the maximum levels of anti-oxidative state and inhibition of tumor genes.



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INTRODUCTION

Cancer is among the main leading cause of death worldwide. In 2020, there were 18.1 million new cases and 9.5 million cancer-related deaths worldwide according to WHO.

There is abundant evidence that the activation of Nrf2 can suppress carcinogenesis, especially in its early stage. Under the physiological condition, Nrf2 maintains the cellular redox homeostasis and exerts anti-inflammatory functions and further anticancer activities, hence supporting cell survival(1). Peroxisome proliferator-activated receptor (PPAR γ) is a member of the nuclear hormone receptor superfamily of ligand-activated transcription elements. The expression of PPAR γ has proven to correlate with the degree of differentiation and survival rate in cancer patients. In addition to adipogenic and anti-inflammatory outcomes, PPAR γ activation was shown to modulate numerous hallmarks of cancer through its pleiotropic effects on different cell types in the tumor microenvironment. An overwhelming number of studies demonstrate the efficacy of PPAR γ agonists within the control of tumor progression through their effects on various cellular processes, including differentiation, proliferation, apoptosis, angiogenesis, inflammation, and metastasis. (2)

Main Text

NRF2 role against cancer:

NF-E2-related factor2(NRF2) is a master regulator for numerous cytoprotective genes. (3)

The repetitive subject in oxidant flagging and cell reinforcement guard is receptive cysteine thiol-based redox flagging. The atomic factor erythroid 2-related factor 2 (Nrf2) is an arising controller of cell protection from oxidants. Nrf2 controls the basal and instigated articulation of a variety of cancer prevention agent reaction component subordinate qualities to direct the physiological and pathophysiological results of oxidant exposure. (4)

Under ordinary physiological conditions, Nrf2 is bound to cysteine-rich protein Keap1, a repressor protein that ties to Nrf2, and advances its ubiquitination utilizing Cul3-based E3 ligase and corruption by the ubiquitin-proteasome pathway, whereas upon openness to oxidative and xenobiotic stress, responsive cysteine deposits of Keap1 become altered. Nrf2 is accordingly delivered from Keap1 and further on moved into the core where it triggers cytoprotection of the cell by restricting along with little Maf proteins to the ARE in the administrative areas of target quality(5)(9)(18), it is illustrated in fig.2.

The initiation of the Nrf2/Keap1 pathway is perhaps the main system in anti-tumor genesis. In the tumor microenvironment, Nrf2 is enacted by tumor silencer qualities BRCA1 and protein p21 utilizing the restraint of Keap1/Nrf2 complex formation and is hindered by oncogene Fyn-mediated debasement. (1)

Oncogenes (Myc, K-Ras, and B-Raf), transformations of tumor silencer PTEN, and epigenetic changes in Nrf2 lead to the transcriptional expansion in Nrf2 levels. Keap1 methylation transcriptionally lessens Keap1 levels. Exon skipping of Nrf2 and substantial changes of Nrf2, Keap1, or Cul3 upset the Nrf2/Keap1 connection. Succination of Keap1 cysteine and Keap1-competing protein, for example, p62 brings about the decrease of Nrf2-Keap1-binding fondness and blockage of Nrf2 ubiquitination. (1)

Nrf2, a record factor with an extraordinary warmth to oxidative stress, ties to AREs in the core and invigorates the record of numerous cell reinforcement qualities. The operating system makes Nrf2 separate from Keap1 and moves into the core, which brings about its limiting to AREs Excess Nrf2 has been affirmed to be cytoprotective in various tissue. (8)

Carcinogenic role of NRF2: While numerous examinations show that actuation of NRF2 secures typical cells against different poisonous substances and infections, it has been shown that the overactivation of NRF2 upholds malignant growth movement and shields disease cells from oxidative harm driving to chemoresistance and radioresistance Raised degrees of NRF2 in malignant growth to instigate the up-regulation of glucose 6-phosphate dehydrogenase (G6PD), transketolase (TKT), 6-phosphogluconate dehydrogenase (PGD), and other metabolic catalysts The expanded actuation of these metabolic chemicals builds the amalgamation of purine and amino acids and tops off the NADPH pool using the pentose phosphate pathway(PPP) driving to metabolic reinventing for cell expansion and upgraded cancer prevention agent limit. Also, NRF2 manages the basal articulation of Mdm2, an immediate inhibitor of p53. Thusly, expanded Nrf2 articulation in a roundabout way downregulates p53 and adds to tumor endurance by smothering p53-related apoptotic signals. (9)

PPAR- γ ROLE IN CANCER:

PPAR γ is implicated in the oxidative stress response, an imbalance between antithetic pro-oxidation and anti-oxidation forces that may lead the cell to apoptotic or necrotic death. (10)

PPAR γ does not act alone but regulates genes transcription acting as a heterodimer with the retinoid X receptor (RXR)(10). As dimers, PPAR γ :RXR bind to PPAR response elements (PPREs) located in the promoter region of the target gene (10)(11) Fig.2.

Enactment of PPAR- γ assumes an inhibitory part in cell development and multiplication by preferring cell separation. These properties make PPAR- γ actuation by regular and manufactured ligands an alluring alternative in malignancy anticipation and treatment (13). PPAR γ ligands have been accounted for to have against proliferative impacts, instigate cell separation, as well as apoptosis in different sorts of tumors, including bosom disease, prostate malignancy, lung disease, and colon malignancy. (14)

The PPAR γ promotes the apoptosis of the cancer cells by the overexpression of the Bcl-2(15)(17)Cyclin D1 is associated with G1/S movement and expanded multiplication. PPAR γ actuation in intestinal epithelial cells brings about the restraint of cell cycle and S-stage section however an abatement in cyclin D1 articulation. PPAR γ ligand treatment, not just reductions the protein level of cyclin D1, yet in addition builds the CDK inhibitors p21furthermore, p27 K I P 1 through both expanded transcriptional movement and restraint of proteasome corruption in colorectal malignant growth cells. (16)

PPAR- γ inhibition of cell proliferation and induction of apoptosis, upregulation of CDK inhibitors, downregulation of CDK and down-regulation of cyclin D1, upregulation of Bax, and downregulation of Bcl-2.(17)In colon malignancy cells, treatment of the PPAR γ ligands (pioglitazone, troglitazone) actuates apoptosis through upregulation of the proapoptotic protein Bax and downregulation of the antiapoptotic protein Bcl-2. (15)

Cross talk on PPAR- γ and NRF2

Nrf2 and PPAR- γ are connected by positive feedback loop regulate transcription factor and their target antioxidant genes(10)(19). PPAR- γ is direct gene induced by NRF2 transcriptional activation, the NRF2 direct binding to the PPAR- γ promoter for PPAR- γ the levels of PPAR- γ is reduced by nrf2 deletion. The RXR component of the PPAR- γ pathway, PPAR- γ agonists were able to induce transcription of antioxidative defense genes like HO-1, CD36. These genes belong to the nrf2 regulation genes, the presence of PPREs in the promoter region of both the ARES and Nrf2 gene indicates the possibility of direct binding to PPAR- γ on NRF2 promoter for positive regulation of Nrf2 pathway. Both the ARES and PPREs are responsible for the simantenous stimulation of its transcription. (20) The

combinational activation of both Nrf2 and PPAR- γ by different pharmacological agonists can attain the maximum levels of anti-oxidative state and inhibition of tumor genes.

Conclusions:

The Nrf2 and PPAR- γ are activations by different pharmacological agonists that reduce the oxidative stress and attain the antioxidative state and the activation suppresses the genes which are responsible for tumors.

Figures

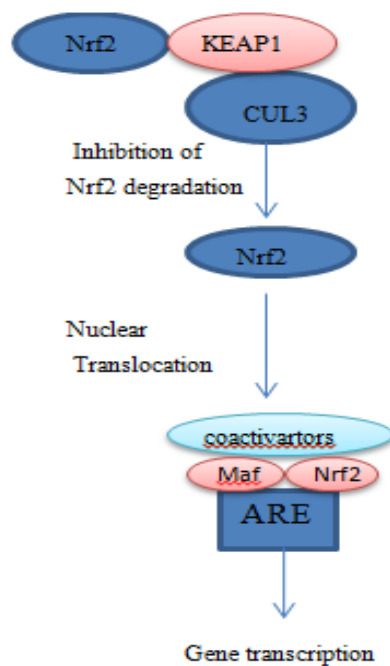


Figure:1-Nrf2/Keap1 signaling pathway

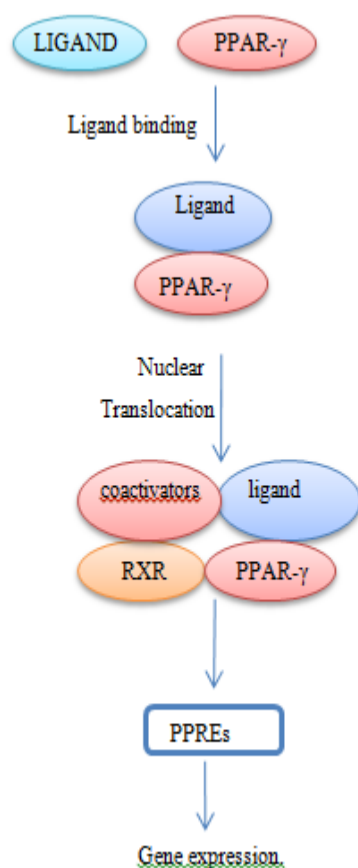


Figure: 2- Mechanism of PPAR γ activation.

Figure legends:

Figure:1-Nrf2/Keap1 signaling pathway

Nrf2 is bound to cysteine-rich protein Keap1, a repressor protein that ties to Nrf2, and advances²² its ubiquitination utilizing Cul3-based E3 ligase and corruption by the ubiquitin-proteasome pathway, whereas upon openness to oxidative and xenobiotic stress, responsive cysteine deposits of Keap1 become altered. Nrf2 is accordingly delivered from Keap1 and further on moved into the core where it triggers cytoprotection, Nrf2/Keap1 signaling pathway. Nrf2 then forms a heterodimer with sMaf protein and binds to ARE to initiate the transcription of varied downstream genes.

Figure: 2- Mechanism of PPAR γ activation.

When ligand binding to the PPAR/RXR heterodimer, a conformational change leads to release of a corepressor and binding of a coactivator; this regulates transcription complex, increased affinity for the specific PPAR response element, which modulates gene transcription.

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Ethical approval and consent to participate

Not applicable

Consent of publication

Not applicable

Availability of data and materials

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Conflicts of interests

The authors declare that they have no conflicts of interest.

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ABBREVIATIONS:

PPAR peroxisome proliferator-activated receptor.

NRF2 nuclear factor erythroid 2- related factor.

PPRE peroxisome proliferator-activated response element.

ARE Adenosine receptor.

KEAP1 kelch like-ECH-associated protein

RXR retinoid X receptor.

ROS reactive oxygen species.

MAF macrophage activating factor.

Raf rapidly accelerated fibrosarcoma.

CDK cyclin-dependent kinase

PKB protein kinase B.

BCL-2 B-cell lymphoma 2.

BAX Bcl-2 associated X-protein.

G6PD glucose 6-phosphate dehydrogenase.

TKT transketolase

FYN family tyrosine kinase.

K-Ras Kirsten rat sarcoma

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