



## Possible role of PPAR- $\gamma$ and COX-2 receptor modulators in the treatment of Non-Small Cell lung carcinoma

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### ARTICLE INFO

#### Keywords:

NSCLC  
PPAR- $\gamma$   
COX-2  
Lung cancer  
Metastasis

### ABSTRACT

Non-Small Cell lung cancer (NSCLC) accounts for 85% of total lung cancers worldwide, affecting more than 1.5 million people every year. Recent studies reported that lung adenocarcinoma express Peroxisome Proliferator Activated Receptor- $\gamma$  (PPAR- $\gamma$ ) which is believed to be inactivated due to cytoplasmic accumulation or somatic 'loss of function' of the gene. PPAR- $\gamma$  reported to play an important role in cell proliferation, cell differentiation and apoptosis via inhibition of NF- $\kappa$ B pathway. Adenocarcinoma also overexpress cyclooxygenase-2 (COX-2), which is reported to promote angiogenesis and metastasis via TX-A<sub>2</sub> production. Therefore, we hypothesize that activation of PPAR- $\gamma$  (through PPAR- $\gamma$  agonists) and inhibition of COX-2 (through COX-2 inhibitors) will have beneficial effects in the treatment of NSCLC.

### Introduction

Lung cancer is one of the mostly diagnosed cancers worldwide. More than 1.5 million people are affected, making it a leading cause of cancer deaths [1]. The causative factors of lung cancer are smoking (including both primary and secondary), inhalation of radon gas, coal mines dust, asbestos; exposure to X-rays or gamma rays, etc. [2]. These agents will lead to progressive pathological modifications in the mutated cell, i.e., preneoplastic to neoplastic invasions [3]. The lung cancer is of 2 types i.e., Non-Small Cell Lung Cancer (NSCLC) and Small Cell Lung Cancer (SCLC). NSCLC accounts about 85% of total lung cancer and it is comprised of Adenocarcinomas, Squamous carcinomas and Large cell carcinomas. SCLC is comprised of Neuroendocrine carcinoma [3–5].

Peroxisome Proliferator Activated Receptors (PPARs) are Type II nonsteroidal nuclear receptors. These have a diverse range of physiological functions like energy homeostasis, Cell differentiation, proliferation and apoptosis. PPARs will heterodimerize with the retinoid X receptor (RXR) and later bind to peroxisome proliferators response elements (PPRE) and regulate transcription of various genes [6,7]. Out of 3 isoforms, PPAR- $\gamma$  is most intensively targeted nuclear receptor. PPAR- $\gamma$  is vastly expressed in adipose tissue and regulates the adipocyte differentiation. Recent studies have shown that PPAR- $\gamma$  is also expressed in tissues like breast, colon, lung, ovary, and thyroid where its function is to regulate the cellular proliferation, differentiation and

apoptosis [8,9]. When activated, PPAR- $\gamma$  interfere with NF- $\kappa$ B pathway leading to decreased cell proliferation and angiogenesis [10].

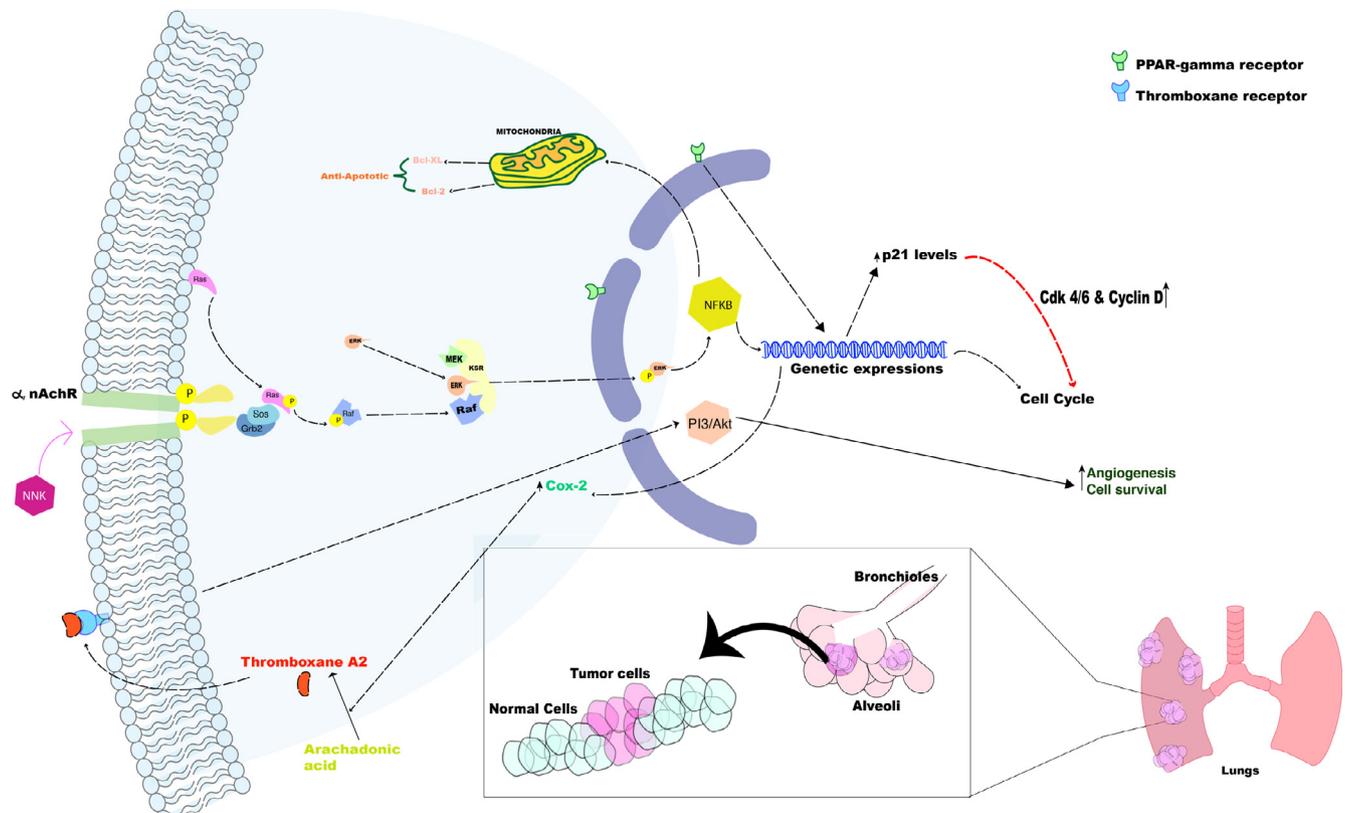
Cyclooxygenase-2 (COX-2) is found to be upregulated in many solid tumors like lung, breast, prostate and urinary bladder of humans [11–13]. COX-2 has been reported to promote tumorigenesis as it is revealed to be involved in fundamental processes to tumor formation, including invasion, angiogenesis and metastasis [14–18]. Inhibition of COX-2 is essential as; (1) Most lung tumors overexpress COX-2 levels and (2) Preclinical data evidenced that COX-2 inhibitors prevent the progression of lung cancer. As the current cancer chemotherapeutics are expensive and having many side effects, it therefore desired to repurpose the present drugs as a novel anti-cancer agent.

### Hypotheses

Various factors like smoking (Nicotine derived Nitrosamine Ketone-NNK), air pollution, asbestos inhalations are reported to initiate Raf/MEK/MAPK pathway leading to activation of NF- $\kappa$ B. This in turn leads to initiation of cell cycle leading to proliferation and also increase of COX-2 production. The COX-2 binds to promotes the formation of Thromboxane A<sub>2</sub> (TX-A<sub>2</sub>), which promotes angiogenesis and cell survival by initiating the PI3K/Akt pathway. As PPAR- $\gamma$  is believed to be inactive in lung adenocarcinomas due to cytoplasmic accumulation or somatic 'loss of function' of gene. As a result, the PPAR- $\gamma$  gene mediated functions like activation of p21 and termination of the cell cycle are lost

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**Fig. 1.** Possible mechanism of action of PPAR- $\gamma$  agonists and COX-2 inhibitors in Non-Small Cell Lung Cancer: Intracellular signaling pathways gets activated when the nicotine derived nitrosamine (NNK) activates  $\alpha_7$  nAChR. The  $\alpha_7$  nAChR activates the Ras/MAPK pathway by phosphorylation of Ras, MEK, ERK, initiating the NF- $\kappa$ B pathway causing cell cycle proliferation, signaling mitochondria to produce anti apoptotic proteins (Bcl-2 and Bcl-XL) and increasing COX-2 levels. PPAR- $\gamma$  agonists increase the gene expression of p21, which in turn increases Cdk4/6 and Cyclin D levels and terminating the cell cycle. PPAR- $\gamma$  agonists and COX-2 inhibitors synergize through inhibition of COX gene expression and inactivate COX-2 enzyme, respectively.

(Fig. 1).

Therefore, we hypothesize that PPAR- $\gamma$  agonists along with COX-2 antagonists will be useful in the management of NSCLC.

#### Justification for the hypothesis

The pathogenesis of NSCLC is associated with mutations in Oncogenes (KRas, EGFR), Tumor Suppressor genes (p53, PTEN), Cell cycle control genes (p21, CDK and Cyclin genes), Apoptosis regulator genes and pathways like Ras/Raf/MEK, PI3K/Akt, Notch pathway, etc. The oncogene products ‘gain a function’ by overexpressing/losing their capabilities to get inactivated. In contrast, Tumor Suppressor gene products get ‘loss of function’ mutation leading to increased rate of cellular proliferation [19].

Nicotine with other polycyclic aromatic hydrocarbons (PAH’s) producing gets converted into Nicotine derived Nitrosamine Ketone (NNK) or N’-nitrosanornicotine (NNN) which binds and activates  $\alpha_7$  nicotine Acetylcholine Receptor ( $\alpha_7$  nAChR) [20–22]. The  $\alpha_7$  nAChR then activates the Ras/MAPK pathway by phosphorylation of Ras, MEK, ERK, initiating the NF- $\kappa$ B pathway causing cell cycle proliferation, signaling mitochondria to produce anti-apoptotic proteins (Bcl-2 and Bcl-XL) and increasing COX-2 gene transcription (Fig. 1) [21,22].

In lung adenocarcinoma the PPAR- $\gamma$  is reported to be inactive due to cytoplasmic accumulation or somatic ‘loss of function’ of the gene [23,24]. As a result, the PPAR- $\gamma$  gene functions like activation of p21 and termination of cell cycle are lost. Many researchers have reported that PPAR- $\gamma$  agonists decrease the cell proliferation, induce apoptosis and decrease angiogenesis [23,25–33]. A study by Ming-Yue Li et al. demonstrated that activation of PPAR- $\gamma$  attenuated the NNK induced proliferation of lung cells [34]. The results showed that PPAR- $\gamma$  agonist

inhibited the cell cycle proliferation by decreasing cell cycle transitions from G<sub>0</sub>-G<sub>1</sub> phase; blocked upregulation of Bcl-2, Bad, HO-1 genes and counteracted NF- $\kappa$ B pathway. The above results revealed that PPAR- $\gamma$  agonists could have potential anti-cancer activity & therapeutic implications in treating NSCLC [34]. In another study by Mattison et al. demonstrated the inhibitory effects of PPAR- $\gamma$  on lung tumors. Their results show that PPAR- $\gamma$  overexpression inhibited tumor progression and invasion [27]. A similar study was carried out by Xiahua Xin and colleagues, show that PPAR- $\gamma$  ligands have anti-angiogenic activity by decreasing VEGF mRNA [26].

It was also reported that increased COX-2 mRNA levels contribute to angiogenesis, cell migration and invasion in lung adenocarcinoma patients, by increasing Thromboxane A2 (TX-A2) synthesis followed by activation of PI3K/Akt pathway [35]. Researchers have demonstrated that in inhibitors of COX-2 decreases angiogenesis and cell survival in cancer tissue. In their studies, the COX-2 inhibitors treated animals showed decreased metastatic nodules and decrease incidence of occurrence of lung adenocarcinoma [35–41]. COX-2 inhibitors, are therefore, can be used to decrease the angiogenesis and cell survival.

Co-administration of PPAR- $\gamma$  agonists with COX-2 inhibitors could be synergetic combination in inhibition of angiogenesis, cell proliferation and metastasis. PPAR- $\gamma$  activation will indirectly inhibit Nf- $\kappa$ B mediated COX-2 synthesis (at nuclear level) whereas the COX-2 inhibition will directly inhibit the enzyme (at cytoplasmic level). As a result, both PPAR- $\gamma$  agonists and COX-2 inhibitors combined together to inhibit COX-2 mediated TX-A2 synthesis & hence prevent TX-A2 mediated angiogenesis and cell survival (Fig. 1).

## Conclusion

Since the pathogenesis of NSCLC is multifactorial, novel anti-cancer agents that simultaneously target multiple pathways are required. In this regard, our hypothesis on the combined effects of PPAR- $\gamma$  agonists and COX-2 inhibitors is viable since PPAR- $\gamma$  agonist induce apoptosis, terminate the cell cycle whereas the COX-2 prevent angiogenesis and cell survival. Further, both PPAR- $\gamma$  agonists and COX-2 inhibitors are existing drugs and can be repurposed.

## Conflict of interest

The author declares that there is no conflict of interest.

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