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MOLECULAR IMPLICATIONS OF PEROXISOME PROLIFERATOR ACTIVATED RECEPTOR INHIBITOR AND OXIDATIVE STRESS

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Abstract: The peroxisome proliferator-activated receptor γ (PPARγ) is a key regulator of metabolism, proliferation, inflammation and differentiation, and up regulates tumor suppressor genes. PPARγ has been considered an orphan member of the nuclear hormone receptor super family, because no high affinity endogenous ligand has been identified for this receptor. Peroxisome proliferator-activated receptor (PPAR) γ is a nuclear hormone receptor that is expressed at highest levels in adipose tissue and lower levels in several other tissues. PPARγ is a major coordinator of adipocyte gene expression and differentiation. The expression of this receptor occurs early during the differentiation of preadipocytes, and it is expressed in a highly adipose-selective manner.

Keywords: Peroxisome Proliferator Activated Receptor, Inhibitor, Retinoid X Receptor, Transcription.

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INTRODUCTION

The peroxisome proliferator-activated receptor (PPAR) nuclear receptor subfamily regulates a number of metabolic processes, including fatty acid β-oxidation, glucose utilization, cholesterol transport, energy balance and adipocyte differentiation. PPARs also play important roles in modulating inflammation, proliferation, angiogenesis and neoplasia[1, 2]. PPARs function as heterodimeric partners with RXR, and require high-affinity binding of PPAR isotype-specific ligands to engage transcription. Of the three subtypes, PPARγ is the major species expressed in the mammary gland and in primary and metastatic breast cancer and breast cancer cell lines[1, 3]. PPARγ and PPARδ modulate cell fate in the mammary gland, suggesting that PPAR agonists or antagonists may have the potential to regulate differentiation and hence tumor progression. PPARγ agonists are potent chemo preventive agents in mammary carcinogenesis, which is consistent with the enhancement of mammary tumorigenesis by PPARγ heterozygosity[4, 5].

Peroxisome proliferator-activated receptor-γ (PPAR-γ) is a ligand-activated transcription factor. In addition to its canonical role in lipid and glucose metabolism, PPAR-γ controls cell proliferation, death, and differentiation in several tissues. Here we have examined the expression of PPAR-γ in ovarian tumors and the cellular and molecular consequences of its activation in ovarian cancer cells. PPAR-γ was expressed in a large number of epithelial ovarian tumors and cell lines. The PPAR-γ ligand ciglitazone inhibited the growth and clonogenic survival of ovarian cancer cells, inducing cell cycle arrest and cell death. Growth inhibition by ciglitazone was reversed by the PPAR-γ antagonist GW9662, indicating the involvement of PPAR-γ-dependent mechanisms. Microarray based gene profiling revealed complex changes in the transcriptional program of ovarian cancer cells on treatment with ciglitazone and identified multiple pathways that may contribute to PPAR-γ ligands' antitumor activity. Gene's up regulated by ciglitazone were predominantly associated with metabolic, differentiation, and tumor-suppressor pathways, whereas down regulated genes were involved in cell proliferation, cell cycle, cell organization, and steroid biosynthesis. Collectively, our data indicate that PPAR-γ activation by selective agonists is a valid strategy for ovarian cancer therapy and prevention, and should be tested alone and in combination with other anticancer drugs[6, 7].

Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear hormone receptor super family that includes several ligand activated transcription factors involved in a variety of physiological and pathological processes. The PPAR subfamily consists of three closely related receptors, namely α, β/δ, and γ, which regulate metabolic, developmental, and differentiation pathways. PPARs play important roles in pathological conditions, such as diabetes, atherosclerosis, and chronic inflammation, and are seen as valid therapeutic targets in a variety of human diseases[8, 9]. PPAR-α is involved mainly in fatty acid metabolism and transport. High-affinity ligands of this receptor, such as fenofibrate and bezafibrate, are

effective hypolipidemic drugs. PPAR-γ controls adipocyte differentiation, glucose metabolism, and lipid homeostasis, and synthetic PPAR-γ agonists, such as rosiglitazone and pioglitazone, are used as antidiabetic drugs. PPAR-δ, which is the least studied of the three subtypes, is ubiquitously expressed and plays a role in cholesterol and lipid metabolism and in wound healing[1, 10, 11].

PPARs have the typical structure of nuclear hormone receptors with DNA-binding, ligand-binding, and trans activation domains. PPARs form hetero dimmers with 9-*cis* retinoic acid receptor (RXR) and bind to specific peroxisome proliferator-activated receptor response elements (PPREs) in the promoter region of target genes. PPARs bind a diverse group of lipophilic molecules, including long-chain fatty acids, prostaglandins, and leukotrienes[12, 13]. Subtle changes in the ligand-binding pocket of each isotype confer distinct ligand specificity. Ligand binding induces conformational remodeling, exposing regions of the receptor needed for interaction with co activator molecules and for transactivation. PPARs can regulate transcription by additional mechanisms leading to transrepression, instead of transactivation. This aspect adds another level of complexity to the study of PPAR functions in physiological and pathological conditions[14-16].

Inactivating mutations, genetic deletions, or chromosomal translocations leading to functional inactivation of PPAR-γ have been detected in cancers of the colon, prostate, and thyroid. Natural and synthetic PPAR-γ ligands, such as thiazolidinediones and 15-deoxy-$\Delta^{12, 14}$ - prostaglandin J_2, induce the growth arrest and death of transformed cells *in vitro*. PPAR-γ ligands inhibit the growth of human tumor xenografts in nude mice and reduce the frequency of spontaneous and carcinogen-induced preneoplastic and neoplastic lesions in animals.

Few studies, however, have reported an increase in the frequency of tumors in mice treated with synthetic PPAR-γ agonists. PPAR-γ ligands have also been the subject of clinical investigations showing some activity in patients with advanced lip sarcoma and prostate cancer[1, 5, 17]. Epithelial ovarian cancer (EOC) is the most lethal gynecologic cancer in Western countries, accounting for more deaths than endometrial and cervical cancer deaths combined. EOC derives from the malignant transformation of the ovarian surface epithelium, which is contiguous with the peritoneal mesothelium. Ovarian cancer is frequently diagnosed in advanced stages, with the disease spread in the peritoneum through direct implantation. In these conditions, surgery is rarely curative, and postoperative chemotherapy is required. Current therapies for advanced ovarian cancer are clearly inadequate, and new agents are needed for the treatment of this disease[18, 19].

Functional Antagonism towards PPAR Receptor

Functional antagonism toward PPAR gamma (PPAR gamma)/Retinoid X Receptor (RXR) could be used to treat obesity and type 2 diabetes. We show herein that moderate reduction of PPAR gamma with an RXR antagonist or a PPAR gamma antagonist decreases triglyceride (TG) content in white adipose tissue, skeletal muscle and liver. These inhibitors potentiate leptin's effects and stimulated adiponectin levels, which increases fatty acid combustion and energy dissipation, thereby ameliorating high-fat (HF) diet-induced obesity and insulin resistance. Paradoxically, severe reduction of PPAR gamma by treatment of heterozygous PPAR gamma-deficient mice with an RXR antagonist or a PPAR gamma antagonist depletes white adipose tissue and markedly decreases leptin and adiponectin levels and energy dissipation, which increases triglyceride (TG) content in skeletal muscle and the liver, thereby leading to the re-emergence of insulin resistance[1, 20, 21].

Proposed Effect of PPARγ Antagonists in Bone Marrow Milieu:

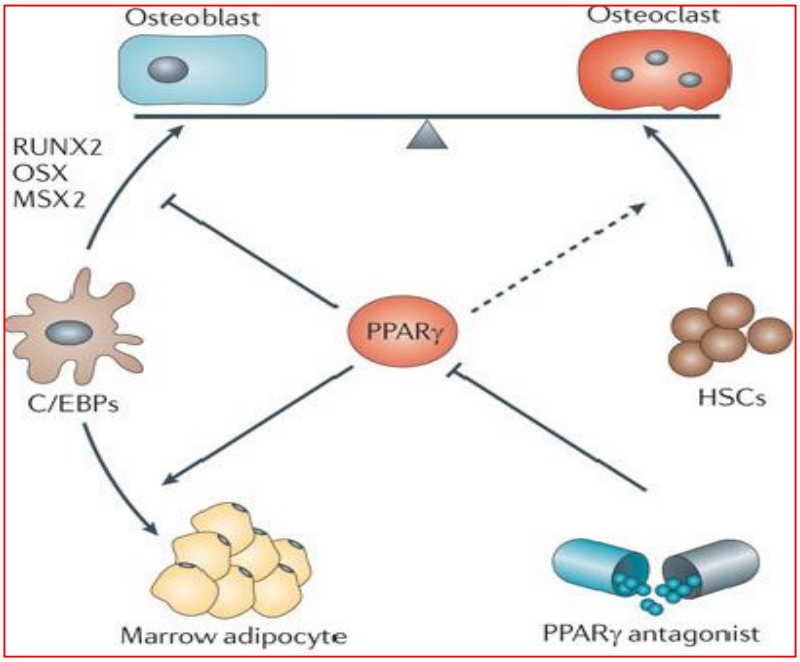

Figure 1: Effect of PPARγ antagonists in bone marrow milieu[23]

Bone remodeling is fine-tuned by the balance between bone formation by osteoblasts and bone resorption by osteoclasts. Peroxisome proliferator-activated receptor-γ (PPARγ) is involved in the cell fate determination of mesenchymal stem cells (MSCs) towards the adipogenic lineage and away from the osteogenic lineage. In addition, PPARγ may be the positive regulator for osteoclastogenesis, although this needs to be clarified. Therefore, PPARγ

antagonists may increase bone mass by switching the cell fate of MSCs towards the osteogenic lineage and therefore suppressing osteoclastogenesis[22, 23].

CONCLUSION:

In addition to their role in lipid and glucose metabolism, PPARs play a role in cancer development and represent promising targets for novel cancer prevention and treatment strategies. Numerous studies have suggested that PPAR-γ may act as a tumor suppressor at least in some tissues and cellular contexts.

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