Prostacyclin in Lung Cancer

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Prostacyclin is a naturally occurring eicosanoid that possesses anti-inflammatory and anti-metastatic properties and has a suppressive role in tumor growth.[1] Prostacyclin synthase (PGIS) is the final committed enzymatic step in the pathway of PGI_2 production, occurring at a branch point where substrate can be directed toward either PGI_2, thromboxane A_2 (TxA_2), or prostaglandin E_2 (PGE_2) (Figure 1). Eicosanoid production and balance is proving pivotal in lung tumorigenesis.

THE BIOLOGY OF PROSTACYCLIN

Prostacyclin (PGI_2) is a lipid mediator derived through the cyclo-oxygenase (COX) pathway. The cascade leading to the production of PGI_2 is shown in Figure 1. Phospholipase A_2 (PLA_2) cleaves arachidonic acid from lipid bilayers to form free fatty acids. It is generally believed that rate-limiting steps in the arachidonic acid cascade occur at both arachidonic acid formation and the formation of prostaglandin H_2 (PGH_2) by prostaglandin H_2 synthases (more commonly known as COX-1 and COX-2).[2] There are two PGH synthase isozymes called COX-1 and COX-2. Each enzyme is coded by a different gene and is under separate regulatory control.[3]

PGI_2 is one of the main products of arachidonic acid in all vascular tissues tested to date.[4] Once released from cells, PGI_2 acts as an autocrine and paracrine effector to regulate the function of various differentiated cells and platelets. Prostacyclin has many important biologic effects. It is the most potent endogenous inhibitor of platelet aggregation yet discovered,[4] and as a product of the vascular wall endothelium and smooth muscle cells, PGI_2 produces vasodilation of all vascular beds studied.[5] PGI_2 also inhibits both proliferation and DNA synthesis in smooth muscle cells.[6]

PROSTACYCLIN SIGNALING AND REGULATION

As illustrated in Figure 1, there are two documented signaling pathways for prostacyclin. The first is through its well-described membrane receptor (IP), and the second is at the nuclear membrane via the peroxisome-proliferator activated receptors (PPARs).[7] The IP is a single canonical cell membrane-specific seven-transmembrane domain G protein-coupled receptor that has been cloned and characterized,[8] with ligand binding resulting in G protein activation and stimulation of adenyl cyclase (thereby increasing intracellular cAMP).[9] PPARs are members of the nuclear hormone receptor superfamily that act as ligand-activated transcription factors. Three isoforms have been identified: PPARα, γ, and δ–-all of which bind to specific DNA sequences as heterodimers with the retinoic acid X-receptors and regulate gene transcription.[10] PPAR expression is increased in lung cancer and may play a critical role in malignant transformation.[11] Eicosanoids, like prostacyclin, are ligands for the PPARδ promoter responsive element[7] and can modify PPAR activity. Prostacyclin analogues can activate the PPARδ receptor and have been shown to inhibit the growth of A549 non-small cell lung cancer (NSCLC) cell lines.[12] PGIS and PGI_2 may also affect PPARγ activity. Our laboratory has shown that lung-specific PGIS overexpression results in a nearly twofold induction of PPARγ expression,[13] and PPARγ activation by ligands (like the synthetic thiazolidinediones) results in growth arrest of human NSCLC cell lines.[14]

The regulation of prostacyclin production has been an area of concentrated research, and plasma lipoproteins, TxA2 analogues, vitamin D3, and plant sterols have all been shown to induce in vitro prostacyclin production.[15–17] Variations in the PGIS promoter may affect PGI_2 synthesis, and the promoter contains highly GC-rich regions and multiple putative AP1 and SP2 transcription factor binding sites.[18] Additionally, a variable number of tandem repeats, varying from three to seven base pairs in length, in the proximal promoter have been correlated with low and high pulse pressures in a Japanese cohort.[19] PGIS promoter polymorphisms in lung cancer and chronic obstructive pulmonary disease are currently being actively investigated by our group.

PROSTACYCLIN AND LUNG CANCER CHEMOPREVENTION

Based on its anti-inflammatory and anti-metastatic effects and its suppressive role in tumor growth, we studied prostacyclin as a lung cancer chemopreventive agent. Comparative immunohistochemical analyses of NSCLC and normal human lung tissue focusing on the COX pathway have shown that tumors are typically positive for TxA_2 synthase, PGD_2 synthase, and PGE_2 synthase, but negative for PGIS.[20] Gene expression analysis of NSCLC shows that PGIS content

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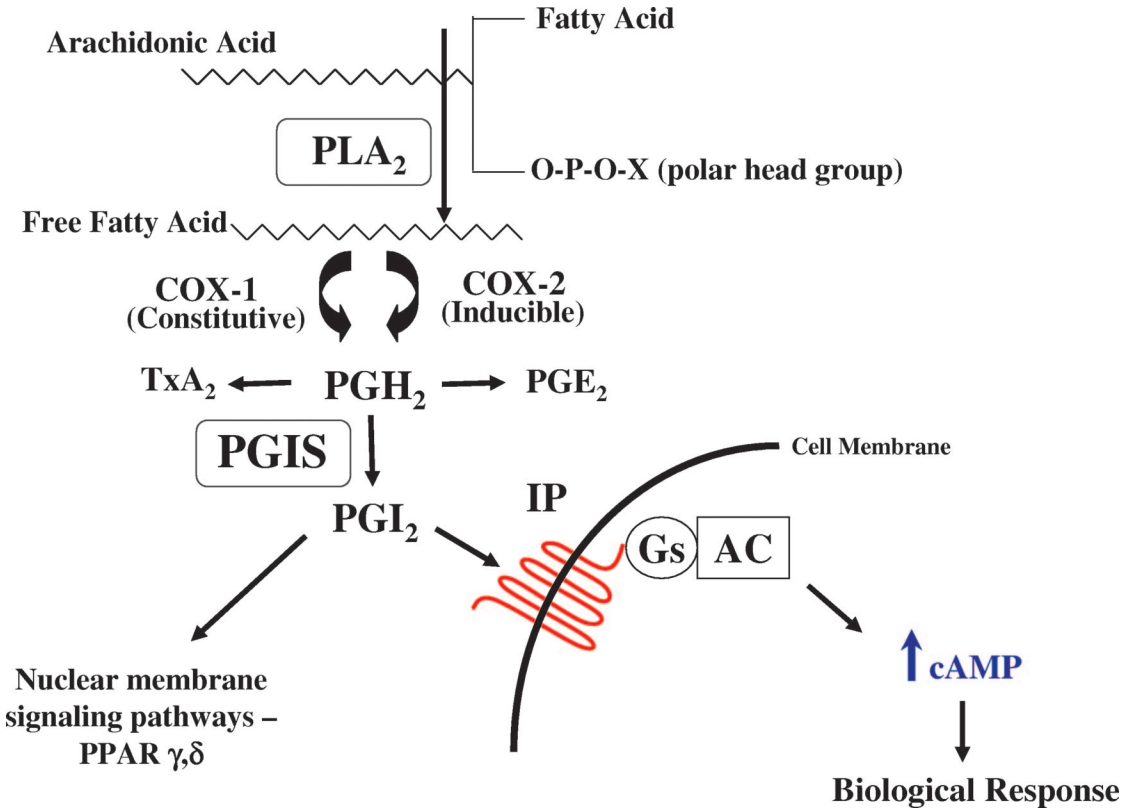

FIGURE 1. Prostacyclin production and signaling. Phospholipase A_2 (PLA_2) cleaves arachidonic acid from lipid bilayers to form free fatty acids that are converted to PGH_2 by COX-1 and COX-2. Prostacyclin synthase (PGIS) catalyzes the formation of PGI_2, which can then bind to the G protein-coupled cell surface receptor (IP) or have effects at the nuclear membrane via the peroxisome-proliferator activated receptors (PPARs).

in human lung adenocarcinomas (AC) is usually down-regulated while PGES content rises.[21] However, a small subset of patients with AC whose lung tumors retained PGIS expression survived significantly longer.[21] Furthermore, murine lung tumor cells lines produce more PGE_2 and less PGI_2 than non-tumorigenic cell lines.[22] In preclinical chemoprevention studies, we have shown that selective pulmonary PGIS overexpression protects against murine lung tumorigenesis in a variety of murine tumorigenesis models, including tobacco smoke exposure.[13,23] The beneficial effects of PGIS overexpression could be the result of either higher levels of PGI_2 or lower levels of PGE_2 as a result of depletion of the precursor substrate PGH_2. In the multiple carcinogenesis models applied to the PGIS overexpressing animals, elevation of PGI_2 (not decreases in PGE_2) was consistently required for chemoprevention to occur.

Based on the preclinical studies summarized above, the National Cancer Institute is currently funding the Lung Cancer Biomarker and Chemoprevention Consortium to conduct a multicenter study investigating the use of Iloprost (an oral prostacyclin analogue) for lung cancer chemoprevention.

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