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Review

An overview on the expression of cyclooxygenase-2 in tumors of the head and neck

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SUMMARY

Cyclooxygenase-2 (COX-2) levels are increased in various tumors, particularly those involving the esophagus, stomach, breast, pancreas, lung, colon, skin, urinary bladder, prostate and head and neck. Nevertheless, the tumorigenic mechanisms of COX-2 overexpression still remain poorly understood and may include mechanisms that may act at different stages of the disease. Thus, the literature shows increasing evidence that overexpression of the COX-2 plays an important role in tumor growth and spread of tumors by interfering with different biological processes such as cell proliferation, cellular adhesion, immune surveillance, apoptosis, and angiogenesis. Furthermore, the expression of COX-2 might shed some light over the physiopathology and clinical behavior of tumors of the head and neck, including benign odontogenic neoplasms of the jaws with an aggressive behavior, such as keratocystic odontogenic tumors (KCOT). Ultimately, the research of molecular markers associated with the biological behavior of tumors will help to understand the underlying molecular mechanisms and to predict the clinical outcome, leading to the development of new therapeutic applications, such as molecular-targeted treatment and patient tailored therapy.

Introduction

Cyclooxygenase-2 (COX-2) levels have been found to be elevated in various tumors.[1–5] Nevertheless, how COX-2 overexpression results in tumorigenesis remains poorly understood.[1,6]

The importance of COX-2 in tumorigenesis was first demonstrated in rodent models of familial adenomatous polyposis, a genetic disease leading to gastrointestinal cancer, in which loss of COX-2 activity by either genetic deletion or selective enzymatic inhibition suppressed intestinal polyp formation.[7]

Recent studies showed increased levels of cyclooxygenase-2 (COX-2) in premalignant and malignant lesions and genetic evidence of COX-2 implication in tumorigenesis.[3,4,8–10]

Additional evidence for the importance of COX-2 in tumorigenesis was reported by Liu et al.[11], who showed that selective COX-2 overexpression in the mammary gland of transgenic mice led to tumorigenesis. COX-2 has been shown to be expressed in neoplastic epithelial cells in a wide variety of human tumor types.[3] It has also been shown that different types of epithelial cancers produce high levels of PGE_2. Moreover, selective COX-2 inhibitors have been shown to affect induction of tumor in epithelial cells,[1,3] by acting upon proteins that are selectively expressed by tumor cells, including growth factors and their receptors, signal transduction molecules, oncogenes, hormones, apoptosis-related molecules, angiogenesis-related factors, as well as inhibitors of cell motility, invasion, and proteolysis.

The cyclooxygenase pathway

Cyclooxygenase is a key regulatory enzyme in the conversion of arachidonic acid, a 20-carbon polyunsaturated fatty acid, to prostaglandins (PGs).[3–5,12] Phospholipase (PLA_2) family of enzymes first catalyzes the hydrolysis of membrane glycerophospholipids producing free arachidonate.[3,12] The cyclooxygenase (COX) enzymes have two catalytic activities:[3,12]

(a) Cyclooxygenase catalyzes the addition of molecular oxygen to arachidonic acid and forms an unstable cyclic endoperoxide hydroperoxide: prostaglandin PGG_2.
(b) The peroxidase function rapidly reduces PGG_2 to PGH_2, which is converted to one of several structurally related prostanoids, including PGE_2, PGD_2, PGF_2 (alpha), PGI_2 and thromboxane A_2 (TXA_2), in reactions catalyzed by distinct, specific synthases.

Prostaglandins are synthesized in most tissues and may act via autocrine or paracrine mediators signaling changes within the immediate environment of the cell.[3,12] The different classes of

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prostaglandins bind to a G-protein coupled surface receptor,[3,13] leading to changes in intracellular cyclic AMP and calcium.[3]

Receptors are also present in the nuclear membrane and there is increasing evidence that prostaglandins also modulate cellular pathways by acting directly within the nucleus.[3,14,15]

Prostaglandins have important functions in almost every system and regulate different physiological processes such as immunity, cell reproduction, maintenance of vascular integrity and tone, nerve growth and development, and bone metabolism.[15,16]

There are two known isoforms of cyclooxygenase, COX-1 and COX-2, which are encoded by different genes and express cell-specific regulation.[3,4,12,17] COX-1 is constitutively expressed in many tissues and mediates the synthesis of PGs required for normal physiological function. It has been termed a "housekeeping enzyme" because it is responsible for the maintenance of homeostatic function in most of the cells, the production of protective mucous by gastrointestinal mucosa and platelet aggregation.[1,3–5,12,17] COX-2 is an enzyme that is not found in normal conditions, but which is induced by a variety of physiopathological conditions affecting the tissues, such as growth factors, inflammatory stimuli, oncogenes, carcinogens, tumor promoting phorbol esters and viral transformation.[1,3–5,12,17–20]

COX-2 and various pathological processes

COX-2 and malignancies

COX-2 activation has been found to be an early event during carcinogenesis, and its increased expression has been associated with the development of genomic instability.[3,8,10]

Prostaglandins produced by COX-2 transactivate members of the PPAR family of nuclear hormone receptors, changing the nuclear level of calcium and activating the RXR receptor.[3] PPAR (delta), stimulated via COX-2-induced PGs, especially PGI_2, may play a role in the accelerated cellular proliferation noted following malignant transformation.[14]

The overexpression of COX-2 in head and neck squamous cell carcinoma (HNSCC) is well documented.[2,4,5,17] Immunohistochemical analysis in 10 cases of HNSCC revealed that COX-2 expression was moderate to strong, and staining pattern was granular and localized in the cytoplasm.[4] Also, immunohistochemical evidence of expression of COX-2 protein in oral mucosal lesions has been reported with a gradient of increasing COX-2 stain from hyperplasia to dysplasia and highest in SCC.[21]

Lee et al. has identified COX-2 in malignant cells, and treatment with COX-2 inhibitors caused significant dose-dependent inhibition of cell growth and significant increase in number of cells in the G0/G1 phase, reduction in S phase and increased apoptosis.[22] Nathan et al study[23] involving COX-2 and elF4E - a potential biomarker identified in individuals at high risk for relapse after treatment for head and neck squamous cell cancer – showed an increased expression of COX-2 in tumor cells in patients with upper aerodigestive tract dysplasia, in contrast with adjacent normal cells. Recent studies also support a correlation between p53 and COX-2 expression, with cells carrying mutant p53, especially in dysplastic lesions and upper aerodigestive tract cancers, expressing high levels of COX-2.[3,24,25] In the oral mucosa lesions, a gradual increase in COX-2 expression from hyperplasia to different grades of dysplasia to cancer was described by Renkonen et al.[21]

The mode of action of COX-2 in tumorigenesis may include multiple mechanisms that may be acting at different stages of malignant disease.[3] COX-2 expression is apparently an early response to growth factors, as well as tumor promoters and carcinogens.[26–28]

The impact of COX-2 inhibition was assessed in a SCC cell line (NS-398), and inhibition of proliferation of cancer cells expressing COX-2 mRNA was reported and attributed to suppression of PGE_2 production.[29] Treatment with a COX-2 inhibitor has also been reported to reduce COX-2 mRNA, COX-2 protein and synthesis of PGE_2 in mammary and oral epithelial cells.[3,30]

Overexpression of the COX-2 gene alters cell adhesion, inhibits apoptosis and alters the response to growth regulatory signals.[31] Inverse relationship between the levels of anti-apoptotic protein bcl-2 and apoptosis has been reported[24] and COX-2 is known to increase the level of the anti-apoptotic protein bcl-2, thus causing resistance to apoptosis.[3,26,31]

Increased synthesis of PGs in transformed cells and tumors can be the result of enhanced expression of COX-2. PGs are believed to be important in the pathogenesis of cancer because of effects on cell proliferation, angiogenesis, immune surveillance, and apoptosis.[12,17,31,32]

Thus, COX-2 plays an important role in tumor growth and spread of tumors by affecting mitogenesis, cellular adhesion, immune surveillance, apoptosis, and angiogenesis. Nonetheless, it still remains unknown whether the earliest induction of COX-2 occurs in the epithelial cells or in the mesenchymal cells.[33]

COX-2, inflammation and immunosuppression

Inflammatory mediators such as cytokines, eicosanoids, and growth factors are thought to play a critical role in the maintenance, survival, and growth of tumor cells.[7,12] The regulation of COX-2 expression is physiologically vital for PGE_2 synthesis.[34,35] Enhanced synthesis of prostaglandins, a consequence of upregulation of COX-2, can increase cell proliferation, promoting angiogenesis and inhibiting immune surveillance.[7,4,17,36,37]

Interleukin-1α (IL-1 α) is a multifunctional pro-inflammatory cytokine, strongly expressed in the epithelial cells of keratocystic odontogenic tumors.[34,35] IL-1 stimulates the production of prostaglandin E_2 (PGE_2) in mesenchymal cells, including keratocystic odontogenic tumors fibroblasts[38–41], which then stimulates osteoclastogenesis by increasing the expression of receptor activation of nuclear factor-κB ligand (RANKL).[41]

Of the two types of IL-1 binding receptors, type I receptor (IL-1RI) and type II receptor (IL-1RII), the IL-1RI transduces a signal, whereas the IL-1RII does not, acting as a decoy receptor.[35] Binding of IL-1α to IL-1RI leads to activation of two transcription factors, nuclear factor-κB (NF-κB) and activator protein-1 (AP-1), through the activation of mitogen-activated protein kinases (MAPKs), such as p38 and c-Jun N-terminal kinase (JNK).[35] IL-1α-mediated transcription of COX-2 is regulated by many factors, such as extracellular signal-regulated protein kinase (ERK 1/2),[38] p38,[38,40] NF-κB signaling pathway[38,40,42] and protein kinase C (PKC).[38,43–45]

A growing body of evidence shows that both EGFR signaling and COX-2 activity play key roles in developing premalignant and malignant diseases. The molecular pathway of signal crosstalk between EGFR and COX-2 is becoming clearer, with emerging evidence suggesting a direct interaction between EGFR signaling and COX-2 activity.[6,13] PGE_2 transactivates and phosphorylates EGFR and triggers the extracellular signal-regulated kinase (ERK) 2-mitogenic signaling pathway.[13] PGE_2 also activates the phosphatidyl inositol 3-kinase/Akt pathway and causes migration, invasion, and proliferation of cancer cells.[6] On the other hand, EGF and transforming growth factor-α (TGF-α) also induce COX-2 expression.[13]

PGE_2 inhibits the production of tumor necrosis factor-α (TNF-α) and induces the production of IL-10, an immunosuppressive cytokine.[12,46,47] Abrogation of COX-2 expression has been shown to promote antitumor reactivity by restoring the balance of IL-10 and IL-12 in vivo.[48]

COX-2 and cell proliferation

p53 protein is a product of the tumor suppressor gene TP53, which functions in G1 arrest to allow the repair of DNA damage and to prevent the cell from entering the S-phase of the cell cycle, or alternatively to guide the damaged cells to apoptosis. As a tran-