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The role of cyclooxygenase-2 in carcinogenesis

Cyclooxygenase (COX) or prostaglandin (PG) endoperoxide synthase plays an important role in the conversion of arachidonic acid to prostanoids (prostaglandin and trombaxanes). This enzyme catalyses two separable reactions: the first that converts arachidonic acid to unstable prostaglandin G_2 (PGG_2) by a COX site and the second being a peroxidase site, which is the reduction of PGG_2 to the more stable PGH_2. Prostanoids, generated by COX, influence many cellular and physiological processes (2,5).

In 1991 two COX isoforms (COX-1 and COX-2) were identified (6). Apart from catalyzing the same reaction both these isoforms are characterized by similar K_m and V_{max} values for arachidonic acid. On the other hand, there are significant differences between COX-1 and COX-2. COX-1 performs "housekeeping" functions and produces prostanoids associated with vascular homeostasis, gastric acid secretion, gastric mucosa protection, renal blood flow and water re-absorption whereas COX-2 is related to processes such as inflammation, ovulation, labor and many other situations in which transient PG production is required (2). Moreover, COX-2 has been reported to be able to take part in the pathogenesis of Alzheimer's disease (7). Recent studies demonstrate that COX-2 isoenzyme is the culprit in carcinogenesis. The over-expression of COX-2 has been found in most of the cancers of the body sites (2,3,9).

STRUCTURE AND LOCALIZATION OF COX-2

COX-2 is an intracellular protein of about 68 kDa. This enzyme consists of 587 amino acids and contains four positions of N-glikozylation. COX-2 exists as a homodimer whose monomers are formed by three domains: epidermal growth factor, a membrane binding domain and globular catalytic domain (2,5).

Gene of COX-2 is located on human chromosome 1 and produces a 4,1-4,5 kb mRNA. Transcription of COX-2 gene is an inducible process that can be stimulated by certain factors, such as cytokines, mitogens, tumor promoters, hormones, endotoxin (1, 9). COX-2 may be also expressed in response to tobacco related carcinogens, i.e. benzopyrene (10). COX-2 resides in the luminal surfaces of the endoplasmic reticulum and in the nuclear envelop (5).

COX-2 EXPRESSION IN CANCER CELLS

A large number of studies have shown that COX-2 over-expression can be elevated in a variety of human cancers including lung, esophageal, gastric, colon, pancreatic, bladder, prostate and breast carcinomas (4). The most compelling data supporting the hypothesis about COX-2 as the culprit come from studies of animal models for human familiar adenomatus polyposis (FAP). FAP is a condition in which numerous adenomatus colorectal polyps are developed and may lead to colorectal carcinomas. During experiments mice that lacked the COX-2 gene were bred with mice that harbored a mutated allele of the APC gene. Results showed that the elimination of COX-2

gene protected mice with a defective APC gene from the development of intestinal tumors. The same investigations confirmed that the application of non-steroidal anti-inflammatory drugs (NSAIDs) or a selective inhibitor of COX-2 also reduced the risk of colon cancer (1, 9).

Immunoblot analysis of cancer specimens with corresponding normal tissue demonstrated over-expression of COX-2 in lung adenocarcinoma compared with the normal tissue (10). Similarly, the level of COX-2 was significantly higher expressed by traditional cell carcinoma of the bladder compared with normal adjacent tissue (10). A study by Hussain et al. analyzed benign and prostate carcinoma tissue and reported that the level of COX-2 mRNA expression was significantly increased in prostate adenocarcinoma (2).

There are multiple mechanisms through which COX-2 might stimulate the growth of cancer cells. However, the precise mechanism that governs the induction of cancer according to COX-2 activity is not well known. One of the possibilies suggests that COX-2 decreases the intracellular level of free arachidonic acid and thereby prevents the cell from apoptosis. The accumulation of free arachidonic acid can promote an apoptotic signal. The second possibility makes the prostaglandins responsible for the development of cancer. Multiple investigations have supported this possibility. The prostaglandins could influence cell growth and differentiation through cell surface receptors (probably one of the family receptors for PGE_2) and subsequently modulate signalling processes coupled to G proteins. Alternatively, the PG could work through a nuclear receptor typified by peroxisome proliferator activation receptor (8). Both of these pathways change in gene transcription and alter growth, differentiation and apoptosis.

PGE_2, the main PG generated by COX-2 contributes cancer development via activation of the IL-6 signalling pathway. Moreover, PGE_2 plays a positive role in angiogenesis. The growth of neoplasm is known to be dependent on its ability to produce new blood vessels.

Since COX-2 is an oxygenase and produces during catalyzing reaction reactive oxygen radicals, there is a possibility that these may damage macromolecules, i.e. DNA.

As it has been mentioned COX-2 is a bi-functional enzyme. Apart from an oxidation, it catalyzes a reduction of PGG_2 to PGH_2. To this process a cofactor is required. Thus, many compounds can be co-oxidized because of serving as this cofactor. For example, estrogens can be oxidized to the product that promotes carcinogenesis (9).

COX-2 overexpression may also have an influence on an enzymatic activity of aromatase causing intratumoral expression (1).

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SUMMARY

Cyclooxygenase-2 (COX-2) is a key mediator of arachidonic acid metabolism that catalyses the oxidation of arachidonic acid to PGG_2 as well as the reduction of PGG_2 to PGH_2. COX-2 expression is associated with processes such as inflammation, labor, ovulation. COX-2 is an inducible enzyme whose synthesis can be stimulated by such factors as cytokines, mitogens, tumor promoters, hormones, endotoxin. An increased COX-2 expression was found in many human and animal cancers. COX-2 may stimulate the growth of caner cells via many pathways. Regular taking non-steroidal anti-inflammatory drugs (NSAIDs) or selectively inhibitors of COX-2 reduces risk of developing cancer.

Rola cyklooksygenazy-2 w procesie powstawania nowotworu

Cyklooksygenaza typu drugiego (COX-2) jest kluczowym mediatorem metabolizmu kwasu arachidonowego, który katalizuje w równym stopniu reakcję utleniania kwasu arachidonowego do PGG_2 oraz redukcji PGG_2 do PGH_2. Ekspresja COX-2 jest związana z takimi procesami, jak: odczyn zapalny, poród, owulacja. COX-2 jest enzymem indukowanym, którego synteza może być stymulowana przez takie czynniki, jak: cytokiny, mitogeny, promotory guzów, hormony, endotoksyny. Wzrost poziomu COX-2 stwierdzono w nowotworach u ludzi i zwierząt. COX-2 może stymulować wzrost komórek nowotworowych różnymi ścieżkami. Regularne przyjmowanie niesteroidowych leków przeciwzapalnych lub wybiórczych inhibitorów COX-2 zmniejsza ryzyko rozwoju raka.