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The Role of Cyclooxygenase-2 in Colorectal Cancer Progression

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Abstract: Colorectal cancer (CRC) represents a major burden for public healthcare as the third most common malignancy globally and the second leading cause of cancer deaths .More than one-third of colorectal cancer cases in Egypt include people under the age of 40 who are found to have the disease at an advanced stage. Due to its function in human tumours, cyclooxygenase (COX), a crucial enzyme in the prostanoid biosynthesis pathway, has drawn a lot of interest. COX-2 regulates cell proliferation, cell transformation, tumour growth, metastasis, and invasion, and so plays an important role in the origin and development of metaplastic and dysplastic tissues, as well as the beginning and progression of cancer. Increased COX-2 expression has been linked to a variety of epithelial-based premalignant and malignant lesions in the gastrointestinal system, including the colorectal area .A review of the available databases and literature and our own data have identified some interesting molecules induced by prostaglandins or COX-2 that have been also described to play a role in colon cancer, being thus potential pharmacological targets in colon cancer. Among those DUSP4, and 10, ,Trop2, and many from the TGFβ and p53 pathways have been identified as genes upregulated in response to COX-2 overexpression or PGs in colon carcinoma lines and overexpressed in colon tumor tissue. In this review we will give an overview about possible role of Cyclooxygenase-2 in Colorectal Cancer Progression. In conclusion, Considerable amounts of evidence in clinical settings further support a role of COX-2 in colorectal carcinogenesis and tumor progression. Thus, COX-2 is expressed early during the adenoma-carcinoma sequence that occurs in CRC, suggesting an important role of this enzyme in colorectal carcinogenesis. COX-2 expression is upregulated in human colorectal adenocarcinomas when compared with normal adjacent colonic tissue

Keywords: *COX-2, Colorectal Cancer*

Introduction

Colorectal cancer (CRC) represents a major burden for public healthcare as the third most common malignancy globally and the second leading cause of cancer deaths. A wide geographical difference in CRC burden exists, with a threefold higher incidence and about 55% of all deaths occurring in transitioning countries**.** The CRC burden is expected to increase given the aging and growth of populations and the adoption of a so-called

Western lifestyle **(1).** Colorectal cancer is the 7th commonest cancer in Egypt, representing 4.2% of male cancers and 3.8% of female cancers. The estimated number of colon cancer patients (excluding rectal cancer) in 2015 was slightly more than three thousand. **(2).**

Cyclooxygenases (COXs) have three isoforms: COX-1, COX-2, and COX-3. COX-2 is a membrane-bound, short-living, and rate-limiting enzyme, discovered in 1991 and has long been known as a target for relief of pain and treatment of inflammation **(3)**. COX-2 is a prostaglandin (PG)–endoperoxide synthase 2 enzyme responsible for generation of prostanoids like prostaglandin E2 (PGE2) that are contributed to the modulation of multiple procarcinogenic effects. COX-2 expression is negligible in normal cells in which its basal expression only occurs within stomach**,** kidney, central nervous system, and in organs of female reproduction **(4)**.

However, it is expressed frequently at the tumorigenic nests in most types of cancers, including adenocarcinoma, squamous cell carcinoma (SCC), cholangiocarcinoma, transitional cell carcinoma, endometrial carcinoma and hepatocellular carcinoma. In fact, the tumor microenvironment (TME) is an inducer for COX-2 overexpression. This overexpression is due to dysregulated control over its transcriptional or post-transcriptional levels, so it could be a promising marker for identification of the tumor from normal cells **(5)**.

COX-2 Structure, Activation, And Degradation

COX-2 gene is located on the chromosome 1q25.2-q25.3 in human subjects. Degradation of COX-2 occurs in the proteasome in association with endoplasmic reticulum. Due to existence of many polymorphisms in the COX-2 gene, susceptibility among individuals to cancer is different. Proteins specifically binding to the COX-2 promotor would take an important role in promotion of tumorigenesis. COX-2 promoter contains a 3-untranslated region (3-UTR) that could be a target for microRNAs (miRNAs) like miR-144 for suppression of cancer progression. There are AU-rich elements (AREs) in the 3-UTR of COX-2. These AREs could influence messenger RNA (mRNA) decay and protein translation probably through interaction with Hu antigen-R **(6)**.

The COX pathway:

The arachidonic acid is a polyunsaturated fatty acid present in most mammalian cell membranes and a major component of animal fats. Mostly released from the membrane by phospholipase A2 (PLA2), this fatty acid can be substrate from the generation of distinct eicosanoides, being metabolized by the cyclooxygrnase (COX) pathway, the lipooxygenase (LOX) pathway or the cytochrome P450 monooxygenase pathway. Several reports show that both COX and LOX pathways are frequently over activated during chronic inflammation and cancer, which may account for the association between high-fat diets and higher incidence of chronic inflammation settings and malignant growths **(7**).

Cyclooxygenase catalyze the two-step conversion reaction of arachidonic acid into prostaglandin H2 (PGH2), which constitutes the precursor for the subsequent synthesis of a number of structureally related prostanoids, the prostaglandins and thromboxanes, by specialized ecosanoids synthesaes. Importantly, not only the prostanoid production, but the presence of specific G protein coupled receptors at the cell surface as well, is determined for the establishment of downstream prostanoid-dependent signaling. These surface receptors are designed according to the concomitant ligand. In addition, prostanoid such as prostacyclin are able to bind nuclear receptors from the peroxisome proliferator-activated receptors family **(8).**

PGs Are Important Targets for COX-2 in Cancer Promotion

It is accepted that COX-2's contribution to carcinogenesis is mediated through overproduction of PGs. Metabolites of these PGs released into the urine are now considered as approved biomarkers for prediction of cancer risk. PGE2 is a cardinal mediator of inflammation playing a key role in carcinogenesis **(9)**.

There is a positive-feedback loop between COX-2 expression and PGE2 **(8)**. The effects of PGE2 are exerted through interaction with its putative transmembrane G-protein-coupled EP receptors (EP1–EP4), especially EP1 and EP4 **(10).**

Cox-2 Is a Mediator of Cancer Inflammation

Cyclooxygenases-2 (COX-2) and Prostaglandin E2 (PGE2) are important inflammatory factors, associated with survival, invasion, growth and immune escape of cancer cells. One of the "hallmarks" of cancer is chronic inflammatory disease, which often promotes tumorigenesis and tumor progression. There is a reciprocal positive feedback between COX-2 and inflammatory mediators with either one inducing another **(11)**.

COX-2 Is a Mediator of Cancer Cell Growth

There is strong evidence for the contribution of COX-2 in the promotion of cancer cell growth **(12)**. There are several ways for COX-2-mediated cancer cell proliferation as follows:

a) Induction of aromatase gene activity (aromatase cytochrome P450 [CYP19]). Activation of CYP19 is contributed to estrogen biosynthesis. COX-2/PGE2 also induces cytochrome P450 1B1 (CYP1B1) that is responsible for conversion of the estrogen into estrogen quinones involved in tumor mitogenic and proliferative features **(13)**.
b) Activation of neutrophils. COX-2 derived from cancer cells is able to activate neutrophils for the release of elastase relying proliferative signals on cancer cells **(13)**.
c) Activation of stromal CAFs. CAFs also send proliferative signals on cancer cells **(14)**.
d) inactivation of adhesion molecules involved in regulation of cancer cell proliferation. An example for these molecules is E-cadherin that it makes a complex with catenin **(15)**.

COX-2 Is an Inhibitor of Apoptosis in Cancer Cells

COX-2 is related to apoptosis suppression in many cancers. COX-2 causes apoptosis resistance in cancer cells by making a delay in G1 phase, induction of the expressions for Survivin, Mcl-2 and Bcl-, and repression of caspase-3 **(7)**.

The apoptosis mediator wild-type p53 is a suppressor for COX-2 expression. In cancer cells, however, mutations in the p53 occurs, so a positive-feedback loop between COX-2 and the mutant p53 is an interesting event that might be a target for chemotherapeutic agents **(16)**.

COX-2 Is Mediator of Tumor Migration, Invasion, & Metastasis

COX-2 has been identified as one of the key metastasis progression genes involved in the metastasis into lymph nodes, bone, liver, brain, and so forth. COX-2 induces factors like IL-11 that are related to cancer metastasis. Epithelial–mesenchymal transition (EMT) in cancer cells is a promoter of cancer invasiveness **(17)**.

COX-2 induces EMT through increasing the activity for miR526b **(10).** and factors like signal transducer and activator of transcription-3 (STAT3), and that inhibition of COX-2-mediated EMT occurs after application of cannabinoids for cancer. COX-2 also induces β1-integrin and membrane proteases like matripase that are responsible for cancer cell invasion **(18)**.

COX-2 As An Inducer Of Csc Activity In Cancer Cells

COX-2 is identified to be implicated in maintenance of tissue resistance CSC populations through promotion of CSC-like properties including tumorosphere formation, stemness, and metastatic propensity. Inducible effect of COX-2 on TGF-β is related to the enrichment of CSCs. Subcellular localization of COX-2 within mitochondria favors mitochondrial recruitment (translocation) of p53 that in turn induces the activity for mitochondrial fission Drp1 for the promotion of stemness. In addition, COX-2 induces Id1 that serves as a marker of CSC self-renewal **(19)**

Mechanisms for Cox-2 Contribution to Cancer Progression

1. **Sirtuin (SIRT)/COX-2**

SIRT6 induces COX-2 in cancer cells by suppressing AMPK. AMPK activation is a downstream target for the tumor suppressor LKB1 **(20)**.

2. **NF-κβ/COX-2**

There are five related NF-κβ proteins including p50 (NF-κβ1), p52 (NF-κβ2), p65 (RelA), RelB, and c-Rel **(17)**, among them p65 has been identified for its role in the activation of COX-2 in cancer cells. IKK and IkB are

upstream signaling molecules for NF-κβ acting in its nuclear translocation **(17)**. NF-κβ/COX-2 could be a target for chemotherapeutic agents for exerting their anticancer roles **(21)**.

3. COX-2/STAT3

COX-2/STAT3 signaling is responsible for the promotion of an immunosuppressive microenvironment, EMT, and proliferation of cancer cells. This signaling could be a part of the extended NF-κβ/COX-2/BCL-2/IL-6/STAT3 pathway **(22)**.

4. PI3K/AKT/COX-2

COX-2 takes a role for activation of PI3K/AKT pathway by suppressing phosphatase and tensin homologue (PTEN, an essential tumor-suppressing factor) in cancer cells either directly or indirectly through suppression of TET-1-induced PTEN activation **(23)**.

MiR-221/222 is able to block PTEN resulting in activation of the PI3K/AKT/NF-κβ/COX-2 pathway. Phosphoinositide 3-kinase (PI3K) acts as both a positive or negative activator of COX-2. Activation of COX-2 by PI3K/AKT is mediated by induction of NF-κβ **(24)**.

5. MAPK/COX-2

Members of MAPK family including p38, ERK1/2, and c-Jun NH_2-terminal kinase are contributed to induction of COX-2. ERK1/2 and p38 are also downstream targets for COX-2. These MAPK members are mediator of PKC inducible effects on COX-2 in both cancer cells and CAFs **(25)**.

In addition, MAPK activity mediates inducible activity of EGFR on COX-2, in which a possible interaction between EGFR/p38 with COX-2 favors angiogenesis in cancer cells. P38/COX-2 is also involved in cancer cell resistance to apoptosis **(25)**.

6. COX-2/hypoxia inducible factor (HIF)

HIF-1α is a marker of angiogenesis in cancer cells **(17)** and a target for COX-2. An existing interplay between COX-2 and HIF-1α is contributed to induction of hypoxia within the TME. In the hypoxic conditions, hypoxia can induce COX-2 expression and reveal that hypoxia/HIF1α can bind directly with the promoter region of COX2, whose overexpression can promote proliferation and metastasis of cancer.**(26)**

COX-2 in Colorectal Cancer

The potential role of COX-2 in CRC has received considerable attention in the last several years. Many clinical trials and epidemiological studies have suggested that the use of non-steroidal anti-inflammatory drugs (NSAIDs), which are classic inhibitors of COX enzymatic activity reduce the risk of developing cancer in general, and more specifically in CRC **.(27).**

Considerable amounts of evidence in clinical settings further support a role of COX-2 in colorectal carcinogenesis and tumor progression. Thus, COX-2 is expressed early during the adenoma-carcinoma sequence that occurs in CRC, suggesting an important role of this enzyme in colorectal carcinogenesis. COX-2 expression is upregulated in human colorectal adenocarcinomas when compared with normal adjacent colonic tissue. Moreover, polymorphisms of the *PTGS2* gene were associated with risk of CRC **(28)**. Many reports of colorectal tumor cells either overexpressing COX-2 or having it silenced have correlated increased COX-2 expression with their invasive and metastatic properties in xenografted tumors in mice

In view of the abundant biological and phenotypic evidence, several clinical trials have been performed, aimed to evaluate the efficacy of specific inhibitors of COX-2 (COXIBs) to prevent or delay the onset (or recurrence) of tumors in high-risk patients, including those with prior removal of colon tumors. These studies indicate that specific inhibition of COX-2 prevents the (re)appearance of tumors but also show cardiovascular side-effects. Recent studies, remark the role of COX-2 in constitutive IDO1 expression by human tumors and substantiate the use of COX-2 inhibitors to improve the efficacy of cancer immunotherapy, either by reducing constitutive IDO1 expression, which contributed to the lack of T-cell infiltration in tumors that fail to respond to immunotherapy, or by synergizing with anti-checkpoint antibodies **(29)**.

COX-2 Downstream Genes in CRC

COX-2 activity regulates gene expression, which confers cells advantages for growth, migration, invasion, and metastasis. stable COX-2 overexpression in carcinoma cell lines (HT-29, HCT116, and Caco2) significantly affects gene transcription. Analysis of genes modified by COX-2 overexpression indicates that many genes involved in transcription, growth, apoptosis, angiogenesis, and migration were elevated. Moreover, a review of the available databases and literature in other carcinoma cell lines overexpressing COX-2 or repressed siRNA also identify some COX-2 downstream effectors responsible for the pro-tumorigenic properties of COX-2. **(29)**.

Dual-Specificity MAPK Phosphatase 10

Dual-specificity Mitogen Activated Protein Kinase (MAPK) phosphatase 10 (DUSP10), also named MPK5, was found altered by COX-2 overexpression in CRC cell lines in several data sets. Most of those studies have found increased DUSP10 mRNA in tumor tissue, thus suggesting a pro-tumorigenic role for this phosphatase **(30)**

Cancer progression is related to an uncontrolled cell division and DUSP10 overexpression produces the loss of cell-contact inhibition through the dephosphorylation of Yes-associated protein (YAP) at Ser397. This dephosphorylation retains YAP in the nucleus. In fact, high amounts of DUSP10 and YAP1 are located in the nucleus of CRC cells **(30).** Additionally, the quantity of nuclear DUSP10 in CRC tumor biopsies is directly correlated with high tumor stage CRC and poor prognosis and survival in a large cohort of CRC patients, being also associated to high expression of nuclear YAP1. All these data point at DUSP10 as a downstream protein in COX-2 signaling and provide evidence of the role of DUSP10 in CRC progression via YAP1 regulation **(30)**

Dual-Specificity MAPK Phosphatase 4

Another dual-specificity MAPK phosphatase, DUSP4/MKP-2, was also upregulated by COX-2. DUSP4 role in several cancers has been documented**.** An altered expression of DUSP4 is related to colon tumorigenesis. Thus, elevated DUSP4 expression is associated with microsatellite instability in CRC patients being also associated with liver and lung metastases of CRC **(31).**

Interestingly, DUSP4 overexpression in CRC cell lines decreases their sensitivity to doxorubicin, a drug used to treat CRC**.** All these data together point at DUSP4, enzyme regulated by COX-2, as a factor whose overexpression leads to CRC development and invasion, and which can be a promising therapeutic target. Moreover, DUSP4 specific inhibitors have been described supporting its clinical testing in CRC at least in some drug resistant tumors. **(31).**

Matrix Metalloproteinase- 7

Matrix metalloproteinases (MMPs) are proteolytic enzymes which degrade and remodel the extracellular matrix (ECM) in physiological processes, such as in cell migration, and have also been involved in metastasis**.** It has been reported that MMP7 is one of the most important MMPs in colorectal tumorigenesis, promoting angiogenesis, invasiveness, and tumor survival. Thus, MMP-7 may enhance CRC progression due to its proteolytic activity on several cell surface molecules as EGFR, Fas-L, etc. **(8)**. MMP7 is abundantly synthesised by colon carcinoma cells**.** A study of CRC patients demonstrated an increase in COX-2 and MMP-7 expression when compared to normal tissue and colon polyps' sample**.** High levels of MMP-7 together with PTEN down-regulation were detected in CRC and were related to tumor stage and progression**.** Moreover, COX-2 overexpression in carcinoma cells modulates the adhesive properties of MMPs**.** PGE2 can transactivate EGFR thereby inducing the proliferation of CRC cell lines and exerts its functions in part through molecules such as MMP-7 **(32)**

Trophoblast Cell-Surface Antigen 2

Trophoblast cell-surface antigen 2 (TROP2), also called TumorAssociated Calcium Signal Transducer 2 (TACSTD2), is a cellsurface glycoprotein expressed during embryonic and fetal development which is involved in cell proliferation, cell binding, motility, and metastasis**.** TROP2 overexpression can induce cancer growth and is associated with poor prognosis and drug resistance in cancer cells**.** COX-2 overexpressing colon carcinoma cells present high levels of TACSTD2. Previous studies in CRC patients, already showed the correlation between

high expression of TROP2 and metastasis in CRC**.** The overexpression of TROP2 together with MMP7, another COX-2 induced gene, is a predictor of worse prognosis and relapse in CRC**.** TROP2 expression enhances anchorage-independent growth in colon carcinoma cell lines **(8)** and its activation of TROP2 by Tumor Necrosis Factor (TNF)-alpha induces cell migration and invasion**.** More importantly, an anti-TROP-2 antibody, sacituzumab govitecan, is a potential therapeutic drug for metastatic solid tumors **(33).** Since TROP2 is consistently induced by COX-2 overexpression, this makes it an alternative target to COX-2 blockade therapy in CRC.

COX-2 AND THE p53 PATHWAY

The role of p53 in cancer in general and CRC in particular is well known. Mutations in the tumor suppressor gene TP53, which encodes the protein p53, are frequently found in human cancers. Mutations in K-ras, adenomatous polyposis coli (APC), and p53 induce the transition from healthy colonic epithelia to CRC**.** Among the genes induced by COX-2, we found in our arrays many genes of the p53 pathway. , there is a well-known crosstalk between p53 and COX-2, in which COX-2 decreases p53 transcription, and p53 also regulates COX-2 expression**.** Furthermore, many COX-2 inducers, such as hypoxia, cytokines, oncogene activation, carcinogens, and inflammation, can also activate p53. The role of p53 in the regulation of COX-2 expression and activity has been extensively described. Thus, it has been reported the increase in COX-2 transcript in human tumor cells expressing p53**.** COX-2 upregulation by p53 has been attributed to an increase on the binding of NF-kB to COX-2 promoter in response to p53 overexpression **.** Conversely, COX-2 avoids the transcriptional activity of p53 on target genes **(34).**

In conclusion, Considerable amounts of evidence in clinical settings further support a role of COX-2 in colorectal carcinogenesis and tumor progression. Thus, COX-2 is expressed early during the adenoma-carcinoma sequence that occurs in CRC, suggesting an important role of this enzyme in colorectal carcinogenesis. COX-2 expression is upregulated in human colorectal adenocarcinomas when compared with normal adjacent colonic tissue.

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