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J Vet Res 63, 215-224, 2019
DOI:10.2478/jvetres-2019-0030

REVIEW ARTICLE

Significance of cyclooxygenase-2 in oncogenesis

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Received: November 9, 2018 *Accepted: April 23, 2019*

Abstract

The cyclooxygenase-2 (COX-2) enzyme catalyses the first stage of biosynthesis of prostanoids, proteins that are implicated in various physiological and pathological processes in humans and animals. The expression of COX-2 increases significantly during pathological processes accompanied by inflammation, pain and fever. Overexpression of COX-2 was determined in tumour tissues, which suggests that this enzyme participates in oncogenesis. In this paper the topics discussed are mechanisms regulating COX-2 expression, COX isoforms, their role in the body and the oncogenic mechanisms triggered by the overexpression of COX-2, including inhibition of apoptosis, intensification of neoangiogenesis, increased metastatic capacity, and weakening of the immune system. The significance of and the mechanisms by which COX-2 participates in oncogenesis have been studied intensively in recent years. The results are highly promising, and they expand our understanding of the complex processes and changes at the molecular, cellular and tissue level that promote oncogenesis and cancer progression. Notwithstanding the knowledge already gleaned, many processes and mechanisms have not yet been elucidated in human medicine and, in particular, in veterinary medicine. Further research is required to develop effective tumour diagnostic methods and treatment procedures for humans and animals.

Keywords: cyclooxygenase-2, oncogenesis, COX-2 expression mechanisms.

Introduction

Cyclooxygenase (COX), also known as prostaglandin G/H synthase (PTGS), is an enzyme of the myeloperoxidase family which catalyses the first stage of biosynthesis of prostanoids (prostaglandins, PG; prostacyclin, PGI_2; and thromboxane, TXA_2), bioactive proteins which are implicated in various physiological and pathological processes in humans and animals (7, 14, 73) (Figs 1 and 2).

In humans and animals, COX exists in three isoforms: constitutive COX-1 (PTGS-1), inducible COX-2 (PTGS-2), and COX-3. COX-1 and COX-2 share than 60% of their nucleotide sequences but are encoded by different genes. COX-3 is expressed mainly in the central nervous system and the aortic wall as a splice variation or posttranscriptional modification of COX-1 encoded by the same gene, but with an additional first intron (13). Other COX variants have been identified, but they do not exhibit enzymatic activity and are not regarded as isoforms of COX. These variants result from mRNA splicing errors and single nucleotide polymorphism. Their significance has not yet been fully elucidated, but they possess important pathophysiological properties (14).

COX-1 is found in most cells, and it is responsible for the healthy function of bodily organs and maintenance of homeostasis. The enzyme has a cytoprotective effect on mucous membranes, it regulates renal blood flow, inhibits blood platelet aggregation, relaxes vascular smooth muscles, and participates in sensory processes, and control of the autonomic nervous system (14). Higher levels of COX-1 expression were also observed during pathological processes in vascular endothelial cells and myocytes near atheromatous plaques and in pathological foci and synoviocytes in rheumatoid arthritis (75).

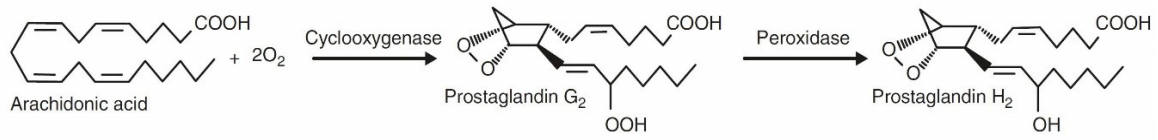

Fig. 1. The two reactions converting arachidonic acid to prostaglandin G_2 by cyclooxygenase activity and prostaglandin G_2 to prostaglandin H_2 by peroxidase activity (14)

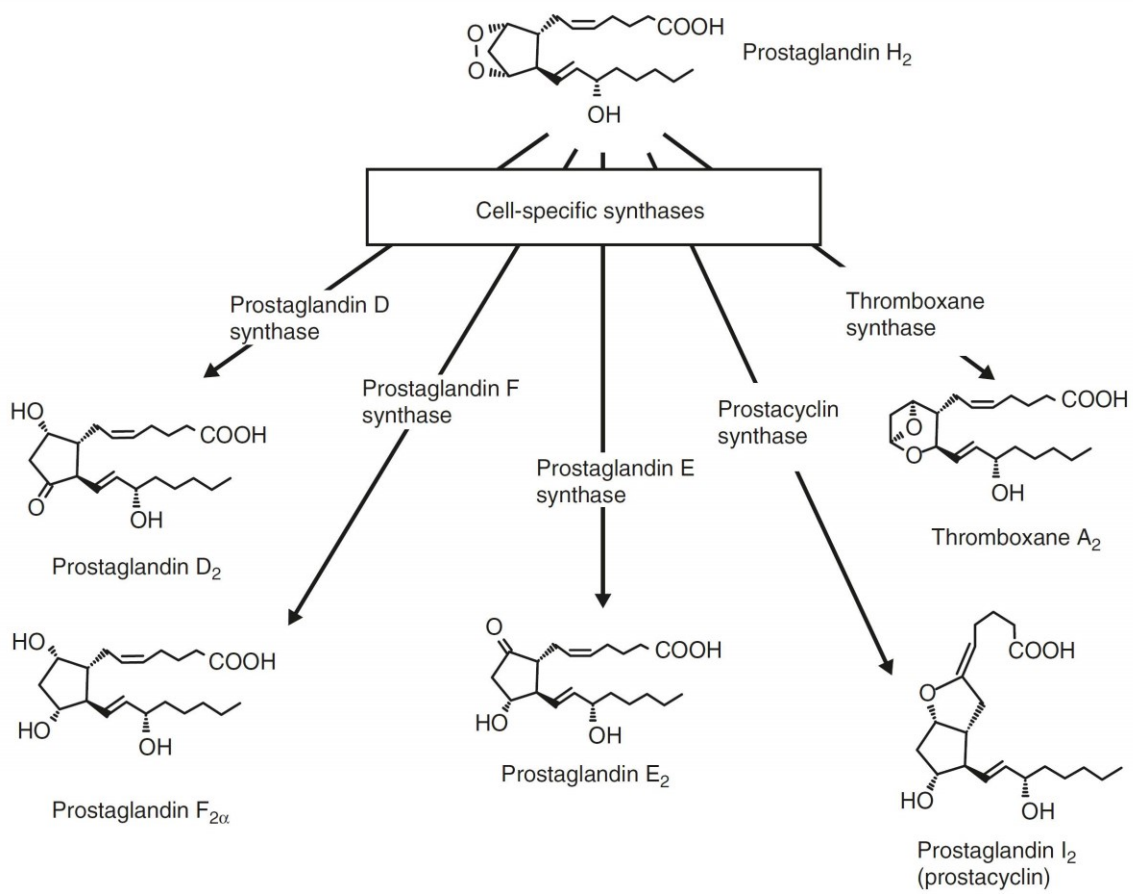

Fig. 2. The cell-specific synthases involved in the conversion of prostaglandin H_2 to the five principal prostaglandins (14)

Mammalian cells contain low levels of COX-2, and this inducible isoform is rarely detected in healthy individuals. However, COX-2 has been found in the nervous system, gastrointestinal tract, heart, kidneys, eyes, and the reproductive system (41). In the nervous system expression of all COX isoenzymes is found, although it is differentiated in various areas. In the forebrain and spinal cord physiological COX-2 expression was determined (84, 96). In the gastrointestinal tract minimal physiological COX-2 expression was noticed (47), while in the vascular system permanent COX-2 expression is necessary to maintain regular blood flow (7). COX-2 in blood vessel endothelium is responsible for synthesis of PGI_2, which is a strong antagonist of TGX_2 produced by thrombocytes. Inhibition of PGI_2 synthesis *e.g.* during the application of COX-2 inhibitors (coxibs) causes disturbance of the balance between PGI_2 and TXA_2, leading to the intravenous coagulation observed after the use of drugs of this class, *e.g.* celecoxib and rofecoxib (20). In the respiratory tract once again physiological COX-2 expression is observed and here it is limited to the bronchiolar and alveolar epithelia (65). In the urinary tract COX-2 expression was found in the juxtaglomerular apparatus, epithelial cells, and nephron tubules, in endothelial cells of renal papilla and in

podocytes (50). The studies with the use of COX inhibitors demonstrated that these compounds hamper the synthesis of PG, mainly PGE_2, restrict blood flow through kidneys and glomerular filtration, decrease absorption of sodium and affect the release of renin and activation of the renin-angiotensin-aldosterone pathway (16). COX isoenzymes play a very important role in reproduction processes. In the females COX-2 expression is a factor which determines correct ovulation, fertilisation and embryo implantation, whereas application of COX inhibitors can disturb these processes (7). COX-2 activity is responsible for angiogenesis and the beginning of placenta formation. The increase of COX-2 expression was manifested in amnion epithelium, chorion reticular stratum, and decidua (78). Taking into account the permanent COX-1 expression, differences in prostanoid amount in the uterus derive exclusively from the induction of COX-2 (7). In the males COX-2 expression was shown in the epithelium of the vas deferens and epididymis as well as in seminal vesicles (56). Until recently, COX-2 had been associated only with the stress response and inflammatory factors (7). According to recent research, the expression of COX-2 increases significantly during pathological processes that involve inflammation, pain, and fever (41, 94). Changes in COX-2 expression were noted in patients with Alzheimer's disease (69) and glaucoma (41).

Overexpression of COX-2 in tumour tissue suggests that this enzyme is involved in oncogenesis (73, 94). An increase in COX-2 expression reprograms benign cancer cells to a malignant phenotype, disrupts cell growth and proliferation, enables cancer cells to evade apoptosis and the immune response, creates new blood vessels, and promotes cancer cell invasion (30, 95).

The mechanisms by which COX-2 participates in oncogenesis are complex and poorly understood, in particular in animals. This enzyme mediates interactions between cancer cells and their surroundings to create optimal conditions for their survival, growth, and proliferation (36). The presence of COX-2 is also closely correlated with chronic inflammations and oncogenesis, and its overexpression can instigate inflammation to become cancer (58). It is generally believed that most neoplastic processes are not induced by COX-2 alone and that they involve other factors and processes, such as exposure to dietary, occupational and environmental carcinogens, toxins and genetic mutations (45). Oshima *et al.* (68) provided the first genetic evidence to indicate that COX-2 is an important promoter of oncogenesis. They found that COX-2 was overexpressed in mice with colon polyps and that its expression and polyposis were radically decreased in knockout mice and mice treated with COX-2 inhibitors. In a clinical study, Eberhart *et al*. (25) observed an increase of COX-2 expression in 50% of human patients with colorectal adenomas and in 86% with carcinomas, as well as the absence of COX-2 expression in healthy intestinal epithelia. There is also evidence to indicate that COX-2 has a tangible effect every stage of metastasis, but the associated mechanisms are not yet fully understood (23).

Overexpression of COX-2 promotes oncogenesis by inhibiting apoptosis, intensifying neoangiogenesis, promoting metastasis, and weakening the immune system (73).

Apoptosis

Apoptosis, also known as programmed cell death is a genetically conditioned physiological process which plays a key role in the development and maintenance of tissue and organ homeostasis (29). Apoptosis is a crucial process in embryogenesis, organ involution, tissue regeneration and death of differentiated cells. It is essential for healthy growth and bodily functions. This process is a series of morphological, biochemical and molecular events which lead to cell death and thereby eliminate old, redundant, pathologically changed cells and cancer cells (33). An imbalance between cell proliferation and cell death can promote oncogenesis (95).

Apoptosis is associated with damage to proto-oncogenes, suppressor genes and regulator genes as well as enzyme activation (6). The intrinsic pathway of apoptosis is induced by changes in the mitochondrial membrane, and the release of cytochrome c to the cytoplasm and apoptosome formation, whereas the extrinsic pathway is induced through the activation of specific cell receptors, including receptors of the tumour necrosis factor receptor superfamily. Around 50 genes (including *p-53, mdm2, bcl-xS* and *bax*) are activated in this process, and the expression of other genes (including *bcl-2* and *bcl-xL*) is suppressed. In these ways the caspase cascade is activated and cell death is provoked. Cancer cells are resistant to most apoptosis-inducing signals, and the accumulation of errors related to replication, the cell cycle and adhesion contributes to oncogenesis (55).

Apoptotic pathways are influenced by the balance between pro-apoptotic (such as Bax and Bak proteins) and anti-apoptotic factors (such as Bcl-2 and Bcl-xL proteins). Overexpression of COX-2 and the related increase in PGE_2 synthesis inhibit Bax-induced apoptosis by increasing the activity of Bcl-2, an antagonist of Bax (1). COX-2 can influence apoptosis not only *via* the Bcl-2-dependent pathway, but also by activating the serine-threonine protein kinase (Akt) pathway (43). On its own, Akt rarely initiates oncogenesis, but it contributes to tumour progression by inhibiting apoptosis, promoting changes in cell metabolism and proliferation, and regulating the migration and invasion of cancer cells (54). Krysan *et al.* (53) demonstrated that COX-2 overexpression increases the concentration and stability of survivin, an anti-apoptotic protein which binds caspases and increases resistance to apoptosis.

Selective COX-2 inhibitors induce apoptosis in cancer cells, however, this process was also observed in cells not expressing COX-2, which suggests that non-steroidal anti-inflammatory drugs (NSAIDs) stimulate apoptosis in cancer cells through both COX-2-dependent and COX-2-independent pathways (87). The apoptotic effects of radiotherapy were intensified and the efficacy of chemotherapy was improved in patients with moderate or high overexpression of COX-2 who were administered COX-2 inhibitors (27, 39).

Neoangiogenesis

Angiogenesis is a process during which new blood vessels are formed from the endothelial cells of pre-existing vessels. Vascularisation is essential for cell development and differentiation during embryogenesis, and it is fundamental in various physiological and pathophysiological responses to metabolic processes in tissues (9, 85).

Angiogenesis is also important during oncogenesis. Blood vessels supply cancer cells with nutrients and enable the transit of primary tumour cells to other organs. The process by which new blood vessels are formed in a tumour is known as neovascularisation, and it is essential for the growth of even very small tumours with a diameter of 1–2 mm (79, 85). Neovascularisation is important in tumour progression, and it is referred to as the angiogenic switch (3). There are various types of neovascularisation processes, including sprouting angiogenesis, intussusceptive angiogenesis which involves the formation of an endothelial-lined pillar that extends to the tumour and causes a larger blood vessel to split into smaller vessels, glomeruloid or looping angiogenesis which involves the formation of closed loops and capillary networks, and vasculogenic mimicry (23). According to Folkman (30), tumour growth and metastasis are closely related to vascular development. In the prevascular phase, most tumours can survive *in situ* for months or even years, while indicators of cell proliferation and apoptosis remain within the norms. This state is maintained until mutations in proto-oncogenes and suppressor genes induce an angiogenic phenotype in certain cell groups (9). The location and duration of angiogenesis are closely regulated under physiological conditions, but during oncogenesis, this process is no longer controlled. Tumour cells release pro-angiogenic paracrine factors which stimulate endothelial cells to proliferate and form new vessels. However, the induction of an angiogenic phenotype requires the suppression of angiogenic inhibitors and a predominance of stimulating factors (30, 85).

Neoangiogenesis involves several stages, including the activation of endothelial cells inside pre-existing vessels, degradation of the basement membrane and the extracellular matrix, migration and proliferation of endothelial cells, formation of the vascular lumen and new vascular loops, formation of the basement membrane and maturation of new vessels, incorporation of pericytes which stabilise vessels, and incorporation of smooth muscle cells into vessels (9, 79, 85). Neoangiogenesis largely resembles physiological angiogenesis (17).

Factors regulating neoangiogenesis are produced by both tumour cells and bodily cells, and they can be of endocrine (circulatory), paracrine (adjacent tumour, stroma, or extracellular matrix) or autocrine (endothelial cell) origin (79, 85). Several endogenous stimulators and inhibitors of angiogenesis have been identified to date. Vascular endothelial growth factor (VEGF) is the main and the most specific growth factor in neoangiogenesis (91). Other stimulating factors include fibroblast growth factor, transforming growth factor β, platelet-derived growth factor, hepatocyte growth factor, insulin-like growth factor, angiogenin, angiopoietin-1, tissue factor, proliferin, erythropoietin, heparin and the 22-kDa heparin fraction, tumour necrosis factor α, interleukin-8, granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor and chemokines. Angiogenesis inhibitors include thrombospondins 1 and 2, angiostatin, endostatin, vasostatin, restin, troponin I, angiopoietin-2, antithrombin III fraction, interferons α and β, the N-terminal fragment of platelet factor 4, the N-terminal fragment of prolactin, proliferin-related protein, tissue inhibitor of metalloproteinases 1, 2, and 3, interleukins 1, 2, 6, 10, 12, and osteopontin VEGF digestion product (30, 79). Angiogenesis also induces cellular hypoxia as the result of tumour growth without neovascularisation, which induces hypoxia-inducible factors-1α and -2α and activates the transcription of genes that enable cells to survive under hypoxic conditions and contribute to cancer progression (57). Other stimulators of angiogenesis include hypoglycaemia, proteolytic enzymes of the extracellular matrix, factors of the fibrinolytic system, integrins, and nitric oxide (19, 28, 30).

An imbalance between pro-angiogenic and anti-angiogenic factors leads to the stimulation or inhibition of angiogenesis. A predominance of angiogenesis stimulators promotes vascularisation, whereas a predominance of inhibitors leads to angiogenesis silencing or even vascular regression and apoptosis in endothelial cells (86).

The factors conditioning angiogenesis and its intensity are evaluated to determine pathological processes in oncogenesis and select the optimal treatment. These factors also have prognostic and predictive value (79). The expression of COX-2, which catalyses PG production, is highly correlated with the intensity of angiogenesis and tumour development (48). Studies conducted *in vivo* and *in vitro* demonstrated that an increase in COX-2 expression in tumours contributes to neovascularisation by stimulating the synthesis and activity of pro-angiogenic factors and exerts a direct influence on endothelial cells by the products of reactions with COX-2 - PGE_2, PGI_2 and TXA_2 (97).

Overexpression of COX-2 and VEGF was correlated with higher vascular density and poor prognosis in lung, breast, and cervical cancer (97, 99). COX-2 inhibitors have been found to suppress neoangiogenesis in cancer progression and deliver positive therapeutic effects (74). Angiogenesis inhibitors such as anti-VEGF antibodies (bevacizumab) and tyrosine kinase inhibitors which suppress the expression of VEGF receptors (sorafenib, sunitinib, and pazopanib) show certain promise in cancer treatment (26). However, long-term therapy involving the above inhibitors can promote cancer invasion and metastasis, which is why further research into the molecular mechanisms of neoangiogenesis is required to increase the efficacy of cancer treatments (93).

Metastasis

Cancer progression is related to metastatic capacity, and it involves the spread of circulating tumour cells which are carried by lymph and blood to distant parts of the body (93). This process is known as metastasis, and it leads to the formation of a secondary tumour or tumours from the primary tumour. Metastasis is a complex process that proceeds in several stages, including separation of cells from the primary tumour, cell migration across the basement membrane into lymphatic and blood vessels, cell survival during transport due to resistance to *anoikis*, *i.e.* apoptosis caused by the loss of connections with the extracellular matrix and other cells, cell migration from vessels to the surrounding tissues, colonisation of new sites, and formation of secondary tumours which adapt to the local microenvironment and change it according to their needs, *e.g.* through stimulating stromal cells to produce growth factors (93, 98).

Oncogenesis can be preceded by chronic inflammation which creates a specific inflammatory microenvironment characterised by lymphocyte and macrophage infiltration, and the presence of cytokines and chemokines (38). Tumour-associated macrophages and their tumour-promoting mediators play a special role in all stages of cancer invasion and metastasis (59, 88). The cellular composition of the tumour microenvironment is determined by the cell genome. The interactions between tumour cells, stromal cells (fibroblasts and endothelial cells), and immune system cells influence the prognosis, and the relevant information is useful for selecting the optimal immunotherapy (5, 70).

Tumour cells influence the extracellular matrix and adhesion proteins, which leads to tissue infiltration by cancer cells and metastasis. Adhesion to the extracellular matrix is the key stage which initiates metastasis (93). In many tumours, this process is determined by the presence of the CD44 antigen, a glycoprotein which acts as a surface receptor for hyaluronic acid, the main structural component of the matrix which participates in intercellular interactions, adhesion and cell migration. Research has demonstrated that non-small cell lung cancer (NSCLC) cell lines with COX-2 overexpression were characterised by increased expression of CD44, and their invasive capacity was significantly compromised under the influence of specific CD44 inhibitors. Research into colorectal and lung cancers also revealed that COX-2 overexpression increases cancer invasiveness via a CD44-dependent pathway (21, 61).

An invasive phenotype of epithelial cancer cells is formed in the process of epithelial-mesenchymal transition (EMT) during which cells lose their polarity and adhesive capacity and become more able to migrate (45). This process is observed during cytoskeletal rearrangement and changes in the expression of selected surface markers, such as E-cadherin, where the relevant mechanisms are controlled by Akt (54). The expressions of COX-2 and E-cadherin are inversely proportional in gastric cancer and NSCLC (22, 77).

Matrix metalloproteinases (MMPs), zinc-dependent proteolytic enzymes which weaken the basement membrane by degrading extracellular matrix proteins, play an important role during cancer invasion, in particular during the migration of tumour cells across the basement membrane. MMPs produced by tumour cells contribute to local infiltration and metastasis, and propel neoangiogenesis (49). Somiari *et al*. (81) observed significantly higher serum concentration and activity of MMP-2 in breast cancer patients than in their control subjects, which implies that this parameter can be monitored during preoperative evaluations. In invasive breast cancer, higher expression levels of COX-2 and MMP-2 were associated with decreased survival, which indicates that both parameters are markers of poor prognosis in breast cancer. Overexpression of COX-2 stimulates the activity of MMP-2 and MMP-9 and contributes to infiltration and metastasis. The Akt1 and Akt2 isoforms are also important actors during cancer cell migration and metastasis (54).

Overexpression of heterodimer receptor HER2 (p185), which involves three mutually regulating proteins – HER2 and HER3 heterodimer receptors, autocrine heregulins and COX-2 – has also been implicated in the development and progression of the malignant tumour phenotype. HER2 and /HER3 are blocked with Herceptin (trastuzumab), an anti-p185 monoclonal antibody, to neutralise the mitogenic activity of heregulins and induce oncogenic activation of the COX-2 gene. This discovery led to the development of receptor enhancement chemosensitivity (REC), a new tumour targeting strategy where Herceptin is used to sensitise cancer cells overexpressing HER2 to chemotherapy drugs. The drug is conjugated with the antibody, and it is administered directly to cancer cells overexpressing this receptor (51).

Immunosuppression

The immune system plays a very important role in the destruction of tumour cells. These cells are eliminated from the body at the intracellular level, and they are destroyed at the stage of genetic mutation and during cellular responses involving T lymphocytes and natural killer cells. Helper T1 lymphocytes are vital in the anti-cancer immune response; they activate cytotoxic T lymphocytes and B lymphocytes which produce antibodies against cancer cells. Mature antigen-presenting dendritic cells (APC) are vital components of local lymphoid structures. Tumours weaken the immune system and decrease the absolute counts of T lymphocytes, $CD4^+$ lymphocytes, and the $CD4^+/CD8^+$ ratio, impair mitogen-stimulated proliferation of lymphocytes and decrease the cytotoxic activity of NK cells (31).

The inflammatory process itself is a pro-oncogenic mechanism that stimulates the production of regulatory T (Treg) cells, myeloid-derived suppressor cells (MDSCs), and immunosuppressive soluble factors such as TGF-β, and it has certain immunosuppressive effects. In the future, complete knowledge of the tumour microenvironment will support the development of targeted immunotherapy to restore immune responses that are compromised by pro-oncogenic inflammatory processes (59).

COX-2 plays an important role in cancer immunosuppression. APCs control the initiation of T cell responses and mature under the influence of prostanoids whose synthesis is catalysed by COX-2 *via* IL-10-dependent and IL-10-independent pathways (40). Overexpression of COX-2 stimulates PGE_2 synthesis, decreases the activity of dendritic cells, contributes to the accumulation of MDSCs in the tumour microenvironment and disrupts the balance between the concentrations of IL-10 and IL-12, cytokines that directly regulate cellular responses (40, 76). In lung cancer, an increase in the concentration of the IL-10 immune suppressive factor and a decrease in the concentration of the IL-12 immune inducing factor led to immunosuppression, intensified angiogenesis and contributed to poor prognosis (72). Huang *et al.* (44) found that PGE_2 produced by NSCLC in the presence of COX-2 stimulated lymphocytes and macrophages to produce IL-10 and inhibited IL-12 synthesis by macrophages. In a study performed on a murine model of Lewis lung carcinoma, Stolina *et al.* (83) observed that specific genetic or pharmacological inhibition of COX-2 overexpression prompted APCs to restore the IL-10 and IL-12 balance, increased lymphocytic infiltration around the tumour, suppressed tumour growth, and delivered anti-carcinogenic effects. Immunotherapy combined with COX-2 inhibitors also produced promising results in the treatment of pancreatic and breast cancer (4, 63). Holmgaard *et al.* (42) reported that indoleamine 2,3-dioxygenase (IDO) is an integral part of the poorly understood immunosuppressive mechanisms. The expression of IDO in cancer cells increases malignancy and intensifies local and general immunosuppression by activating MDSCs *via* a Treg-dependent mechanism. In human melanoma, IDO expression was strongly correlated with MDSC infiltration, and the administration of IDO inhibitors decreased immunosuppression by lowering MDSC counts, which implies that IDO is a promising therapeutic target for the treatment of cancer. In a study of canine malignant mammary tumours, positive interplay between $CD3^+$ T lymphocytes and concurrent expression of COX-2 and epidermal growth factor receptor was significantly associated and positively correlated with tumour size, tumour necrosis, mitotic index, histological grade of malignancy and presence of lymph node metastasis. The results obtained suggest that the $COX\text{-}2^+/EGFR^+$ status may be part of the strategy adopted by tumour cells to evade the cytotoxic tumour-specific immune responses (10).

Mechanisms regulating COX-2 expression

The mechanisms which control COX-2 levels and activity in cancer cells are complex and poorly understood (73). According to research, COX-2 expression is regulated at three levels: transcription, translation and degradation.

Transcriptional activities initiated in response to oncogenes, inflammatory factors, growth factors, viral factors, xenobiotics, toxins, mutations of suppressive factors, hypoxia, radiotherapy, and chemotherapy have an important effect on controlling COX-2 levels in cancer cells. These factors trigger signalling pathways that converge in the cell nucleus, and control the expression of the *PTGS-2* gene and the transcription of COX-2 (89).

Abnormal post-transcriptional regulation of COX-2 is recognised as a signal that stimulates COX-2 expression in cancer cells during translation (18).

The mechanisms responsible for the degradation of COX-2 in cancer cells and its influence on oncogenesis are imperfectly known (73). Two COX-2 degradation pathways have been identified *in vitro* and *in vivo*: the proteasome-dependent pathway and the proteasome-independent pathway (92). According to Chen *et al.* (15), membrane protein caveolin-1 participates in the degradation of COX-2, and the decrease in caveolin-1 levels in cancer cells could contribute to COX-2 overexpression and protect the enzyme against degradation. Research indicates that ceveolin-1 is capable of inhibiting oncogenesis, and a decrease in or absence of its expression could play a significant role in the transformation of normal cells to cancer cells. However, the formation of a malignant phenotype in cells is often accompanied by an increase in caveolin-1 levels, which suggests that disruptions in the expression of caveolin-1 influence oncogenesis and cancer progression (52).

Clinical significance of COX-2 expression

Evaluation of COX-2 expression could be used in the diagnostics and therapy of tumours and COX-2 could be the prognostic and/or predictive biomarker. An increase of COX-2 expression was found in tumours of various organs in humans *e.g.* lung, colon, pancreas, ovary, uterus, breast, and prostate (71, 82). COX-2 expression, besides being proved in solid tumours, was also observed in leukaemia, lymphoma, and myeloma (12, 34, 67).

The studies concerning evaluation of COX-2 expression in animals revealed its overexpression in various types of canine and feline tumours found in the skin, mammary gland, urinary bladder, intestines, and bones for example (24, 60). COX-2 overexpression was also found in some equine tumours, mainly localised in reproductive organs and eyes (88).

COX-2 overexpression is often connected with increased tumour malignancy, a tendency to distant metastases, a worse prognosis, and shorter overall survival (OS) and/or progression-free survival (PFS), although prognostic and/or predictive significance of COX-2 overexpression as a biomarker has not yet been clearly defined (62, 71). Some studies showed the relationship of COX-2 overexpression with shorter OS and/or PFS (62, 66), however in others no such relationship was found (32). Contradictory data concerning any connection between increased COX-2 expression and a bad prognosis, shorter OS and a worse response to treatment were also obtained in the studies of some tumours in dogs and cats (11, 37, 80).

The experimental, epidemiological and clinical studies conducted in humans and animals showed that the use of NSAIDs in the form of nonspecific or (and more effectively) specific coxibs is beneficial in the prophylaxis of tumours, effectively inhibits tumour progression by negative influence on tumour cells and improves the treatment results of patients with tumours (46, 90). Positive results of NSAIDs use in tumours treatment were confirmed in several studies, in which the application of NSAIDs alone or combined with chemotherapy or radiotherapy in humans and animals were evaluated (2, 8, 27). COX-2 as a specific biomarker could be used to detect the oncology patients for whom application of COX-2 inhibitors might decrease COX-2 expression, retard tumour progression and extend life (64).

Conclusion

The significance of and the mechanisms by which COX-2 participates in oncogenesis have been studied intensively in recent years. The results are highly promising, and they expand our understanding of the complex processes and changes at the molecular, cellular and tissue levels that promote oncogenesis and cancer progression. Notwithstanding the knowledge already gleaned, many processes and mechanisms have not yet been elucidated in human medicine and, in particular, in veterinary medicine. Further research is required to develop effective tumour diagnostic methods and treatment procedures for humans and animals.

Conflict of Interests Statement : The authors declare that there is no conflict of interests regarding the publication of this article.

Financial Disclosure Statement: Not applicable.

Animal Rights Statement: Not applicable.

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