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REVIEW PAPER

Cyclooxygenase-2 – characteristics, functions and possible use as a biomarker in human and animal oncology – a review

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Abstract

Neoplastic diseases are currently one of the most common causes of mortality in both animals and humans. Therefore, much of the recent research focuses on the search for biomarkers to enable qualitative and temporal improvement in the detectability as well as prognostic and predictive assessments in patients suffering from neoplastic diseases. One such biomarker seems to be cyclooxygenase-2 (COX-2), also known as prostaglandin G/H synthase (PTGS). The wide dissemination of COX isoforms and prostanoids synthesized with their involvement in the tissues indicates the significant role they serve in the regulation of the functioning of several organs and systems, particularly the gastrointestinal, nervous, circulatory, reproductive, urinary and respiratory systems. Until recently, COX-2 has only been associated with the response to stress and inflammation initiators. It is currently known that its expression increases significantly in the course of numerous pathological processes that involve inflammation, pain or fever. Results obtained during previous studies demonstrated a significant increase in COX-2 expression in several types and subtypes of neoplasms in humans and animals, particularly in dogs and cats, the two animal species that have been studied the most frequently. COX-2 has not been adopted yet as one of the biomarkers for routine oncological diagnostics, which indicates the possibility for wider use of the assessment of its expression in the diagnostics and therapy of neoplasms in humans and animals. It may therefore be possible to use an assessment of COX-2 overexpression to improve cancer diagnostics and therapy and for prognostic and/or predictive purposes.

Keywords: cyclooxygenase-2, biomarkers, neoplasm, prostaglandin G/H synthase

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INTRODUCTION

Neoplastic diseases in humans are currently ranked the second, after cardiovascular diseases, most common cause of mortality worldwide, including Poland. WHO data indicate that 8.8 million people died of cancer worldwide in 2015 (Roco et al. 2018). In Poland, the number of malignant neoplasm cases over the last 50 years has more than doubled (Religioni 2020). Besides infectious diseases, neoplasms in pets, particularly in dogs and cats, are also an increasingly more common cause of mortality (Pinello et al. 2022).

Research carried out in many scientific centers is focused on the search for biomarkers to enable qualitative and temporal improvement in the detectability as well as prognostic and predictive assessments in humans and animals suffering from neoplastic diseases (Mehta et al. 2010). Dramatic progress in knowledge, especially in terms of understanding the molecular mechanisms of formation and development of neoplastic processes, offers opportunities for the development of new methods in the field of cancer diagnostics and therapy (Mehta et al. 2010, Rawat et al. 2019). To date, although several biological, clinical, histological, immunohistochemical and molecular diagnostic, prognostic and predictive biomarkers have been investigated with varying results, the selection of the most appropriate markers is still an open question (Elston, Ellis 1991, Łopuszyński et al. 2009, Mehta et al. 2010, Noordhuis et al. 2011).

An interesting diagnostic and prognostic biomarker that has recently become the subject of research (mainly in human oncology and currently, to a significantly lesser extent, in veterinary oncology) is cyclooxygenase-2 (COX-2) (Doré 2011, Rizzo 2011). COX-2 has not been recognized yet as a routine biomarker in oncological diagnostics in humans (Mehta et al. 2010) but research results demonstrating COX-2 overexpression in several neoplasm types in humans and certain neoplasms in animals (particularly in dogs) suggest the possibility for using an assessment of COX-2 overexpression to improve cancer diagnostics and therapy and for prognostic and/or predictive purposes (Millanta et al. 2006, Mehta et al. 2010). However, these issues require more research, particularly on animals, since the results of the assessment of COX-2 expression in different neoplasm types are not always unequivocal (Hida et al. 1998, Beam et al. 2003, Mohammed et al. 2004, Fux et al. 2005, Richardsen et al. 2010).

COX-2 characteristics

Cyclooxygenase (COX), also known as prostaglandin G/H synthase (PTGS), is an enzyme belonging to the myeloperoxidase family, which catalyzes the conversion of arachidonic acid to prostanoids, i.e. prostaglandins (PG), prostacyclin (PGI_2) and thromboxane (TXA_2), bioactive proteins that regulate several different physiological and pathological processes in humans

and animals (Chandrasekharan, Simmons 2004, Simmons et al. 2004, Burdan et al. 2006, Rizzo 2011).

The discovery and subsequent understanding of the structure and mechanisms of action of this enzyme group offered new possibilities for the treatment of inflammation and cancers, and the alleviation of symptoms such as pain and fever (Dumusc et. al. 2014, Willoughby et al. 2000, Warner, Mitchell 2004).

Research initiated by Vane led to the discovery in 1971 of the role of aspirin and, subsequently, other non-steroidal anti-inflammatory drugs (NSAIDs) in inhibiting the synthesis of PG (Vane 1971). In 1976, cyclooxygenase (COX) was isolated for the first time from bovine and ovine acinous glands (Miyamoto et al. 1976, DeWitt, Smith 1988) and later named COX-1. In 1988, the human and ovine gene encoding this enzyme was first cloned (Merlie et al. 1988, Yokoyama, Tanabe 1989). Despite the initial belief that COX-1 was the only COX occurring in eukaryotic cells, another isoform named COX-2 was identified in 1991 (Xie et al. 1991, Vane et al. 1998). In 2002, a third isoform of COX-3 was detected in humans and certain animal species (Chandrasekharan et al. 2002).

Until recently, COX-2 has only been associated with the response to stress and inflammation initiators (Burdan et al. 2006). It is currently known that its expression increases significantly in the course of numerous pathological processes that involve inflammation, pain or fever (Seibert et al. 1994, Williams et al. 1999, Dumusc et. al. 2014). Changes in COX-2 expression were demonstrated in the course of Alzheimer's disease (Pasinetti 1998) and glaucoma (Hinz, Brune 2001).

Research also demonstrated COX-2 overexpression in neoplastic tissues, which suggests the involvement of this enzyme in oncogenesis (Williams et al. 1999, Rizzo 2011). COX-2 is released by cancer-associated fibroblasts (CAFs), macrophage type 2 (M2) cells, and cancer cells to the tumor microenvironment (TME) (Hashemi Goradel et al. 2019). An increase in COX-2 expression was found in neoplasms of various organs in humans, e.g. the lungs, large intestine, pancreas, kidney, breast, uterine cervix, ovary and prostate (Tucker et al. 1999, Soslow et al. 2000, Kulkarni et al. 2001, Denkert et al. 2002, Kankuri-Tammilehto et al. 2010, Richardsen et al. 2010). The significance of COX-2 overexpression in neoplasms of the colon, prostate and breast was proven in extensive epidemiological research which demonstrated their regression and reduced mortality after long-term use of aspirin and other NSAIDs (Khuder, Mutgi 2001, Chan et al. 2005, Salinas et al. 2010).

Overexpression of COX-2 is also associated with increased tumor malignancy, tendency to metastasize, poorer prognosis and reduced survival time, as demonstrated in human cases of lung, gastric, breast, ovarian, uterine cervical and prostate neoplasms (Khuri et al. 2001, Denkert et al. 2002, Denkert et al. 2003, Kim et al. 2004, Mrena et al. 2010, Richardsen et al.

2010). Besides solid tumors, increased COX-2 expression is also observed in leukemias, lymphomas and myelomas (Giles et al. 2002, Cetin et al. 2005, Ohsawa et al. 2006).

Research concerning the assessment of COX-2 expression in animals showed its overexpression in several neoplasm types in dogs and cats, e.g. cancers of the skin, oral cavity, mammary gland, intestines, pancreas, kidney, bladder and bones (Pestili et al. 2001, McEntee et al. 2002, Beam et al. 2003, Newman, Mrkonjich 2006, Doré 2011, Millanta et al. 2016*a*,*b*) and in horses, particularly in the reproductive system and the eye (Thamm et al. 2008). In dogs and cats, as in humans, COX-2 overexpression is often associated with the histological degree of tumor malignancy as well as the worsening of the prognosis and shorter survival time (Queiroga et al. 2005, Millanta et al. 2006*a*,*b*, Lavalle et al. 2009, Anadol et al. 2017, Carvalho et al. 2017, Gregório et al. 2017).

The action of COX-2 on PGs, especially PGE2, has a variety of tumor-promoting functions. It has been shown that in the development of many cancers, including breast cancer, it improves resistance to apoptosis by increasing the level of Bcl-2, promotes angiogenesis by up-regulating vascular endothelial growth factor, and stimulates tumor growth by up-regulating the epidermal growth factor receptor (Majumder et al. 2015, Hosseini et al. 2018). Moreover, it increases cancer cell survival by interacting with PI3K/AKT and cancer cell invasion by upregulating extracellular signal-regulated kinase (Majumder et al. 2018).

Furthermore, it influences the modulation of the immune system by increasing the activity of regulatory T cells (Sharma et al. 2005) via the induction of the expression of Nr4a and the activity of M2 protumor cells (Esbona et al. 2018).

COX-3, as a splice-variant of COX-1, also plays an important role in the course of many pathological processes. It was demonstrated to be active in the development of chronic inflammation, neoplastic lesions and possible involvement in Alzheimer's disease (Cui et al. 2004, Kam, So 2009). Moreover, COX-2 is induced during seizures, and is considered to be a potential neurotherapeutic target for epilepsy management (Rawat et al. 2019).

To date, few studies in Poland have evaluated COX-2 expression in neoplasms in animals. These mainly concerned the evaluation of COX-2 expression in mammary gland neoplasms in female dogs (Nowak et al. 2005*a*,*b*, Badowska-Kozakiewicz, Malicka 2010) and mast cell tumors (Kandefer-Gola et al. 2015, Śmiech et al. 2017).

COX-2-encoding gene

COX-2 encoding gene (*PTGS-2*) is located on chromosome 1, is comprised of 10 exons and 9 introns and has a length of 8.3 kilobase pairs (kbp). The other gene encoding COX-1 (*PTGS-1*), same as its splice-variant COX-3, is located on chromosome 9, is much larger than COX-2, as it is comprised

of 11 exons and 10 introns and has a length of 22 kbp (Tazawa et al. 1994, Burdan et al. 2006). Both genes exhibit an almost 60% homology and single nucleotide polymorphism (SNP), which determines their different functions in the body and the response to drugs inhibiting their activity (Kraemer et al. 1992, Tazawa et al. 1994, Halushka et al. 2003).

PTGS-2 gene expression is stimulated by a broad spectrum of agents, mainly growth factors: vesicular endothelial growth factor (VEGF), epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF) as well as proinflammatory cytokines (IL-1β, IL-2, TNFα, INF-γ), lipopolysaccharides and oncogenes, e.g. benzopyrene found in tobacco smoke. However, it is inhibited by anti-inflammatory cytokines (IL-4, IL-10, IL-13) and glucocorticosteroids (Hinz, Brune 2001, Millanta et al. 2006, Queiroga et al. 2011, Rizzo 2011).

Since the *PTGS-2* gene has sites for binding several cellular transcription factors, including cAMP response element-binding protein (CREB), nuclear factor κB (NF-κB), activating protein-1 (AP-1), nuclear factor for activated T-lymphocytes (NFAT) – Mejza, Nizankowska (2001), as well as numerous regulatory sequences, its expression is variable (Warner, Mitchell 2004).

However, the *PTGS-1* gene belongs to the housekeeping gene group and, unlike the *PTGS-2* gene, lacks TATA regulatory sequences in the 5' region and has only single transcription factor binding sites, although disturbances of intracellular or local homeostasis may intensify the transcription of this gene (Mejza, Nizankowska 2001, Burdan et al. 2006).

In mitochondrial genes encoding all COX isoforms, SNP and mutational changes were found, suggesting an effect of these changes on breast cancer incidence in women (Tan et al. 2002, Czarnecka et al. 2010, Ma et al. 2010). A recent study has also demonstrated the presence of SNP and mutational changes in mitochondrial genes encoding COX-2 and COX-3 in mammary gland tumors in dogs, which indicates their relationship with neoplastic transformation and implicates them as a risk factor (Surdyka, Slaska 2017).

The COX-2 enzyme

COX proteins (isoenzymes) are homodimers located mainly on the inner surface of the endoplasmic reticulum membrane and on the inner and outer surface of the nuclear envelope (Burdan et al. 2006). In neoplastic cells, COX-2 was also detected in fat bodies, where it affects cell growth through additional PGE_2 supply (Accidy et al. 2008) and in the mitochondria, where it plays an important role in inhibiting apoptosis (Liou et al. 2005).

Human COX-2 protein is composed of 604 amino acids and has a mass of approx. 72 kDa. As regards COX-1, these values are similar and amount to 599 amino acids and 70 kDa (Garavito et al. 2002), while in COX-3, there are 633 amino acids and 65 kDa, respectively (Chandrasekharan et al. 2002).

In the COX amino acid chain, the following are distinguished: N-terminal hydrophobic signal peptide, an epidermal growth factor-like dimerization domain, a membrane-binding domain consisting of four alpha-helices, a catalytic domain with two catalytic sites – one with cyclooxygenase activity and the other with peroxidase activity, as well as a terminal unstable membrane domain and a short sequence serving as a retention signal (Kiefer et al. 2000, Malkowski et al. 2000, Chandrasekharan, Simmons 2004). The schematic structure of the human COX-2 protein is presented in Figure 1. In the endoplasmic reticulum membrane, all COXs undergo N-glycosylation, which is essential for conferring activity to the enzyme (Chandrasekharan, Simmons 2004).

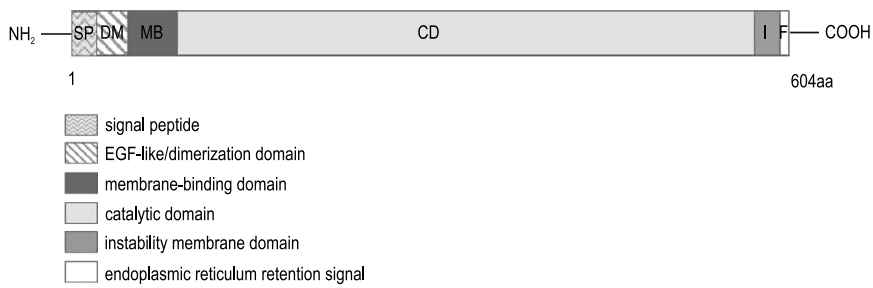

Fig. 1. Schematic structure of the human COX-2 protein

COX-2 biochemical transformations

The substrate for COX are unsaturated fatty acids, mainly arachidonic acid, released from cell membrane phospholipids, either directly by phospholipase A_2 or indirectly with the involvement of phospholipases C and D (Sadurska and Szumiło 2005). Arachidonic acid is then converted to prostaglandin G_2 (PGG_2) in the cyclooxygenase reaction, and, subsequently, to prostaglandin H_2 (PGH_2) in the peroxidase reaction (Figure 2). PGH_2

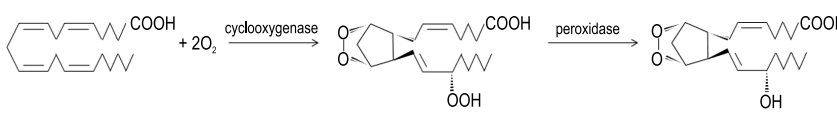

Fig. 2. Cyclooxygenation and peroxidation reactions catalyzing the biosynthesis of prostaglandins G2 and H2

penetrates the endoplasmic reticulum membranes into the cytosol, where, with the involvement of tissue-specific synthases, it is further converted to other PGs (Needleman et al. 1986), of which five basic ones are PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2, TXA_2. Alternatively, PGH_2 may be converted to malondialdehyde, a metabolite with mutagenic properties (Marnett 1999). The location of COX in the endoplasmic reticulum membrane is presented in Figure 3.

In addition to fat substrates, COX-2 can also metabolize various xenobiotics, including nutritional and dietary, occupational, and environmental

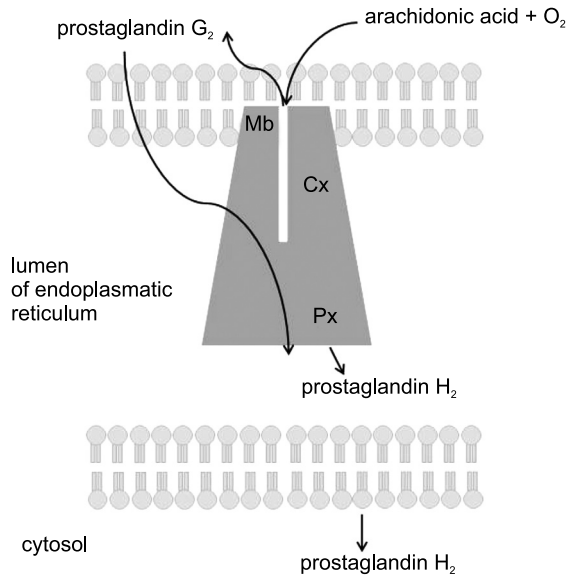

Fig. 3. Localization of COX in the endoplasmic reticulum membrane Cx - COX catalytic site; Px – peroxidase catalytic site; Mb – Membrane binding domain

carcinogens. These compounds are converted, due to COX-2 peroxidase activity, into highly active molecules that react with cellular DNA and activate oncogenes or inhibit tumor suppressor genes (Wiese et al. 2001).

COX functions in the body

The wide dissemination of COX isoforms and prostanoids synthesized with their involvement in the tissues indicates the significant role they serve in the regulation of the functioning of several organs and systems, particularly the gastrointestinal, nervous, circulatory, reproductive, urinary and respiratory systems.

In the gastrointestinal tract, physiological COX-1 expression and minimum COX-2 expression are found (Jackson et al. 2000). Induced COX-2 overexpression usually occurs in pathological lesions, especially neoplastic ones (Ristimaki et al. 1997, Jackson et al. 2000, Fux et al. 2005). It was demonstrated that even minor nucleotide variations in the COX-2 gene (SNP) could be a predisposing factor, e.g. polymorphism at position 765 (G>C) in the COX-2 gene is associated with a higher risk of gastric cancer (Sitarz et al. 2008). COX-2 overexpression is also found in colorectal adenomas and cancers (Eberhart et al. 1994) as well as in the pancreatic cancer (Tucker et al. 1999). Long-term intake of COX-2 inhibitors was demonstrated to reduce the risk of neoplasms of intestinal epithelial origin (Hull 2005), although their antineoplastic activity may be independent of the effect on COX-2 (Tegeder et al. 2001).

In the nervous system, expression of all COX isoenzymes was demonstrated, albeit varying in particular areas. The highest COX-1 expression was found in the telencephalon and diencephalon, while physiological COX-2 expression was demonstrated in the prosencephalon and spinal cord (Yamagata et al. 1993, Svensson and Yaksh 2002). COX-2 overexpression occurs in long-term stress situations, inflammation and degenerative and neoplastic diseases (Burdan et al. 2006). In the hypothalamus and the spinal cord, the expression of the nervous system-specific COX-3 was also demonstrated (Chandrasekharan et al. 2002).

In the cardiovascular system, continuous COX expression is essential for maintaining normal blood flow (Burdan et al. 2006). COX-1 expression in the vascular endothelium under physiological conditions is low, but increases significantly when the vessel wall is damaged, suggesting an atherosclerotic process (Schonbeck et al. 1999). COX-2 is also present in the vascular endothelium, where it is responsible for the synthesis of PGI_2 that can also occur with the involvement of COX-1 (Cheng et al. 2002). PGI_2 is a potent antagonist of TXA_2 produced by platelets, and when its synthesis is inhibited, e.g. during the use of COX-2 inhibitors, an imbalance between PGI_2 and TXA_2 occurs, which may cause intravascular coagulation observed with the use of coxibs, e.g. celecoxib and rofecoxib (Dogne et al. 2005). These complications occur less frequently after the administration of non-selective COX inhibitors due to their simultaneous blockade of COX-1 in platelets (Scott, Watts 2005). Currently, the assessment of COX-1 and COX-2 expression is considered to be an important diagnostic marker in the assessment of damage to blood vessel walls and the myocardium (Wong et al. 1998, Schonbeck et al. 1999).

Cyclooxygenase expression plays a very important role in reproductive processes. High COX expression was demonstrated in the epithelium of the fallopian tubes and the uterine body mucous membrane (Van Voorhis et al. 1990). COX-2 expression is a determinant of normal ovulation, fertilization and embryo implantation (Burdan et al. 2006), while the administration of COX inhibitors can interfere with these processes (Salhab et al. 2001). COX-2 activity is responsible for angiogenesis and the initiation of placenta formation, and was demonstrated to intensify in the amniotic epithelium, chorionic reticular layer and decidua with the development of pregnancy (Slater et al. 1994). However, COX-1 expression was found in the amniotic epithelium, chorionic, amniotic mesoderm and decidua, yet it is lower and exhibits no differences, depending on the gestational period (Slater et al. 1994, 1999). Since COX-1 expression is generally constant, the differences in the amount of prostanoids in the uterus are determined exclusively by COX-2 induction (Burdan et al. 2006). In males, COX-1 expression was found within different genital segments, while COX-2 expression was found in the epithelium of the deferent duct and epididymis and the seminal vesicles (Lazarus et al. 2004). Irrespective of numerous important physiological func-

tions in the reproductive system, COX-2 overexpression occurs in ovarian, uterine cervical and prostatic neoplasms, and is often associated with poor prognosis, while the use of COX-2 inhibitors improves treatment outcomes (Kulkarni et al. 2001, Denkert et al. 2002, Kim et al. 2004, Queiroga et al. 2005).

In the urinary system, COX-1 expression was detected in endothelial cells and the smooth muscular coat of arteries and veins, in the collecting tubule epithelium and in the interstitial cells of the cortical and medullary layers of the kidney. COX-2 expression was found in the juxtaglomerular apparatus, nephron tubule epithelial cells, renal papillary interstitial cells and podocytes (Komhoff et al. 1997). A study evaluating the role of COX in the urinary system using its different inhibitors demonstrated that by inhibiting the synthesis of PG (mainly PGE_2 and PGI_2) these compounds decrease the renal blood flow and glomerular filtration rate, increase sodium absorption, and contribute to renin release and the activation of the renin-angiotensin-aldosterone pathway (Cheng, Harris 2005). COX-2 overexpression was also found in bladder and kidney neoplasms (Ristimaki et al. 2001, Kankuri-Tammilehto et al. 2010).

In the respiratory system, COX-1 expression was demonstrated within the upper and lower airways (Burdan et al. 2006). COX-2 expression under physiological conditions is low and restricted to the bronchiolar and alveolar epithelium (Asano et al. 1996). Moreover, COX-2 overexpression accompanies inflammatory, proliferative and neoplastic lesions (Hida et al. 1998, Hasturk et al. 2002).

CONCLUSIONS

In recent years, COX-2 has been the subject of numerous studies in human oncology and, to a lesser extent, in veterinary oncology, and it appears to be an important biomarker of diagnostic, prognostic, predictive and therapeutic significance. Studies conducted to date have demonstrated a significant increase in COX-2 expression in several types and subtypes of neoplasms in humans and animals, particularly in dogs and cats, the two animal species which have been studied the most frequently. COX-2 has not been adopted yet as one of the biomarkers for routine oncological diagnostics, which indicates the possibility for wider use of the assessment of its expression in the diagnostics and therapy of neoplasms in humans and animals. Although this still requires research into several relevant issues remaining to be clarified, it is a promising direction to pursue in a time of an increasing number of cancer cases in both humans and animals.

Author contributions

MS, AR – conceptualization; MS, IB, EK, WS, – literature review; AR, KM – supervision; MS, KM – visualization; MS, KM – writing – original draft preparation; MS, AR, IB, EK, WS, KM – writing – review & editing. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

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

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