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Celecoxib: Antiangiogenic and Antitumoral Action

Celecoxib: Acción Antiangiogénica y Antitumoral

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SUMMARY: Angiogenesis, a process by which new blood vessels are generated from pre-existing ones, is significantly compromised in tumor development, given that due to the nutritional need of tumor cells, pro-angiogenic signals will be generated to promote this process and thus receive the oxygen and nutrients necessary for its development, in addition to being a key escape route for tumor spread. Although there is currently an increase in the number of studies of various anti-angiogenic therapies that help reduce tumor progression, it is necessary to conduct a review of existing studies of therapeutic alternatives to demonstrate their importance.

KEY WORDS: Angiogenesis Celecoxib; COX2, Tumor; Anti-angiogenic therapy.

INTRODUCTION

The angiogenesis process is defined as the formation of new blood vessels from pre-existing vascularization, through the migration, growth and differentiation of endothelial cells, which line the internal walls of blood vessels. This phenomenon is mediated by various factors, among which the most relevant is vascular endothelial growth factor (VEGF), which promotes this process. Although it has great physiological importance, being involved in the processes of embryonic development, tissue repair, when there is an imbalance between its stimulators and inhibitors, it can be associated with pathological processes, such as tumor growth, in which due to nutritional need from the tumor cells, pro-angiogenic signals will be generated to obtain new blood vessels that deliver the oxygen and nutrients necessary for their development (Griffioen & Molema 2000; Carmeliet & Jain, 2011a; Bikfalvi, 2017; De Palma *et al*., 2017; Viallard & Larrivee, 2017).

In order to control the formation of new vascularization in the tumor, anti-angiogenic therapy is used, for which various targets of the process have been studied, among which is the regulation of Cyclooxygenase 2 (COX-2), which Normally its increase is attributed to inflammatory processes, but according to evidence based on present studies, it is also increased in tumor cells producing prostaglandin E2, responsible for stimulating the generation of angiogenic mediators, such as VEGF (Roa, 2014).

As a therapy for the regulation of COX-2, Celecoxib can be used, a non-steroidal anti-inflammatory drug with anti-inflammatory, analgesic and antipyretic properties that acts by inhibiting the synthesis of prostaglandins through the selective inhibition of COX-2. This drug has been studied for anti-angiogenic treatment in some cancers, in order to increase the survival of patients, which has had positive results, but presents some obstacles, such as dose toxicity, for which the best mechanism of treatment is being investigated.. Furthermore, various studies have proposed that it produces an anti-angiogenic effect at the level of other routes of action (Roa, 2014). For this reason its study is of great importance, analyzing aspects such as the antitumor and antiangiogenic role of celecoxib.

METHODOLOGY

For the search methodology, a bibliographic review of scientific articles published in English and Spanish was carried out, with a date of less than 5 years to date (from 2018 to 2023) from the databases PubMed, ScienceDirect, Web of Science, selecting articles that had relevant and verified information on angiogenesis, anti-angiogenic therapy and Celecoxib today. Relevant bibliography on this subject from previous years was included.

Angiogenesis. Angiogenesis is defined as the formation of

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new blood vessels from preexisting vessels, playing an important role in physiological processes such as tissue regeneration, wound healing and embryonic development, among others, as well as in pathological processes, as tumor growth, metastasis, rheumatoid arthritis and diabetic retinopathy among others (Kretschmer *et al*., 2021). It begins to be carried out at the beginning of the embryonic stage in conjunction with vasculogenesis (Hanahan & Folkman, 1996), involving the proliferation, migration and maturation of endothelial cells (EC), in addition to being the phenomenon that generates most of vascular growth throughout life (Jeong *et al*., 2021).

Angiogenesis is driven by the need for oxygen and nutrients from the surrounding tissue, which stimulates the production of vascular endothelial growth factor (VEGF), fibroblast growth factors (FGF), and other proangiogenic stimuli by non-vascular cells (Carmeliet & Jain, 2011b). Upon reaching the pre-existing vessel, VEGF binds to its VEGF receptor, receptor 2 (VEGFR2) in the EC, causing the cell-endothelial cell contacts to give way, the pericytes detach and the basement membrane to rupture, allowing a new vessel to emerge (Eelen *et al*., 2018).

Physiological angiogenesis processes are essential during embryonic development, the female reproductive cycle and wound healing (Rajabi & Mousa, 2017). However, abnormally accelerated angiogenesis processes or pathological angiogenesis are associated with various disorders, among which we can highlight tumor development.

Pro and Anti angiogenic factors. Angiogenesis is regulated by pro- and anti-angiogenic factors, through an “angiogenic switch,” which refers to a time-limited event during tumor progression in which the balance between pro- and anti-angiogenic factors tips toward a pro-angiogenic outcome. The molecular actors and mechanisms underlying angiogenic change have been intensively investigated for the study of therapies (Table I) (Karamysheva, 2008; Baeriswyl & Christofori, 2009; Kopec & Abramczyk, 2022)

Vascular endothelial growth factor (VEGF). Although many molecules are known to participate as positive regulators of angiogenesis, not all of these factors are specific to endothelial cells (Ferrara, 2001); VEGF has been proposed as a key regulator of normal and abnormal angiogenesis, in based on the evidence accumulated in studies, supporting their hypothesis in the high expression of VEGF mRNA in human tumors, the presence of VEGF protein in ocular fluids of individuals with proliferative retinopathies and in the synovial fluid of patients with rheumatoid arthritis. Regarding current studies on the subject, it continues to support that VEGF is a key regulator in this process (Ferrara, 2001; Melincovici *et al*., 2018).

Tumor angiogenesis. Tumor angiogenesis begins in the tumor itself, in response to the pro-angiogenic signal, composed of the stimuli already mentioned, which are produced by tumor endothelial cells (TEC), because, as tumor size increases, hypoxia and acidity, which are usually associated with the tumor microenvironment (Marmé, 2018; Lugano *et al*., 2020), resulting from the lack of blood vessels that deliver sufficient oxygen and nutrients for cell growth and proliferation.

The condition of tumor hypoxia, that is, the decrease in oxygen concentration in tumor tissues, causes tumor cells to activate and stabilize the transcription factor hypoxia-inducible factor 1 (HIF-1), a heterodimeric transcription factor that It comprises two subunits, an oxygen-regulated a subunit (HIF-1a) and a constitutively expressed b subunit (HIF-1b). This factor is responsible for transcriptionally regulating a series of hypoxia-inducible genes, which includes vascular endothelial growth factor (VEGF) (Rattner *et al*., 2019; Jeong *et al*., 2021).

EC are normally inactive, but can be induced to initiate angiogenesis by proangiogenic factors (Maishi *et al*., 2019). These factors bind to the receptors on endothelial cells of nearby blood vessels, initiating the formation of new vessels that They penetrate the tumor and promote its further growth. The main angiogenic growth factor, oversecreted by tumor cells, is VEGF (Marmé, 2018).

Table I. Pro-angiogenic and anti-angiogenic factors of the angiogenesis process. Adapted from Kopec & Abramczyk (2022).

Phase	Proangiogenic factor	Antiangiogenic factor
Basement membrane degradation	Tissue plasminogen activator (tPA), Urokinase plasminogen activator (uPA), Metalproteinases (MMP)	Tissue inhibitors of metalloproteinases (TiMP), plasminogen activator inhibitor (PAI)
Endothelial cell migration	Vascular endothelial growth factor (VEGF-A, VEGF-B, VEGF-C, VEGF-D)	Thrombospondin, angiostatin
Endothelial cell proliferation	Platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), platelet-derived endothelial cell growth factor (PDECGF)	Endostatin, prolactin
Creation of lumen carrying cords	epidermal growth factor (EGF), angiogenin, Angiopoietin 1, tumor growth factor (TGF-_)	interferons, angiopoietin 2

Due to the imbalance that exists between pro and anti-angiogenic factors within the tumor environment, the vasculature that originates presents differences from the normal vasculature, such as distribution, which is normally distributed in a network of arterioles, capillaries and venules, while the tumor blood vessels are very disorganized and deformed. Furthermore, these vessels are mostly undifferentiated or immature, presenting reduced mural cell coverage by pericytes and an absent or collapsed lumen. Therefore, tumor blood vessels are highly permeable, causing alterations in blood flow and diffusion of tumor cells in the interstitial space, generating an increase in hypoxia in the tumor microenvironment, thus promoting the angiogenesis process (Fujita & Akita, 2017; Teleanu *et al*., 2019).

Anti angiogenenics. Antiangiogenic therapy is a method that aims to slow down tumor growth, proposed in 1971 by Folkman, who hypothesized that this therapy would be useful in tumor diseases, since it could interrupt pre-existing blood vessels and prevent the formation of new ones, decreasing the supply of oxygen and nutrients to cancer cells (Sherwood *et al*., 1971; Lopes-Coelho *et al*., 2021).

In the development of antiangiogenic agents, four strategies are mainly used: the inhibition of endogenous factors that promote the formation of blood vessels, the identification and application of natural inhibitors of angiogenesis, the inhibition of molecules that promote the invasion of surrounding tissue through tumor blood vessels, and the incapacitation of actively proliferating endothelial cells (Mousa & Davis, 2017).

Although there are different signaling pathways involved in angiogenesis, most of the anti-angiogenic drugs used are based on VEGF, since it signaling is considered a key regulator, being the main promoter of angiogenesis. In addition, it is the one that is overexpressed in the majority of solid tumors. For this reason, drugs targeting VEGF have been developed and approved for clinical use, such as Bevacizumab, a recombinant humanized monoclonal antibody (mAb) that acts by preventing the interaction of VEGF with its receptors, as well as by neutralizing the release of VEGF from the cells. cancer cells, which despite being approved to interrupt angiogenesis in some cancers, was not able to increase survival in all (Zirlik & Duyster, 2018).

On the other hand, studies have been carried out on the relationship between angiogenesis and inflammation, in which Cyclooxygenase (COX-2) stands out as a target for anti-angiogenic therapy, since it has been found overexpressed in tumor and endothelial cells, which through Their metabolic reaction produces prostaglandin E2, which stimulates the production of angiogenic mediators, such as VEGF (Frejborg *et al*., 2020). In more recent studies, efforts have been made to suppress this event, for which selective COX-2 inhibitors have begun to be used, such as Celecoxib (Cx) (Rosas *et al*., 2014).

CELECOXIB. Celecoxib (Cx) is a non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic and antipyretic properties that selectively inhibits COX-2. Commonly used to treat rheumatoid arthritis, osteoarthritis and acute pain, but in recent years it has been proposed to have chemopreventive capabilities, including being considered an agent that can intervene in the signal transduction pathways associated with COX-2 expression and increase the levels of endogenous inhibitors of angiogenesis (Harris, 2009; Gong *et al*., 2012; Tudor *et al*., 2021).

Route of action of Celecoxib. Like other NSAIDs, their pharmacological properties depend on their ability to inhibit the activity of the enzyme cyclooxygenase (COX) and, consequently, the synthesis of inflammatory prostanoids, such as prostaglandins (PGE1, PGE2) and thromboxanes (Carranza, 2013).

As can be seen in Figure 1, Celecoxib, like other NSAIDs, acts by inhibiting the synthesis of prostaglandins through the inhibition of COX, in this case COX2 (PTGS2). Cox enzymes (PTGS1 and PTGS2) catalyze the committed step leading to the production of prostaglandins (PGH2) from arachidonic acid. PGH2 are then converted into active metabolites (prostaglandin E2 (PGE2), prostacyclin (PGI2), thromboxane (TXA2), prostaglandin D2 (PGD2), prostaglandin F2 (PGF2)) that mediate various physiological responses, such as inflammation, fever, regulation of blood pressure. and coagulation (Gong *et al*., 2012).

Mechanism of Celecoxib in tumor angiogenesis. The inhibition of COX-2 is related to the suppression of angiogenesis and metastatic processes (Peng *et al*., 2013), which is why it is an important target in antiangiogenic therapeutics. The overexpression of COX-2 in tumor cells affects angiogenesis through the production of eicosanoids (TAX2; PGI2 and PGE2) (Wang *et al*., 2013), which stimulate the migration of endothelial cells and angiogenesis through the increase in the expression of VEGF stimulating the proliferation of endothelial cells. To also prevent the production of pro-angiogenic factors such as VEGF and TXA2 (Harry & Ormiston, 2021) (Fig. 2). Celecoxib would reduce the immunosuppressive and angiogenic properties of PGE2, by inhibiting the PG synthesis pathway (Li *et al*., 2013; Perroud *et al*., 2013). Other authors report the favorable effects of the use of celecoxib/PLGA, in the decrease in angiogenesis and induction of apoptosis of tumor cells (Cui *et al*., 2010).

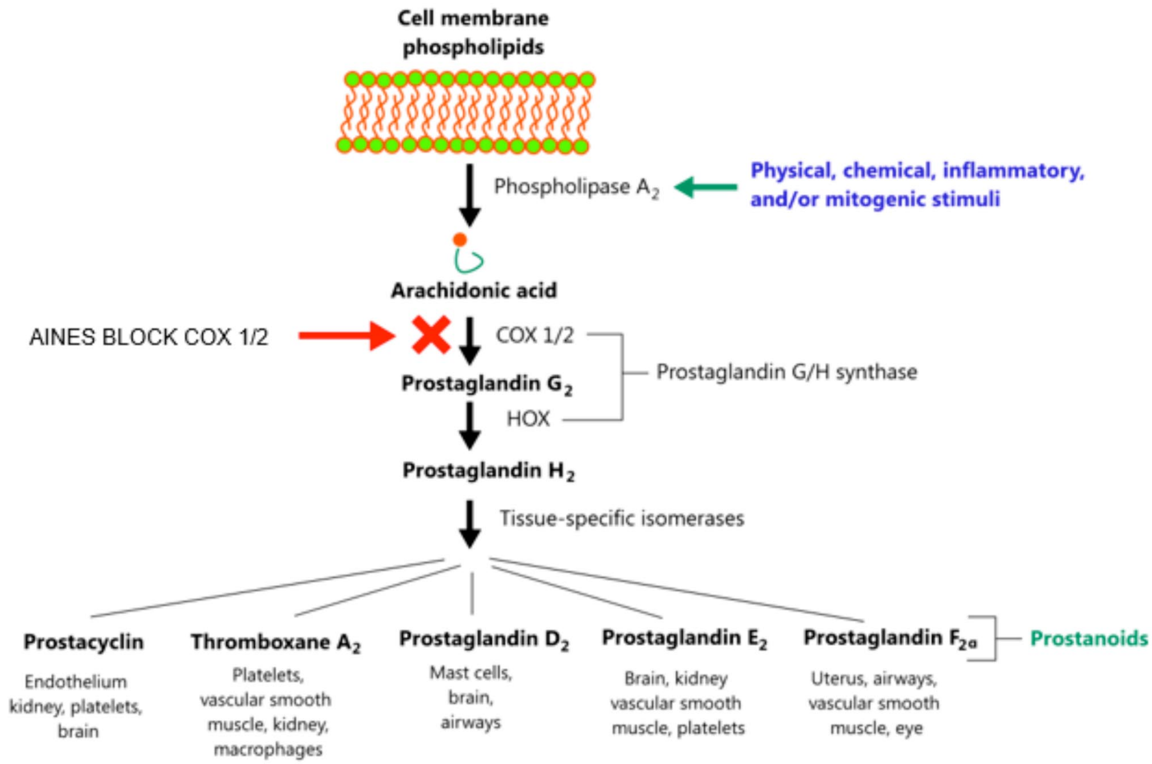

Fig. 1. Mechanism of action of NSAIDs. In the event of stimulus-mediated inflammation, the enzyme phospholipase A2 is activated, which releases arachidonic acid. The enzyme prostaglandin G/H synthase has cyclooxygenase (COX) and hydroperoxidase (HOX) activity. Prostaglandin G/H synthase converts arachidonic acid to prostaglandin H2. Prostaglandin H2 is then converted by tissue-specific isomerases into several different inflammatory mediators called prostanoids. The type of prostanoid produced depends on the type of tissue/cell. NSAIDs inhibit the cyclooxygenase (COX) component of phospholipase A2 and block the formation of prostaglandin G2. Adapted from Fitzgerald & Patrono (2001).

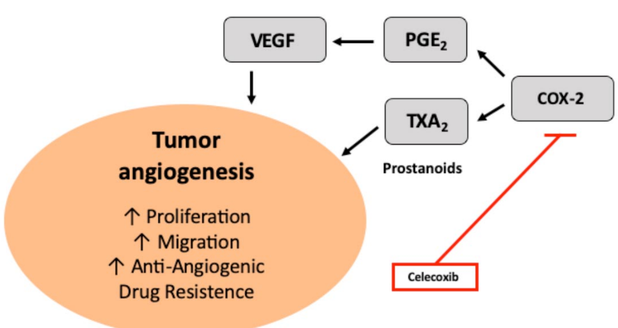

Fig. 2. Route of action of Celecoxib in tumor angiogenesis. The COX-2 inhibitor, Celecoxib, prevents the synthesis of prostaglandin E2, responsible for promoting tumor angiogenesis, endothelial proliferation and migration through the production of angiogenic factors such as VEGF. Adapted de Harry & Ormiston (2021).

Experimental studies indicate that the administration of Celecoxib at a concentration of 1000 ppm decreases microvascular density, also reducing the presence of VEGF in multidrug-resistant TA3 tumor cells, which would make it a good candidate for use alone, or in combination with other anti-tumor molecules, ideally with the aim of obtaining synergistic effects (Rosas *et al*., 2014). For their part, Roa *et al*. (2017) indicate that the CX/PLGA association inhibits microvascularization, VEGF expression at the tumor level, as well as cell proliferation and increased apoptosis. On the other hand, it has been shown that Celecoxib reduces serum levels of VEGF and COX-2 (Han *et al*., 2014), which would explain the decrease in vascularization, knowing that VEGF is the most critical factor associated with vasculogenesis, angiogenesis and lymphangiogenesis, VEGF-A being an essential regulator of angiogenesis, acting mainly by promoting cell division and migration in endothelial cells (Oklu *et al*., 2010). Previous Studies show that Cx reduces serum levels of VEGF and COX-2.

On the other hand, the combination of Cx with other antiangiogenic drugs helps to improve the effect; as is the case of how Cx improved the effect of Vandetanib, an antiangiogenic drug that has the RET protoncogene of VEGFR as its target, in the inhibition of angiogenesis in vitro and the combination of these two drugs led to even greater degrees of inhibition than Vandetanib alone (Qadir *et al*., 2023).

An increasing number of studies have shown that non-selective non-steroidal anti-inflammatory drugs (NSAIDs), as well as selective COX-2 inhibitors, can reduce cell proliferation, induce apoptosis, promote immune surveillance, and/or reduce AG (Husain *et al*., 2002; Hilmi & Goh, 2006). The mechanisms by which Cx acts by inhibiting AG would be given by its ability to inhibit endothelial motility and by the inhibition of the production of proangiogenic factors such as VEGF-A (Ghosh *et al*., 2010).

Furthermore, Dhanda & Kompella (2005) described the use of Celecoxib encapsulated in PLGA microparticles, administered at the level of the trachea, which significantly reduced the levels of VEGF and PGE2, in a lung tumor model in mice of the strain AJ.

CONCLUSIONS

Angiogenesis is one of the most relevant processes during tumor progression, contributing not only to the nutrition process of tumor cells as well as invasion, giving the cells a dissemination route that will finally allow them to proliferate outside their original site. Therefore, thorough knowledge of the different processes involved, allows angiogenesis to be established as the main target of action of antineoplastic therapies. Undoubtedly, much remains to be understood of all processes, both of the tumor cells and the microenvironment that surrounds them and how they contribute to vascular neoformation. Ongoing research of new drugs, as well as the use of minimally invasive and financially viable methods will in the future serve as part of the global strategy aimed at eradicating cancer.

ROJAS, V. & ROA, I. Celecoxib: acción antiangiogénica y antitumoral. *Int. J. Morphol.42(1)*:40-45, 2024.

RESUMEN: La angiogénesis, proceso por el cual se generan nuevos vasos sanguíneos a partir de otros preexistentes, se encuentra comprometida de forma importante en el desarrollo tumoral, dado que por necesidad nutritiva de las células tumorales se generarán señales pro angiogénicas para promover este proceso y así recibir el oxígeno y los nutrientes necesarios para su desarrollo, además de ser una ruta de escape clave para la diseminación tumoral. Si bien, actualmente existe un aumento en la cantidad de estudios de diversas terapias anti angiogénicas que ayudan a reducir el avance tumoral, es necesario realizar una revisión de los estudios existentes de alternativas terapéuticas para demostrar su importancia.

PALABRAS CLAVE: Angiogénesis; Celecoxib; COX2; Tumor; Terapia anti angiogénica.

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