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Review Article

The Role of Cyclooxigenase-2 Inhibitor in Basal Cell Carcinoma: A Literature Review

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ABSTRACT

Basal cell carcinoma (BCC) is the most common skin malignancy worldwide. It has low mortality but can cause significant morbidity primarily due to local destruction. The incidence and associated cost are rising in recent years causing a burden in healthcare system. BCC incidence are continue to increase due to lack of effective chemopreventive option. Several risk factors are associated with the pathogenesis of BCC. One of the major risk factors of BCC is exposure to ultraviolet (UV) rays, hence the prevention strategy for this malignancy include avoidance of natural and artificial sources of UV radiation. However, these methods are still less than optimal in inhibiting the emergence of basal cell carcioma. In recent years, there is accumulating evidence that cyclooxygenase-2 (COX-2), may be involved in the pathogenesis of BCC. Several recent studies have shown that the use of cyclooxygenase-2 (COX-2) inhibitor drugs can prevent the development of nonmelanoma skin tumors including BCC. In this review, we described the potential of COX-2 inhibitors as chemoprevention for BCC.

Key words: Cancer, Chemoprevention, Cyclooxygenase, COX-2 inhibitor, Skin malignancy, Basal cell carcinoma.

INTRODUCTION

Basal cell carcinoma (BCC), along with squamous cell carcinoma, grouped into nonmelanoma skin cancer. It is the most common human malignancy with worldwide incidence of 75% - 90% of all skin tumors.[1,2] The incidence is increasing by 4% to 8% annually and developing in younger age groups. This tumor grow slowly, rarely metastasizes with low mortality rate. However, it can destruct and invade surrounding tissues which could lead to disfigurement and cause significant morbidity. Thus, the treatment of this skin tumor requires high cost. The problem of morbidity and the high cost required for the therapy resulted in the need for prevention strategies against BCC.[1-3]

The major risk factor for BCC is exposure to Ultraviolet (UV) rays, therefore the prevention strategy that has been developed so far is to avoid exposure to UV rays. The use of sunscreen and photoprotective clothing is one of the strategy to prevent UV exposure.[4] Prevention strategies using sunscreen alone have been considered not effective enough, so in recent years chemopreventive strategies for BCC have been developed, one of which is the use of cyclooxygenase (COX) inhibitors. The COX-2 enzyme is known to have role in the development of various tumors, including nonmelanoma skin tumors. Several recent studies have shown that the use of cyclooxygenase-2 (COX-2) inhibitor drugs can prevent the development of nonmelanoma skin tumors including BCC.[1,2] Here, we described the potential of COX-2 inhibitors as chemoprevention for BCC.

BASAL CELL CARCINOMA

BCC is a malignant neoplasm of non-keratinized cells in the basal layer of the epidermis, locally invasive, and rarely metastasizes.[5] BCC has the largest proportion of total skin tumors. A total of 3 million new cases are diagnosed annually in the United States.[3,6,7] BCC tends to develop slowly, so it has a good prognosis. Metastasis of these tumors only occurs in 0.55% of cases after several years. The risk of metastases and death from BCC occurred in 6.5% of cases with tumor size greater than or equal to 2 cm. The prognosis for the tumor is poor if regional lymph node metastases occur followed by bone, liver, and lung metastases. The median survival in these metastatic cases is 3.5 years after diagnosis.[8] Although the cure rate of BCC reaches 99%, the problem of treating this tumor is associated with high morbidity, recurrency and the high cost.[6]

Pathogenesis

Skin carcinogenesis is a complex process with the accumulation of genetic events leading to gradual dysplastic cellular expression, downregulation of cell growth, and carcinomatous development. The major factor associated with the development of BCC is environmental factors, namely exposure to ultraviolet (UV) B light which has a wavelength of 290-320 nm. Exposure to UV light can cause damage to DNA resulting in genetic changes and malignancies. In DNA damage there is the formation of 6,4-photoproducts and cyclobutane pyrimidine dimmers repaired with Nucleotide Excision Repair (NER). If DNA repair fails and the cell remains alive, permanent DNA damage will occur, resulting in mutations in the gene concerned. If this mutation affects the gene that encodes the synthesis of growth factors (proto-oncogenes) or that encodes tumor suppressor genes, carcinogenesis will occur. Mutations in the tumor suppressor gene p53 are found in about 50% of cases of BCC. The accumulation of this gene mutation plays a role in triggering BCC. BCC is associated with activation of the Hedgehog pathway. Activation of this Hedgehog (HH) signaling pathway is the hallmark pathogenesis in all cases of BCC.[3,5]

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COX-2 and pathogenesis of basal cell carcinoma

Several animal and epidemiological studies had revealed that COX is involved in the formation and progression of nonmelanoma skin tumors. Exposure to UV light is known to increase the expression of COX-2 in human skin.[9] Studies on normal human skin exposed to UV light of 1 Minimal Erythema Dose (MED) of 1-2 times showed an increase in the expression of COX-2, but there was no change in COX-1 expression.[4] Immunohistochemical studies showed that COX-2 was found in actinic keratosis (AK) and squamous cell carcinoma (SCC). COX-2 is also expressed in the parenchyma and stroma around the BCC tissue.[1]

Upregulation of COX-2 plays an important role in the production of prostaglandin (PG) and vascular epidermal growth factor (VEGF) for tumor proliferation. The proliferative effect of COX-2 is mainly due to increased synthesis of PG, which directly affects cell growth after binding to certain cell surface receptors, including the PG-E, F, and I receptor groups. The protumorigenic effect of prostacyclin can be mediated by a specific receptor as EP2 and various forms of PG that mediate their biologic effects *via* EP, FP and IP receptors. PG can also increase cells damaged by UV exposure through inhibition of apoptosis.[9]

The expression of COX-2 induced by UV light exposure can increase prostaglandin E2 (PGE2). PGE2 is the largest product of cyclooxygenase which has a role in the development of nonmelanoma skin tumors. PGE2 binds to the G-protein receptor, EP1–EP4, on the surface of cells including keratinocytes. Each receptor activates different signalling pathways, although there are intersections between these pathways. EP1, EP2, and EP4 have been associated with sun exposure-induced carcinogenesis in animal studies. PGE2 increases tumor cell proliferation, inhibits apoptosis, stimulates inflammatory responses, induces immunosuppression, and facilitates invasion of tumors.[4] Besides being induced by COX-2 expression, increased PGE2 production is also triggered by downregulation of the tumor suppressor gene 15-hydroxy-prostaglandin dehydrogenase.[10]

The study conducted by Kuzbicki, *et al*. revealed that there was a difference between SCC and other epithelial skin lesions including BCC. SCC lesions showed higher COX-2 expression compared to BCC and other benign epithelial skin lesions. Both COX isoenzymes are highly expressed in SCC and are derived from a more differentiated layer of the epidermis. Although COX-2 expression in BCC is not as high as in SCC, COX-2 expression is considered as a risk factor of BCC recurrency and plays a role in determining BCC.[11] In animal's study Ptch1+/- heterozygous mice, deletion of COX-2 reduces BCC by 75%. Deletion of COX-1 and COX-2 also reduced the number and size of microscopic BCCs. In contrast, one study found that transgenic mice exposed to ionizing radiation (overexpressing COX-2 on basal keratinocytes of the interfollicular epidermis, outer root sheath of the follicle and the BCC area) experienced a 2-fold increase in the microscopic size of BCC compared to other wild mice.[1]

COX-2 INHIBITOR FOR THE PREVENTION OF BASAL CELL CARCINOMA

COX-2 inhibitor drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are anti-inflammatory drugs that lack steroidal structures. Based on whether they inhibit the cyclooxygenase enzymes COX-1 and COX-2 to similar or different degrees, NSAIDs can be categorized as nonselective COX inhibitors, such as aspirin, and selective COX-2 inhibitors, such as celecoxib. By inhibiting the activity of COX-1 and COX-2, NSAIDs prevent the synthesis of prostaglandin (PG) and thromboxane (TX) from arachidonic acid. NSAIDs have antipyretic, analgesic, and anti-inflammatory activity due to the reduction of PG level. In the field of dermatology, NSAIDs are often used as therapy, both definitive and symptomatic, in various dermatoses such as erysipelas, cellulitis, erythema nodosum, lupus erythematosus, and many others.[3]

In recent years, various studies have developed regarding the use of NSAIDs for cancer therapy and prevention. Several studies suggest that various malignancies have a close relationship with inflammation. This gives rise to a logical thought that drugs that inhibit inflammation can be useful in the treatment and prevention of malignancy. In addition to anti-inflammatory effects, several other mechanisms that may play a role in the treatment and prevention of malignancy are the ability of NSAIDs to induce apoptosis, inhibit angiogenesis, and enhance cellular immune responses.[12]

Oral preparation

Selective COX-2 inhibitor: BCC has a strong association with UV exposure. It can increase the expression of COX-2 thereby triggering various chronic inflammatory mechanisms and activating various signaling pathways. The chemopreventive effectivity of COX-2 inhibitors against BCC has been suggested in several studies. Elmets CA and colleagues conducted a clinical trial to determine the effectiveness of celecoxib as a chemoprevention agent for BCC. A total of 60 patients with basal cell nevus syndrome were randomized into 2 groups. A total of 33 patients received celecoxib therapy and 27 other patients were included in the control group with placebo administration. The results showed that celecoxib decreased the development of new BCC lesions by 50% in subjects with moderate disease (BCC lesions <15 at study baseline). Celecoxib decreased the development of new BCC lesions by 30% in subjects, but this figure was not statistically significant (P = 0.069 for BCC burden) [1]. This results are consistent with previous observational studies showed the effect of NSAIDs on BCC and SCC.[13]

Previous studies conducted on PTCH1+/- heterozygous mice also showed similar results. The correlation between the effect of NSAIDs in preventing BCC in PTCH+/- heterozygous mice and the significant anti-BCC effect in patients with basal cell nevus syndrome supports the hypothesis of prediction which chemopreventive agent should be used that tend to have an anti-BCC effect in humans, at least in PTCH1+/- (basal cell nevus syndrome) patients.[1] Celecoxib is said to be more effective in reducing the size of BCC lesions than the number of lesions in mice and humans. This is similar to the results of a previous study of celecoxib in reducing the size of colorectal adenoma lesions compared to the number of lesions.[14]

The chemoprevention effectiveness of celecoxib is also evident from the results of a randomized controlled clinical trial of 240 subjects with actinic keratosis (AK). It is well known that actinic keratosis is a premalignant precursor which in its development can turn into a nonmelanoma skin tumor. Subjects in this study were randomized into 2 groups, receiving 200 mg Celecoxib or placebo twice daily, for 9 months or placebo only in the control group. Patients were evaluated at 3, 6, and 9 months (during the treatment period) and at 11 months. The results showed no significant difference in the number of actinic keratosis changes in the two groups during the 9th month evaluation. However, at the 11th month evaluation, the mean number of BCC per patient in the celecoxib-treated group was 0.07 (95% CI = 0.03 – 0.13) compared with 0.16 (95% CI = 0.1 – 0.25) in the group receiving placebo (RR = 0.44; 95% CI = 0.19 – 0.99; P = .049).[2] This shows that celecoxib can have a chemopreventive effect on BCC.

Nonselective COX-2 inhibitor: Other NSAIDs had also been extensively studied for chemoprevention of nonmelanoma skin tumors (Table 2). Aspirin is one of NSAIDs that has been studied as chemopreventive agent for BCC that works by inhibiting the COX-1 and COX-2 enzymes. It has been widely used in medical field and

Table 1: Studies of selective COX-2 inhibitor drugs as chemoprevention of basal cell carcinoma.

Drugs	Years	Samples of Study	Study design	Results	Ref
Celecoxib (200 mg, twice daily, oral, for 9 months)	2010	240 patients with 10 – 40 AK	Randomized controlled trial, phase II – III	The average number of BCC is less than the control group (placebo)	1
Celecoxib (200 mg, twice daily, oral, for 24 months)	2010	60 patients of Basal cell nevus syndrome	Randomized controlled trial, phase II	Decreased BCC burden only in patients with lesions <15 at baseline	2
Celecoxib	2015	65.398 Patients BCC (General Practice Research Database)	Case Control	There is an increased risk of BCC with celecoxib	16
COX-2 inhibitor	2019	121.700 women from NHS (2000 – 2010) 116.430 women from NHS II (2001 – 2011) 51.529 women from HPFS (2022 – 2012)	Cohort Study	The use of COX-2 inhibitors is associated with a slightly increased risk of BCC	30

Table 2: Studies of nonsteroid antiinflammatory and nonselective COX-2 inhibitor drugs as chemoprevention of basal cell carcinoma.

Drugs	Years	Samples of Study	Study design	Results	Ref
NSAID, aspirin, NSAID non-aspirin	2009	321 OAINS 170 aspirin-only 151 NSAID non-aspirin only 1081 do not take aspirin	Cohort study	The use of NSAIDs has a protective effect on the development of BCC	13
NSAID	2011	535 SCC 487 BCC 462 control group	Case-control	NSAID decrease the risk of SCC, but not BCC	18
NSAID	2011	2291 BCC 55.922 non BCC	Cohort study	There was no correlation between NSAID consumption and the risk of BCC	20
Aspirin, NSAID non aspirin	2012	92.125 Caucasian Women	Cohort study	Aspirin and other non-aspirin NSAIDs are not associated with a reduced risk of developing melanoma, SCC, or BCC	19
Aspirin, Non-selective NSAID, Selective COX-2 inhibitor	2012	1.974 SCC 1.313 BCC 3243 Melanoma maligna (MM)	Case control	OAINS reduced the risk of MM and SCC, but there was no significan results for BCC	17
Aspirin (<325 mg) Dclofenac Ibuprofen Naproxen	2015	65.398 BCC patients (General Practice Research Database)	Case control	There is no evidence of a reduction in the risk of BCC with overall systemic NSAID use. Long term use of ibuprofen statistically reduces the risk of BCC The risk of BCC is slightly decreased with long-term aspirin use	16
Aspirin (81mg/ day and 325 mg/day, oral, for 3 years)	2018	1121 Adenoma colorectal patients, Hispanic, 21 – 80 years old	Randomized clinical trial	The cumulative incidence of BCC was higher in the aspirin group than in the placebo. The risk of BCC in patients with a history of previous skin cancer is lower than in patients without a previous history of skin cancer. Aspirin has no statistically significant effects on the incidence of BCC	21
Aspirin Ibuprofen Indometacin Acetaminophen	2019	34.630 Patient registered in Qskin Sun and Health	Cohort Study	There is a weak and inconsistent correlation between the use of NSAIDs and the incidence of BCC or SCC	22

has analgesic, antipyretic, and antiplatelet activity.[15] A cohort study conducted on 92,125 Caucasian women showed that neither aspirin nor the NSAID nonaspirin reduced the risk of skin tumors development, including melanoma, basal cell carcinoma and squamous cell carcinoma. For the association between BCC and aspirin use, all risk ratios were close to unity. There was a significant reduction in risk of 2% for every 10 years of aspirin use (P trend = 0.02). Separate analysis of the use of COX-2 inhibitors, with a shorter observation period (8 years), found no association between the use of COX-2 inhibitors and skin tumor development (RR [95% CI] = 1.05 [0.96 – 1.15]) (30). Three other case-control studies also reported insignificant results from the use of NSAIDs on the incidence of BCC.[16-18]

Study by Johannesdotir SA, *et al.* also showed parallel results with study conducted by Jeter JM, *et al.* The use of aspirin, other nonselective NSAIDs and selective COX-2 inhibitors was confirmed through the prescription database. In this study, there were no significant results on the use of NSAIDs to reduce the risk of BCC. NSAID use was not associated with a reduced risk of overall BCC (IRR, 0.97 [95% CI] 0.93 – 1.01), however the risk of BCC in areas other than the head and neck was reduced, associated with long-term use (IRR, 0.85 [95% CI], 0.76 – 0.95), and high intensity (IRR, 0.79 [95% CI] 0.69 – 0.91) of this drug.[17,19]

From several studies above, inconsistent results appear from the use of NSAIDs as chemoprevention against BCC. Selective COX-2 inhibitors are known to have good effectivity as chemoprevention agents against BCC, on the other hand the use of aspirin and other NSAIDs in several studies did not show a significant relationship to reduce the risk of BCC.[2,6] Those inconsistencies are due to higher COX-2 expression

compare to COX-1 in BCC. Therefore, the use of COX-2 inhibitors was more effective than other non-selective NSAIDs.[1]

Study by Johannesdotir SA, *et al*. revealed that the reduced risk of BCC with NSAID use was greater in areas other than the head and neck (which were not exposed to the sun). A possible explanation for these results is related to the phototoxic side effects of some NSAIDs. These phototoxic side effects may block the protective effect of these skin tumors in areas that are frequently exposed to sunlight, especially in BCC. BCC has a stronger relationship with UV exposure than SCC. In addition, the harmful effects of exposure to UV light may be stronger, thereby lowering the protective effect of NSAIDs.[19]

Inconsistent results in various studies related to the use of NSAIDs as BCC chemoprevention may be due to several factors, including differences in study design and population settings (general population and high risk), definition of outcome (BCC or SCC, analyzed separately or in combination), type of exposure (aspirin or nonaspirin, selective COX-2 inhibitors), definition of exposure (have or never, current or past, frequency or number of tablets used) and different analytical techniques.

Topical preparation

COX-2 inhibitor drugs have some side effects. One of the dangerous side effects is cardiovascular events which can be in the form of heart attacks and strokes. The serious side effects of using oral COX-2 inhibitors have led to the idea of using topical preparations of COX inhibitors as chemopreventive agents for BCC.[6] Diclofenac is one of the NSAIDs group that formulated in topical preparations. This drug works by reducing the production of prostaglandins by inhibiting the formation of COX-2, thereby reducing dysplastic keratinocytes in cancerous lesions. Another mechanism of this drug is the induction of apoptosis by sensitizing neoplastic keratinocytes to ligand-induced apoptosis and is responsible for the inhibition of angiogenesis in cancer cells. Currently, topical diclofenac has been approved for the treatment of AK by twice daily application for 2-3 months. This drug has an effectiveness between 38% - 47% for complete healing of AK lesions mentioned in several studies.[23] In one study, topical diclofenac sodium gel had a complete healing response rate of up to 58% (within a 30-day follow-up period). A healing response was demonstrated up to 1 year after treatment.[24] In a controlled study of organ transplant patients, no invasive BCC was seen within 24 months of follow-up. This suggests that topical 3% diclofenac sodium gel can prevent the development of nonmelanoma skin tumors.[25]

Topical diclofenac sodium can be used in solid organ transplant recipients, but there is no enough evidence for its effectiveness against BCC and SCC. Two case series have reported clearance of Bowen's disease in a total of 7 patients treated with topical diclofenac for 56 to 90 days.[26] A phase II randomized controlled study was conducted to determine the effectiveness of 3% diclofenac sodium gel and 3 mg/g calcitriol ointment (as monotherapy and in combination) for superficial BCC and nodular BCC. A total of 64 patients with superficial BCC and 64 patients with nodular BCC were randomized into 3 treatment groups (topical diclofenac, calcitriol, and combination) and 1 control group. Topical diclofenac sodium applied 2 times daily. After 8 weeks of therapy, immunohitochemical markers of proliferative (Ki-67) and antiapoptotic (B-cell lymphoma [Bcl-2]) expression levels were evaluated. Patients also get an evaluation of histological clearance of the lesion, side effects, and local reactions to the skin of the treatment area. Basal cell carcinoma treated with topical diclofenac showed decreased Ki-67 ($P < .001$) and Bcl-2 ($P = .001$). A decrease in Ki-67 ($P = .012$) was also seen in superficial BCC receiving topical diclofenac and calcitriol therapy. Complete regression of the tumor histologically was seen in 64.3% ($P = .0003$) superficial BCC with diclofenac topical therapy and 43.8% ($P = .007$) superficial BCC with combination therapy. However, there was no significant change in nodular BCC. Further studies must be conducted before this drug can be recommended as a treatment for NMSC and to determine its effectiveness as a BCC chemoprevention.[27]

Safety profile

NSAIDs are known to have several side effects, including gastrointestinal bleeding, the cardiovascular system disorder and kidney toxicity. Gastrointestinal side effects of NSAIDs include nausea, mild discomfort, dyspepsia symptoms, to severe complications such as bleeding, peptic ulcer perforation and intestinal obstruction. Important risk factors that can trigger gastrointestinal side effects are medical history of peptic ulcer disease, age, and concurrent use of aspirin.[28]

A meta-analysis study examining the safety of NSAIDs on the cardiovascular system. The cardiovascular risks of naproxen, ibuprofen, diclofenac, celecoxib, etoricoxib, rofecoxib, and lumiracoxib were examined. This study showed that the highest risk of myocardial infarction was associated with rofecoxib (rate ratio 2.12, 95% credibility interval (CI): 1.26-3.56), followed by lumiracoxib (rate ratio 2.00; 95% CI; 0.71-6,21). As for stroke, the highest risk was associated with ibuprofen (rate ratio 3.36, 95% CI: 1.00-11.6), while diclofenac was associated with the second highest risk (rate ratio 2.86, 95% CI: 1.09-8.36). On the other hand, two drugs were associated with the highest risk of cardiovascular death, namely, etoricoxib (rate ratio 4.07, 1.23-15.7) and diclofenac (rate ratio 3.98, 95% CI: 1.48-12, 7). A study concluded that naproxen appeared to be the least dangerous of all NSAIDs.[29]

NSAIDs is effective as a chemopreventive agent of BCC, but the potential cardiovascular risk associated with celecoxib is a consideration for its widespread use. Long-term use of refecoxib and celecoxib has been reported to increase the risk of serious cardiovascular events. The risk of serious cardiovascular events appears to be dose and duration dependent, and in some clinical trials, patients with previous cardiovascular disease have a greater risk of cardiovascular events with selective COX-2 inhibitor. In a clinical trial to determine the chemopreventive effect of celecoxib, there was no statistically significant difference in the number of cardiovascular side effects between the celecoxib-treated group and the placebo group. However, in this study, celecoxib consumption was only carried out for 9 months, while in another study using Rofecoxib (a COX-2 inhibitor), serious cardiovascular side effects occurred after 1 year or more of use.[2]

CONCLUSION

The use of selective COX-2 inhibitor, either orally or topically, may be a strategy for cheoprevention of BCC that is promising and worthy of being used as material for further research. Selective COX-2 inhibitors were more effective at preventing the development of BCC than nonselective COX-2 inhibitors. This drug can be used as a chemoprevention modality in patient with high risk factor of developing and recurrency of BCC. However, this drug is still not widely recommended as BCC chemoprevention due to cardiovascular side effects. Close monitoring and special attention should be paid to the use of this drug in geriatric and patients with cardiovascular disease.

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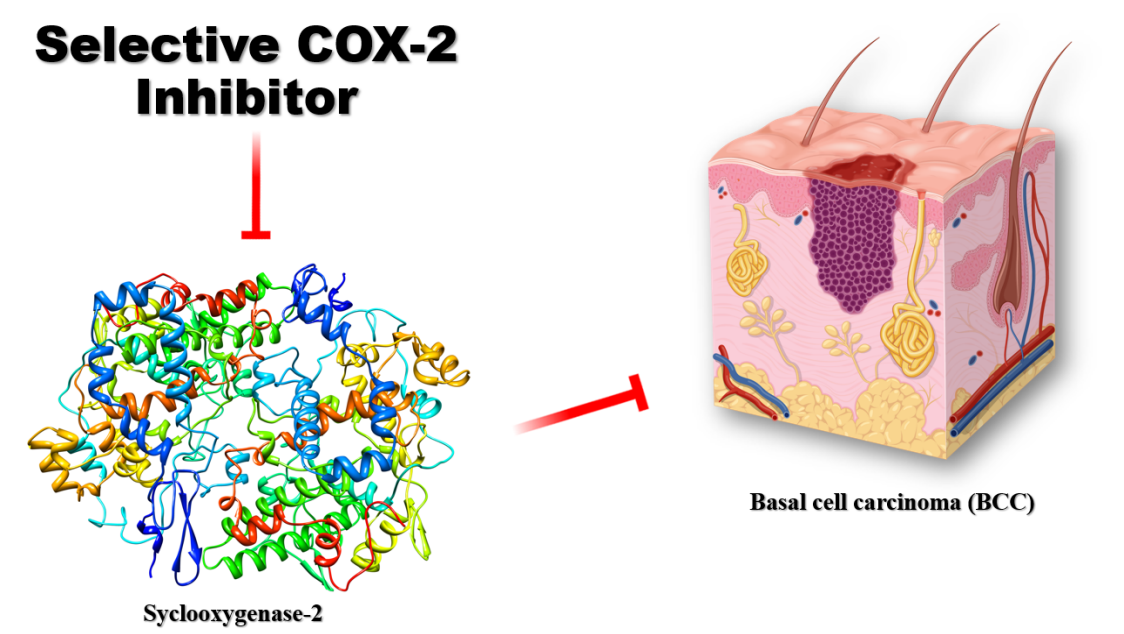
GRAPHICAL ABSTRACT



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