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Cyclooxygenase-1 and -2: Molecular Targets for Cervical Neoplasia

REVIEW

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Cyclooxygenase (COX) is a key enzyme responsible for inflammation, converting arachidonic acid to prostaglandin and thromboxane. COX has at least two isoforms, COX-1 and COX-2. While COX-1 is constitutively expressed in most tissues for maintaining physiologic homeostasis, COX-2 is induced by inflammatory stimuli including cytokines and growth factors. Many studies have shown that COX-2 contributes to cancer development and progression in various types of malignancy including cervical cancer. Human papillomavirus, a necessary cause of cervical cancer, induces COX-2 expression via E5, E6 and E7 oncoproteins, which leads to prostaglandin E2 increase and the loss of E-cadherin, promotes cell proliferation and production of vascular endothelial growth factor. It is strongly suggested that COX-2 is associated with cancer development and progression such as lymph node metastasis. Many studies have suggested that non-selective COX-2 inhibitors such as non-steroidal anti-inflammatory drugs (NSAIDs), and selective COX-2 inhibitors might show anti-cancer activity in COX-2 -dependent and -independent manners. Two phase II trials for patients with locally advanced cervical cancer showed that celecoxib increased toxicities associated with radiotherapy. Contrary to these discouraging results, two phase II clinical trials, using rofecoxib and celecoxib, demonstrated the promising chemopreventive effect for patients with cervical intraepithelial neoplasia 2 or 3. However, these agents cause a rare, but serious, cardiovascular complication in spite of gastrointestinal protection in comparison with NSAIDs. Recent pharmacogenomic studies have showed that the new strategy for overcoming the limitation in clinical application of COX-2 inhibitors shed light on the use of them as a chemopreventive method. **(J Cancer Prev 2013;18:123-134)**

Key Words: Cyclooxygenase, Cyclooxygenase-2 inhibitor, Cervical cancer

INTRODUCTION

Cyclooxygenase (COX) pathway is known to be one of major routes for producing bioactive prostanoids such as prostaglandin (PG) E_2, D_2, $F_{2\alpha}$, I_2 (prostacyclin) and thromboxane (TX) A_2. COX exists as at least two different enzymes in mammalian cells: COX-1 and COX-2, which are located on human chromosomes 9 and 1 respectively.[1,2] COX-1 is constitutively expressed in many normal cells, and PGs produced by COX-1 are important for maintaining the integrity of gastric mucosa and allowing normal platelet aggregation and renal function. On the other hand, COX-2 is induced by oncogene, growth factors and cytokines, and COX-2-derived PGs can stimulate cell proliferation, promote angiogenesis, increase invasiveness and adhesion to the extracellular matrix and inhibit immune surveillance and apoptosis.[3-5] Furthermore, COX-2-derived PGs have been shown to contribute to cancer development, progression and metastasis.[6] Therefore, the inhibition of COX-2 has been anticipated to prevent the development and progression of cancer and to promote the response to cytotoxic agents as well as

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ionizing radiation.[7]

Although non-steroidal anti-inflammatory drugs (NSAIDs), which non-specifically inhibit both COX-1 and COX-2, induce adverse effects on gastrointestinal (GI) tract, selective COX-2 inhibitors such as rofecoxib and celecoxib reduce the adverse effects of NSAIDs on GI tract with relief of chronic pain.[8,9] However, selective COX-2 inhibitors are known to be associated with increased cardiovascular adverse effects.[10] Since many preclinical and clinical studies have shown that COX-2-derived PGs are associated with cervical neoplasia and COX-2 inhibitors have anti-cancer effect, we will show the role of COX-2 and the efficacy of COX-2 inhibitors in cervical neoplasia, and will suggest the new strategy for overcoming the limitation in clinical application of COX-2 inhibitors through this review.

COX-2, INFLAMMATION AND CARCINOGENESIS

Chronic inflammation mediated by COX-2 is associated with carcinogenesis and cancer progression. It is caused by various factors including bacterial infections and chemical irritants. The longer the inflammation persists, the higher is the risk of associated carcinogenesis. Moreover, neoplasia could be caused by inflammatory mediators inducing preneoplastic mutation, stimulation of angiogenesis and resistance to apoptosis, and these inflammatory mediators may activate signaling molecules involved in inflammation and carcinogenesis such as COX-2 and nuclear factor-kappa B (NF-kB).[11]

Carcinogenesis by COX-2 has been explored in terms of the inhibition of apoptosis, promotion of angiogenesis, invasiveness and immunosuppression in various types of malignancy.[7] Especially, PG E_2, an end product of COX-2, may increase the activity of mitogen-activated protein kinase (MAPK),[12] affect ras-controlled signal transduction pathways,[13] and suppress the activity of caspase-3, a key enzyme in apoptotic process.[14] Besides, COX-2-derived PGs may increase the production of vascular endothelial growth factor (VEGF) and promote neovascularization in cancer.[15,16]

COX-2 overexpression may lead to the invasiveness of cancer to basement membrane, stroma, penetration to blood vessels and metastasis, which are mediated by matrix metalloproteinases (MMPs) such as MMP-1, -2 and -9.[6,17] Additionally, carcinogenesis is related with immunosuppression because colony-stimulating factors secreted by cancer cells activate monocytes and macrophages resulting in the synthesis of PG E_2 by COX-2. PG E_2 shows the immunosuppressive effect by inhibiting the production of lymphokines and tumor necrosis factors, proliferation of T- and B-cells and cytotoxic activity of natural killer cells.[18,19]

INDUCTION OF COX-2 GENE BY HUMAN PAPILLOMAVIRUS ITSELF

Human papillomavirus (HPV) is the most prevalent sexually infectious agent and causes cervical cancer. Especially, HPV 16 E6 and E7 oncoproteins stimulate to produce amphiregulin, which induces the transcription of COX-2 gene by activating MAPK cascade (Fig. 1A).[5] HPV 16 E5 oncoprotein also induces the transcription of COX-2 gene in a ligand-dependent and -independent activation of epidermal growth factor receptor (EGFR) and MAPK cascade,[20-22] and causes the increased expression of VEGF by activating MEK/ERK 1/2 and PI3K/Akt, which are associated with cervical carcinogenesis (Fig. 1B).[20,23,24] Moreover, chronic infection of HPV in cervical epithelium increases PG E_2 by COX-2, which leads to the loss of E-cadherin, increased cell proliferation and production of VEGF.[25-27]

COX-2 EXPRESSION IN CERVICAL CARCINOGENESIS

COX-2 is highly expressed in various types of cervical neoplasm such as cervical intraepithelial neoplasia (CIN) (7.4%), adenocarcinoma (13%) and squamous cell carcinoma (28.8%) of cervix, suggesting that COX-2 expression can be associated clinically with cervical cancer development and progression.[28-30] Besides, COX-2 gene has been shown to be involved in early cervical carcinogenesis and accelerate tumor progression by increasing VEGF.[25]

COX-2 has been also shown to be expressed in dysplastic

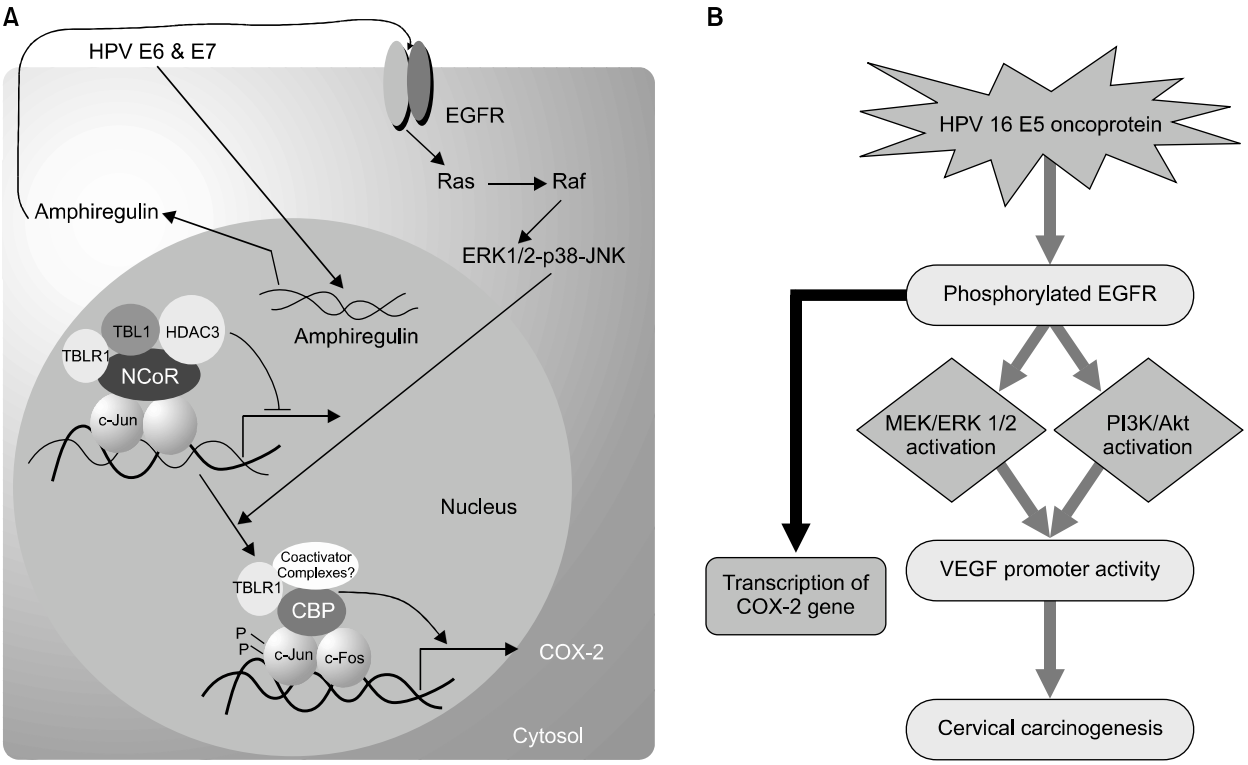

Fig. 1. Schematic of pathway where human papillomavirus (HPV)16 E5, E6 and E7 oncoproteins regulate cyclooxygenase-2 (COX-2) expression associated with the cervical carcinogenesis. (A) HPV16 E6 and E7 oncoproteins stimulate production of amphiregulin and thereby activate EGFR → Ras → MAPK signaling. This results, in turn, in the phosphorylation of c-Jun, leading to transduction β-like protein 1-related protein (TBLR1)-dependent degradation of the nuclear receptor corepressor (NCoR)/histone deacetylase 3 (HDAC3) complex and recruitment of the coactivator cyclic AMP-responsive element binding protein-binding protein (CBP)/p300 and phosphorylated c-Jun/c-Fos heterodimer to the COX-2 promoter. This corepressor/coactivator exchange triggered by HPV oncoproteins leads to enhanced COX-2 transcription[5]; (B) HPV 16 E5 oncoprotein also causes the increase of phosphorylated EGFR, and thereby increases the transcription of COX-2 gene and secretion of VEGF, which enhances cervical carcinogenesis.[20]

epithelium (7.4%) but not in stromal cells of CIN (0%).[31] This fact is contrary to previous studies of COX-2 overexpression in colon cancer where the increased COX-2 expression in stromal cells was related with carcinogenesis, suggesting that PGs derived from COX-2 in stromal cells would be secreted and bind to receptors on adjacent epithelial cells, then might promote carcinogenesis with the "landscaping effect".[32] Unlike colon cancer, the landscaping effect of stromal cells seems to have no role in cervical carcinogenesis because it may be influenced by HPV itself.

Interestingly, COX-2 overexpression may be also associated with old age and menopause in CIN.[31] Although the reason is unclear, the lack of progesterone for menopausal women could explain this fact because progesterone has been shown to suppress COX-2 expression in some cells.[33]

COX-2 CONTRIBUTING TO PROGRESSION IN CERVICAL NEOPLASIA

COX-2 overexpression is associated with lymph node metastasis in cervical cancer.[34,35] Although COX-2 overexpression was not an independent prognostic factor for survival,[36,37] it may enhance metastatic potentials of tumors by inducing genes which promote lymphangiogenesis and increase metastatic properties of cervical cancer.[38]

Moreover, COX-2 overexpression is related with NF-kB activation, which is localized to the cytoplasm in resting cells and binds to the DNA recognition sites in the regulatory regions of target genes after it migrates into the nucleus on various stimuli.[34,35,39] Many studies have been focused on NF-kB as a molecular target for chemoprevention, which plays a crucial role in the regulation of inflammatory and immunes responses and in carcinogenesis.

Stimuli regulated by NF-kB during inflammation can be redirected as tumor growth signals. NF-kB has been found constitutively activated in many human cancer samples, supporting an important role of NF-kB in cancer development.[40] Moreover, COX-2 is inducible via the activation of NF-kB by many factors such as cytokines and growth factors.[41]

EFFICACY OF COX-2 INHIBITORS AGAINST CERVICAL NEOPLASIA IN PRECLINICAL STUDIES

NSAIDs and selective COX-2 inhibitors such as celecoxib have been commonly used as analgesics, anti-inflammatory drugs. After several studies reported their apoptotic effect in various types of cancer cells,[42-44] the efficacy of COX-2 inhibitors has been evaluated for the prevention or treatment of cervical neoplasia. In detail, anti-cancer activity of COX-2 inhibitors is mediated in part through the inhibition of the COX-2 activity.[45-47] However, anti-cancer activity exerted by COX-2 inhibitors is independent of their COX-2 inhibitory properties because the growth of hematopoietic and epithelial tumor cells without COX-2 expression has been reported to be suppressed by COX-2 inhibitors.[48,49] Besides, in cervical cancer cells, celecoxib induces apoptosis independent of COX-2 inhibition through two major pathways: death receptor pathway followed by the activation of caspase-8, which then activates the downstream effector caspases such as caspase-3, -6 and -7, triggering cell death; mitochondrial pathway by the activation of caspase-9, which leads to the loss of mitochondrial membrane potential.[42,50]

Celecoxib-induced apoptosis is mediated by a Fas/Fas-associated protein with death domain (FADD)-dependent mechanism in Fas-ligand (FasL)-independent manner, and involved in the activation of NF-kB.[42] Growth arrest and DNA damage inducible gene (GADD153), a transcription factor involved in apoptosis, also plays a key role in celecoxib-induced apoptosis in cervical cancer cells by regulating the expression of proapoptotic proteins such as Bak.[51]

NSAIDs seem to have comparable efficacy to celecoxib. In a study on the association among COX-1, COX-2 and VEGF expression in cervical cancer, VEGF expression was strongly correlated with COX-1 expression, and COX-2 expression was associated with lymph node metastasis,[28] suggesting that NSAIDs may be efficient to treat cervical cancer.[52,53] Furthermore, NSAIDs including aspirin, sulindac and indomethacin have been reported to decrease cell proliferation and colony formation in a time and dose-dependent manner in cervical cancer cells, and increase apoptosis and radiotherapeutic efficacy by pretreatment of cervical cancer cells through bcl-2 repression and caspase-3 induction.[54]

On the other hand, COX expression in cervical cancer may be associated with the effect of radiotherapy.[55,56] Especially, COX-1 expression decreases significantly radiosensitivity in cervical cancer cell lines in spite of no association between COX-2 expression and radio-resistance. These data suggest that COX-1 might imply more importance than COX-2 regarding the innate radiosensitivity of cervical cancer, and that NSAIDs, non-selective COX-2 inhibitors, might increase the radiotherapeutic effectiveness if cervical tumor cells have not yet lost their ability to express COX-1.[56]

CLINICAL APPLICATION OF COX-2 INHIBITORS IN CERVICAL CANCER

1. COX-2 inhibitors for the prevention of cervical cancer

The efficacy of COX-2 inhibitors has a definite advantage to treat CIN because cervical conization may be avoided, reducing obstetrical complications including preterm delivery, and preterm premature rupture of membrane. In a prospective, randomized, placebo-controlled, double-blind study with rofecoxib 25 mg daily for 6 months for the treatment of 16 patients with CIN 2 and CIN 3, regression rate was higher in patients treated with rofecoxib than those treated with placebo (25% vs. 12.5%) without no severe side effects although the results were statistically not significant due to early withdrawal of refecoxib from the market by increased cardiovascular adverse effect.[57] Also, clinical response rate and complete pathologic response were higher for patients treated with celecoxib than in those treated with placebo (75% vs. 31%; 33% vs. 15%, respectively) in a randomized, double-blind, place-

bo-controlled phase II trial of celecoxib 200 mg twice a day or placebo for the treatment of 25 patients with CIN 2 or CIN 3.[58]

2. COX-2 inhibitors for the treatment of cervical cancer

The efficacy of selective COX-2 inhibitors has been mainly studied for patients with locally advanced cervical cancer receiving radiotherapy. However, the results were disappointing because COX-2 inhibitors showed no clinical benefit and higher toxicity by the addition to chemoradiation. In a phase I-II trial of celecoxib 400 mg twice per day for 2 weeks before and during chemoradiation using cisplatin, 31 patients with locally advanced cervical cancer were enrolled. Higher incidence of grade 3 or 4 acute toxicity (35.5%) was seen with no difference in 81% of response rate, compared with previous studies about the chemoradiation alone. Besides, there was an increase in late complication such as fistula (9.7%). Thus, celecoxib in combination with chemoradiation was associated with acceptable acute toxicity, but higher late complication.[59]

Furthermore, the Radiation Therapy Oncology Group (RTOG) 0128 trial was performed as a phase II study to evaluate the efficacy and toxicity of celecoxib and chemoradiation for patients with locally advanced cervical cancer. In this study, 83 patients were treated with chemoradiation using cisplatin and 5-fluorouracil with the addition of celecoxib at the dose of 400 mg twice daily for 1 year. However, grade 3 or 4 toxicities were developed in 47% and late toxicities such as GI and genitourinary side effects were observed in 13% of all patients, which were higher than expected rates of complication. These data suggest that the toxicities associated with celecoxib may limit the use of this drug.[60]

On the other hand, a randomized clinical trial showed that the treatment of oxyphenbutazone, a non-selective COX-2 inhibitor, at the dose of 300 mg daily improved 5- and 10-year survival rates, compared to placebo in patients undergoing radiotherapy only for cervical cancer (5-year survival rate, 70 vs. 55%; 10-year survival rate, 62 vs. 44%). Taken together, there are two possible explanations for these discrepant results. First, the improvement of survival rates might be due to slowing of tumor spread and improvement of cell repair after radiotherapy by the inhibition of PGs. Second, the inhibition of both COX-1 and -2 might be important to treat cervical cancer.[52]

Thus, many clinical trials are required to evaluate the role of COX-2 inhibitors in the management of cervical cancer. Table 1 depicts clinical studies about the efficacy of COX-2 inhibitors in cervical neoplasia. The clinical trials of selective COX-2 inhibitors, especially celecoxib, are being on the progress for the treatment of cervical neoplasia combined with chemotherapy or radiotherapy or alone.

ADVERSE EFFECTS OF COX-2 INHIBITORS

After selective COX-2 inhibitors were introduced as alternative analgesics to NSAIDs due to fewer GI side effects, the approval of rofecoxib (Vioxx®) and celecoxib (Celebrex®) by the Food and Drug Administration in the United States came in 1999 with their market release. Moreover, selective COX-2 inhibitors had been investi-

Table 1. Clinical trials of cyclooxygenase-2 (COX-2) inhibitors for the treatment of cervical neoplasia

Authors or protocol ID	Sample size	Interventions	Targeted disease	Response rate
Weppelmann and Monkemeier[52]	76 vs. 84 (control)	Oxyphenbutazone	Cervical cancer	5-year survival rate : 70% vs. 55% 10-year survival rate : 62% vs. 44%
Hefler et al.[57]	8 vs. 8 (control)	Rofecoxib	CIN* 2-3	25% vs.12.5%
Farley et al.[58]	12 vs. 13 (control)	Celecoxib	CIN* 2-3	75% vs. 31%
Herrera et al.[59]	31	Celecoxib	Cervical cancer	81%
Gaffney et al.[60]	84	Celecoxib	Cervical cancer	Toxicity: 48%
NCT00081263† (GOG-0207)	100	Celecoxib	CIN* 2-3	-
NCT00152828†	45	Celecoxib	Cervical cancer	-
NCT00072540† (SWOG-S0212)	100	Celecoxib	CIN* 2-3	-

*Cervical intraepithelial neoplasia; †Active clinical trials (available at http://clinicaltrials.gov).

gated for chemoprevention because some studies have demonstrated that inhibiting COX-2 could prevent the formation of premalignant colorectal adenomas.[61-65] However, rofecoxib was withdrawn from the market on September 2004 because of the serious adverse event found in Adenomatous Polyp Prevention on Vioxx® (APPROVe) trial, demonstrating that the group assigned to rofecoxib had a fourfold increased risk of serious thromboembolic events including acute myocardial infarction and cerebrovascular accident compared with the placebo group.[66] Furthermore, rofecoxib has been shown to increase cardiovascular adverse effects by meta-analysis when compared to placebo or NSAIDs (Table 2).

Benefit and risk by COX-2 inhibitors are summarized in Fig. 2. In spite of markedly less GI damage than NSAIDs, selective COX-2 inhibitors are doomed to increase cardiovascular adverse effects because selective COX-2 inhibition may reduce the production of prostacyclin, which normally inhibits platelet aggregation and vasodilation, while still allowing COX-1 mediated synthesis of TX A_2 to induce platelet aggregation and vasoconstriction.[67] After withdrawal of rofecoxib, the safety of celecoxib has also been investigated for cardiovascular adverse effects. Celecoxib has been shown to be safer than rofecoxib in most studies. The first reason is that the degree of COX-2 selectivity of celecoxib is a fifth of that of rofecoxib. Actually, the degree of COX-2 selectivity is known to correlate with cardiovascular and renal risks.[68,69] The second reason is that a reactive metabolite of rofecoxib, a maleic anhydride derivative which contributes to atherothrombosis, cannot be derived from other COX-2 inhibitors including celecoxib, valdecoxib and lumaricoxib.[70] Furthermore, the Celecoxib Long-term Arthritis Safety Study (CLASS) demonstrated no significant difference in

Table 2. Cardiovascular adverse effect of selective cyclooxygenase-2 (COX-2) inhibitors by meta-analysis

Adverse effects	Meta-analysis	Comparison		Relative risk* with 95% CI
		Control	Intervention	
Serious cardiovascular events†	Kearney et al.[97]	Placebo	Selective COX-2 inhibitors‡	1.42 (1.13-1.78)
		Naproxen	Selective COX-2 inhibitors‡	1.57 (1.21-2.03)
		Non-naproxen	Selective COX-2 inhibitors‡	0.88 (0.69-1.12)
	Mukherjee et al.[98]	Naproxen	Rofecoxib	1.89 (1.03-3.45)
	Jüni et al.[99]	Control§	Rofecoxib	1.55 (1.05-2.29)
	Garner et al.[100]	Non-naproxen		
		- Diclofenac	Rofecoxib	0.70 (0.25-1.93)
		- Nabumetone	Rofecoxib	2.90 (0.12-71.01)
		- Arthrotec	Rofecoxib	1.39 (0.63-3.08)
Cardiovascular mortality‖	Kearney et al.[97]	Placebo	Selective COX-2 inhibitors‡	1.49 (0.97-2.29)
		Naproxen	Selective COX-2 inhibitors‡	1.47 (0.90-2.40)
	Jüni et al.[99]	Control§	Rofecoxib	0.79 (0.29-2.19)
Myocardial infarction¶	Kearney et al.[97]	Naproxen	Selective COX-2 inhibitors‡	2.04 (1.41-2.96)
		Non-naproxen	Selective COX-2 inhibitors‡	1.20 (0.85-1.68)
	Jüni et al.[99]	Placebo	Rofecoxib	1.04 (0.34-3.12)
		Naproxen	Rofecoxib	2.93 (1.36-6.33)
		Non-naproxen	Rofecoxib	1.55 (0.55-4.36)
	Garner et al.[100]	Placebo	Rofecoxib	1.48 (0.06-36.06)
		Naproxen	Rofecoxib	4.98 (0.58-42.57)
		Non-naproxen		
		- Diclofenac	Rofecoxib	0.52 (0.05-5.72)
Stroke**	Kearney et al.[97]	Placebo	Selective COX-2 inhibitors‡	1.02 (0.71-1.47)
		Naproxen	Selective COX-2 inhibitors‡	1.10 (0.73-1.65)
		Non-naproxen	Selective COX-2 inhibitors‡	0.62 (0.41-0.95)
	Jüni et al.[99]	Control§	Rofecoxib	1.02 (0.54-1.93)
	Garner et al.[100]	Naproxen	Rofecoxib	0.08 (0.00-1.36)

*A ratio of the probability of the event occurring in the interventiongroup versus the control group; †non-fatal myocardial infarction, non-fatal stroke or cardiovascular death; ‡including rofecoxib, celecoxib, etoricoxib, lumiracoxib and valdecoxib; §placebo and NSAIDs; ‖Death due to cardiovascular events; ¶fatal or non-fatal myocardial infarction; **fatal or non-fatal thrombotic or hemorrhagic stroke.

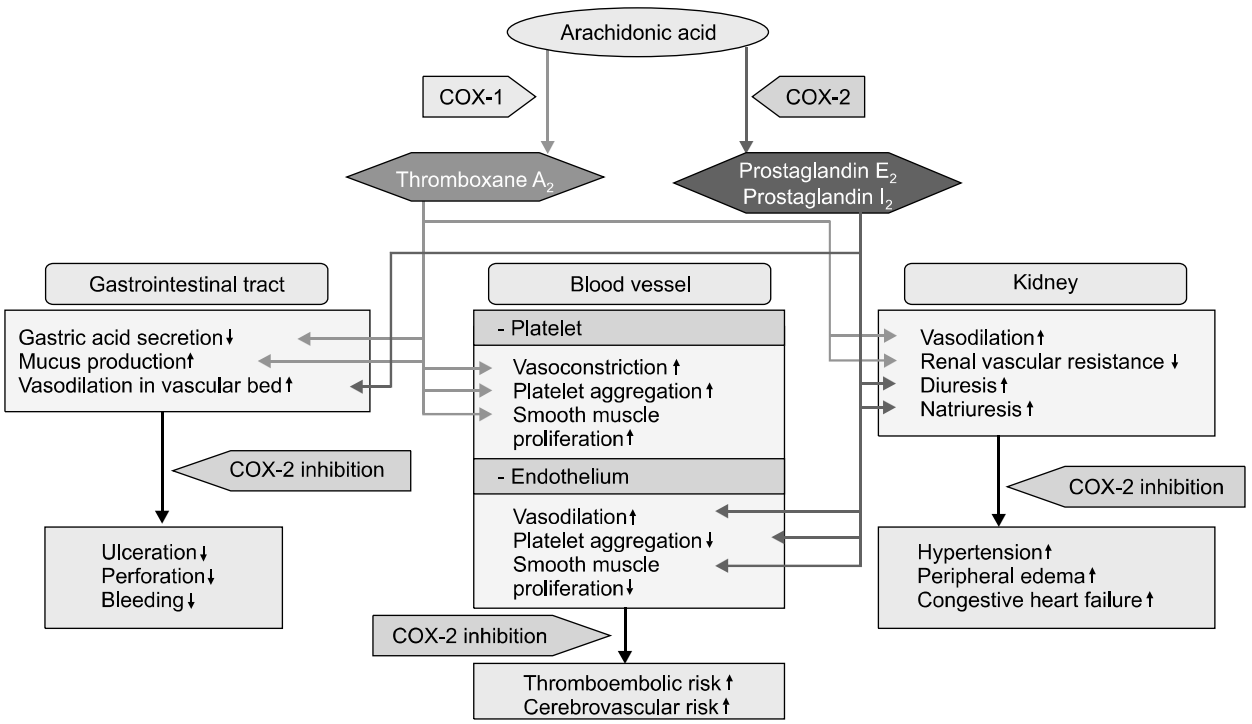

Fig. 2. Role of cyclooxygenase (COX) in human gastrointestinal, cardiovascular and renal functions. COX-1-derived thromboxane A_2 decreases gastric acid secretion in gastrointestinal tract and renal vascular resistance in kidney, whereas it increases mucus production in gastrointestinal tract, vasoconstriction, platelet aggregation and smooth muscle proliferation in blood vessel, and vasodilation in kidney. Moreover, COX-2-derived prostaglandins E_2 and I_2 decrease platelet aggregation and smooth muscle proliferation in blood vessel while they increase vasodilation in gastrointestinal tract and blood vessel, and diuresis and natriuresis in kidney. On the other hand, selective COX-2 inhibitors increase thromboembolic risk, and decrease gastrointestinal side effects and renal function.

cardiovascular event between celecoxib 800 mg/day and NSAIDs, suggesting the safety of celecoxib.[71]

Nonetheless, the Adenoma Prevention with Celecoxib (APC) and Prevention of Spontaneous Adenomatous Polyps (PreSAP) trials comparing celecoxib with placebo for the reduction in recurrent colorectal polyps were stopped early because of significantly higher numbers of cardiovascular adverse effects in celecoxib-treated group.[72,73] Thus, the safety of celecoxib is still on debate, and further trials designed to assess the incidence of cardiovascular adverse effects by celecoxib are needed.

NEW STRATEGY FOR OVERCOMING THE LIMITATION FOR USING COX-2 INHIBITORS

1. Natural products for the chemoprevention of cervical neoplasia

Many natural products are being investigated to inhibit COX-2 overexpression and NF-kB activation as molecular targets for chemoprevention of cervical neoplasia. First, curcumin is a yellow pigment of turmeric, a natural product with diverse biological activities. It has been shown to possess anti-inflammatory, anti-oxidant and anti-tumor properties. Much of its beneficial effect is found to be due to its inhibition of NF-kB and subsequent inhibition of proinflammatory pathways.[74] Besides, curcumin synergistically augments the growth inhibitory effect of celecoxib by down-regulating COX-2 mRNA expression and inhibition of the catalytic activity of 5-lipoxygenase producing leukotrienes associated with carcinogenic process.[75] Phase I trials on curcumin showed that it is safe to human up to 12,000 mg/day when taken orally and caused histological improvement of precancerous lesions including CIN.[76-78] Moreover, curcumin has been shown to confer the radiosensitizing effect in cervical cancer cells.[79]

Second, indole-3-carbinol (I3C) is derived from cruciferous vegetables such as broccoli and cabbage. I3C and its

metabolite, 3,3'-diindoylmethane (DIM) target multiple aspects of cancer cell-cycle regulation and survival including NF-kB signaling, caspases activation and cyclin-dependent kinase activity.[80] I3C and its metabolite have been shown to prevent cervical cancer and have the efficacy in the treatment of cervical dysplasia in the mouse model.[81] A small randomized controlled clinical trial in patients with CIN 2 or 3 indicated the efficacy of I3C for the regression of CIN.[82] In addition, some studies on HPV persistence or cervical neoplasia showed a possible protective effect of fruits, vegetables, vitamins C and E, α- and β-carotenes, lycopene, luterin/zeaxanthin and cryotoxanthin.[83]

2. New methods using COX-2 inhibitors

Since the safety of selective COX-2 inhibitors is controversial, patients treated with selective COX-2 inhibitors should be monitored regularly in terms of blood pressure, edema and cardiac status because regular interruptions of treatment can contribute a great deal to the safe use of selective COX-2 inhibitors.[68] In addition, new methods are being investigated for overcoming the limitation of selective COX-2 inhibitors as follows.

The first is the combination of COX-2 inhibitors with other drugs. The prescription of a combined therapy of NSAIDs and proton pump inhibitors (PPIs) has been shown to have comparable ulcerous bleeding to COX-2 inhibitors (6.4% vs. 4.9%).[84] However, it should be considered that PPIs may be associated with adverse effects independent of concomitant NSAID use, including pneumonia, bacterial diarrhea and hip fracture.[85-87] Moreover, it can be considered that selective COX-2 inhibitors are combined with low-dose aspirin for cardioprotection. However, the CLASS trial demonstrated that a fourfold increase in the incidence of GI bleeding occurred in a subgroup of patients taking celecoxib in combination with aspirin, suggesting that the combination should not be used in patients with high-risk GI bleeding.[71] Furthermore, curcumin can be combined with selective COX-2 inhibitors because it induces cardioprotective effect by scavenging oxygen-free radical.[88] However, large and well-controlled clinical trials are required to determine the role of selective COX-2 inhibitors and curcumin to prevent and treat cancer.

The second method is the structural modification of NSAIDs. Nitric oxide (NO)-donating NSAIDs have been claimed to exert a broader range of anti-inflammatory action while reducing markedly GI and cardiovascular toxicity.[89-91] However, these claims are poorly substantiated by clinical studies to date.

The third method is the modification of schedule for the use of selective COX-2 inhibitors. In some meta-analyses, celecoxib showed dose-dependent cardiovascular effect although rofecoxib was associated with cardiovascular adverse effect at all doses (at doses of 25 mg or less, or greater than 25 mg once daily), suggesting that celecoxib doses of up to 200 mg once daily was not related with increased cardiovascular adverse effect in spite of the need of clinical trials for evaluating dose-dependent toxicity of celecoxib.[92,93] Since the combination of chemoradiation with celecoxib increased late toxicities compare to chemoradiation alone in patients with locally advanced cervical cancer,[59,60] various schedules for the administration of celecoxib are being investigated in clinical trials for gynecologic cancers. For example, in a phase II study of weekly paclitaxel and celecoxib for the treatment of recurrent or persistent platinum-resistant epithelial ovarian or primary peritoneal cancer, patients receive paclitaxel on days 1, 8, and 15 and celecoxib twice daily on days 2-6, 9-13 and 16-27 with the repeat of courses every 28 days in the absence of disease progression or unacceptable toxicity.[94]

CONCLUSION

After withdrawal of rofecoxib from market, other selective COX-2 inhibitors including celecoxib have been focused on many clinical trials to prevent and treat various types of malignancy including cervical cancer. Since the safety of other selective COX-2 inhibitors remains controversial, it is important to select patients with low cardiovascular risk from selective COX-2 inhibitors, and to follow up them regularly for the prevention and early detection of GI, renal and cardiovascular adverse effects. For example, selective COX-2 inhibitors seem to be useful for the treatment of CIN which mainly develops in young women with HPV infection because most of them have relatively

lower cardiovascular risk than old women.[95] Besides, selective COX-2 inhibitors have the advantage that these agents can lessen the risk of preterm delivery by cervical conization for the treatment of CIN with lesser GI toxicity compared to non-selective COX-2 inhibitors.[96]

On the other hand, the role of COX-1 should be reevaluated for the prevention and treatment of cervical neoplasia because some preclinical and clinical studies have shown that the inhibition of COX-1 might increase the radiotherapeutic efficacy in cervical cancer.[52,55,56] Furthermore, new strategies using natural products or COX-2 inhibitors should be proven through preclinical and clinical studies for overcoming the limitation of COX-2 inhibitors.

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