Interplay between cyclooxygenase-2 and microRNAs in cancer (Review)

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Abstract. Tumor-associated inflammation and aberrantly expressed biomarkers have been demonstrated to play crucial roles in the cancer microenvironment. Cyclooxygenase-2 (COX-2), a prominent inflammatory factor, is highly expressed in tumor cells and contributes to tumor growth, recurrence and metastasis. Overexpression of COX-2 may occur at both transcriptional and post-transcriptional levels. Thus, an improved understanding of the regulatory mechanisms of COX-2 can facilitate the development of novel antitumor therapies. MicroRNAs (miRNAs) are a group of small non-coding RNAs that act as translation repressors of target mRNAs, and play vital roles in regulating cancer development and progression. The present review discusses the association between miRNAs and COX-2 expression in different types of cancer. Understanding the regulatory role of miRNAs in COX-2 post-transcription can provide novel insight for suppressing COX-2 expression via gene silencing mechanisms, which offer new perspectives and future directions for the development of novel COX-2 selective inhibitors based on miRNAs.

Contents

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1. Introduction

Cancer is the second leading cause of mortality worldwide, with 18.1 million new cases and 9.6 million mortalities reported in 2018 (1). Previous studies have demonstrated that there is a causal association between inflammation and carcinogenesis (2,3). In addition, inflammation notably contributes to tumor growth, progression, metastasis, recurrence and treatment resistance (2). Cyclooxygenase (COX) is classified into three isozymes: COX-1, COX-2 and COX-3 (3). COX-1 is predominantly expressed in most tissues, such as in blood vessels, stomach and kidney, and acts as a housekeeping enzyme during cellular homeostasis (2,3). COX-2 is constitutively expressed in certain pathological processes and is required to produce prostaglandin E2 (PGE2), an inflammatory mediator expressed in different types of cancer (2). COX-3 is predominantly expressed in the spinal cord and brain (4). Upregulated COX-2 expression is observed at inflammation sites that predispose to cancer development (5). However, COX-2 is expressed at relatively low levels in normal tissues adjacent to tumor tissues (6). COX-2 is considered an important therapeutic target for several diseases, including cancer, autoimmune diseases and gastric inflammation (Fig. 1). Given that COX-2 can exert pleiotropic effects on cancer development, the role of COX-2 in tumor growth and metastasis has been investigated using COX-2-specific microRNAs (miRNAs/miRs) (2,4).

Over the past years, miRNAs have been of great interest in cancer research due to their prominent role as multiple gene regulators. miRNAs are involved in every phase of malignant, premalignant and inflammatory processes, including cytokine production and immunity activation (7-15). miRNAs are a group of small non-coding RNAs that control mRNA stability and translation, and also regulate transcription (7). Upon complementary binding to the 3'-untralsated region (UTR) of the target mRNA, miRNAs can translationally inhibit and degrade mRNAs, which in turn decreases protein

expression (7). Several studies have reported that a single miRNA can bind to >200 target genes with diverse functions, and up to one third of human mRNAs are regulated by miRNAs (8,9). Currently, several miRNAs have been identified in humans, which are expressed in a tissue-dependent manner (10). Active RNA-induced silencing complex utilizes the guide strands to cleave the target mRNAs, thereby inducing translational repression or degradation (11) and affects various cellular processes (12). miRNAs are important regulators of target genes responsible for cell proliferation, apoptosis, and/or differentiation (13). Several miRNAs, such as miR-101, have been reported to play key roles in cancer development and progression (14). Abnormal expression of miRNAs has been observed in different types of human tumors, and each tumor has a distinct miRNA signature (15). Recent studies suggest that dysregulated miRNA expression may exert detrimental effects on cell survival, particularly in cancer cells (9,13).

The present review discusses the role of COX-2 in cancer by targeting upregulated or downregulated miRNAs to provide insight on the future of molecular cancer therapy.

2. Roles of COX-2 in cancer

In addition to cancer cells, the networks of vascular cells, lymphatic endothelial cells, immune cells, stromal cells, endothelial cells and cancer-associated fibroblasts are alternatives but basic choices for tumor cells to invade and survive (16). Tumor-associated inflammation and aberrantly expressed biomarkers have been demonstrated to play crucial roles in the cancer microenvironment. COX-2 is released by macrophage type II cells, cancer-associated fibroblasts and tumor cells to the cancer microenvironment (16). In a healthy state, COX-2 is involved in the maintenance of cellular homeostasis; however, when homeostasis is perturbed by certain diseases, it may respond to homeostatic dysregulation and lead to the development of cancer (17). Several factors affect COX-2 expression (18), and its overexpression may be explained by the mechanisms of transcriptional and/or post-transcriptional regulation (19). The experimental results of cells and animal models have demonstrated that overexpression of COX-2 can inhibit tumor cell apoptosis, enhance cellular adhesion to achieve an invasive phenotype and promote tumor-induced angiogenesis (20,21). These theories have been confirmed in different types of tumors, including gastric (4), lung (22), pancreas (23), bladder (24), head and neck (25) and breast cancer (26). The present review discusses the effect of overexpressing COX-2 on the regulation of tumor growth and carcinogenesis.

COX-2 upregulates survivin expression to decrease apoptosis of tumor cells (27). The COX-2/PGE2 axis increases the expression levels of the pro-angiogenic proteins, surviving (28) and B-cell lymphoma 2 (29), while suppressing the transcriptional activity of caspase-3 (30). Increasing evidence support the role of COX-2 in promoting tumor cell proliferation (31-35). COX-2 can promote the proliferation of cancer cells by regulating aromatase gene expression, activating neutrophils and inducing stromal cancer-associated fibroblasts (32). Furthermore, upregulated COX-2/PGE2 expression induces the levels of aromatase-catalyzed estrogen and aromatase cytochrome P450 in a paracrine manner, resulting in uncontrolled epithelial cell proliferation (33). COX-2 recruits macrophages and neutrophils to consecutively sustain proliferative signaling in cancer cells (34). Cancer-associated fibroblasts also confer a chronic proliferative signal in cancer cells (35). In addition, alterations in cell adhesion molecules are crucial for the proliferation of cancer cells. Downregulated E-cadherin expression is associated with upregulated COX-2 expression (36). Notably, COX-2 can promote cancer cell metastasis in the liver (37) and brain (38). Epithelial-to-mesenchymal transition (EMT) is an inducer of cancer invasiveness (36), and COX-2 promotes EMT by upregulating miR-526b expression (39). In addition, COX-2 induces β1-integrin and membrane proteases-like matriptase, which are involved in tumor cell invasion (40).

Tumors use multiple mechanisms to avoid recognition and destruction by the immune system (41-43). In addition to tumor development and progression, COX-2 has the potential to alter the phenotype of tumor cells into an immunosuppressed milieu (41), in favor of cancer cell activation (42). In addition, COX-2/PGE2 released from tumor cells into this milieu impairs the immune responses against tumor-associated antigens by impairing cytotoxic T lymphocytes (CTLs) effector functions and causing CTLs exhaustion (43). Macrophage type 2 cells, by releasing COX-2, are involved in tumor angiogenesis, invasion and metastasis (44). In addition, COX-2 can modulate the actions of the immune system by constitutively upregulating indoleamine 2,3-dioxygenase 1 expression in human tumor cells (45). However, COX-2 knockdown significantly suppresses the degree of differentiation in genetically modified mice bearing cutaneous cancer (46) and esophageal cancer (47). Notably, the lack of differentiation is an important hallmark of cancer cells (17). A recent study demonstrated that COX-2 can initiate the formation of aggressive cancer cells from tumor-prone stem cells in mouse skin, and is involved in the occurrence and progression of epithelial cancer cells (17).

Based on previous studies, COX-2 is considered an inducer of different types of cancer, which exerts multiple functions (31-45) (Fig. 2). Thus, it is essential to assess the effects of COX-2 on the tumor microenvironment to implement effective prevention measures for cancer. Notably, an improved understanding of the regulatory mechanisms of COX-2 is required to facilitate the development of novel antitumor therapies, particularly with the concomitant use of other chemotherapeutic agents.

3. Expression of miRNAs in cancer

Cancer is a complex, multifactorial disease characterized by uncontrolled proliferation of abnormal cells, mainly due to oncogenes or tumor suppressor genes (48). Recent studies have highlighted the importance of miRNAs in the development and progression of cancer, and deregulated miRNA expression has been observed in different types of cancer, including hepatocellular carcinoma, gastric cancer and colorectal cancer (9,13). A significant association has been reported between miRNAs and cancer incidence (48). miRNAs bind to their target oncogene or tumor suppressor gene (13). As a target of oncogenes, miR-21 is highly expressed in different types of cancer cells (49,50) and is strongly associated with immune-inflammatory responses (51). Conversely, as a target of tumor suppressor genes, miR-101 inhibits the development

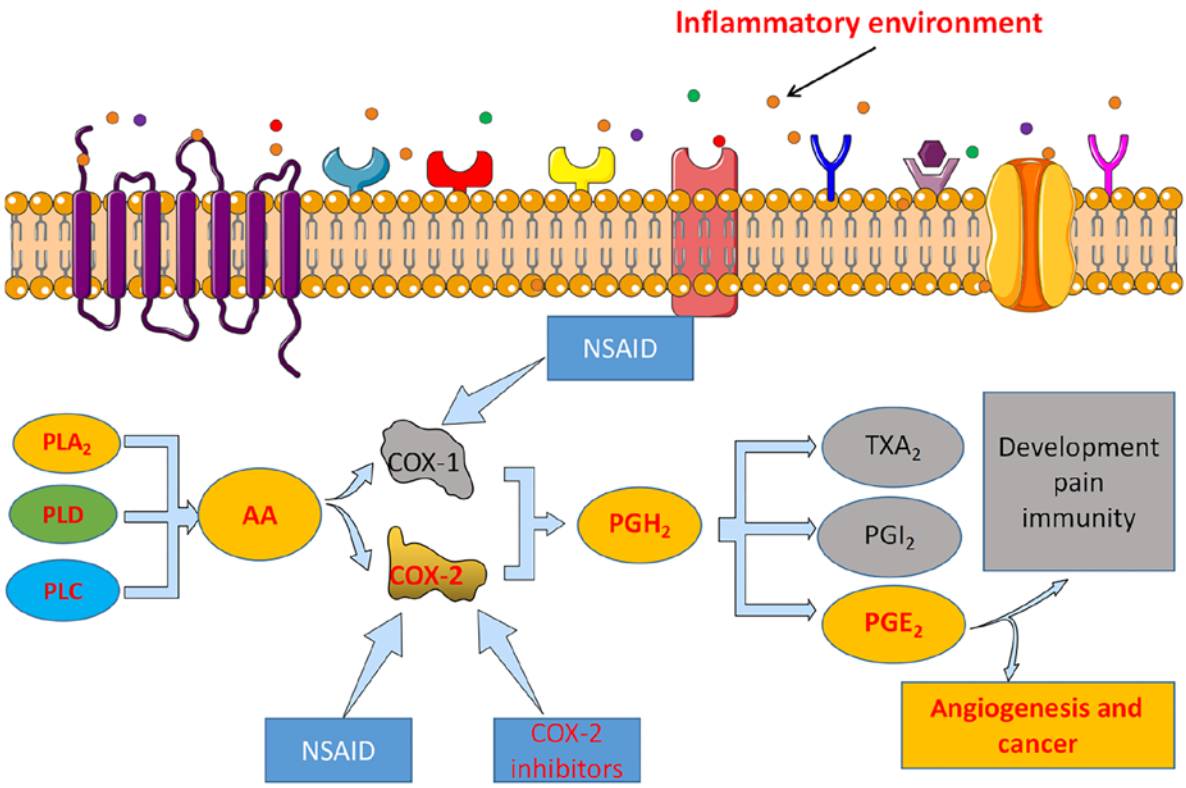

Figure 1. Interaction between COX-2 within the tumor microenvironment. Extracellular environment is exposed to inflammation, COX-2 is overexpressed in the cytoplasm of different types of cells, and converts arachidonic acid into prostaglandins and thromboxanes. PL, phospholipase; AA, arachidonic acid; COX, cyclooxygenase; NSAID, non-steroidal anti-inflammatory drugs; PG, prostaglandin; TXA, thromboxane.

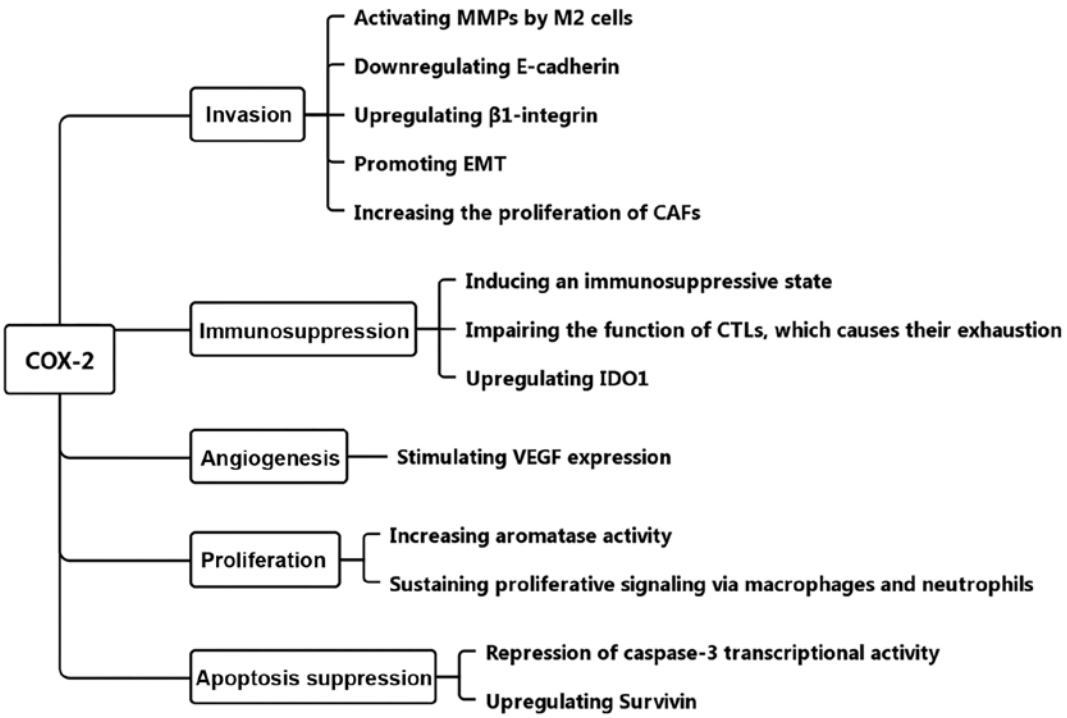

Figure 2. COX-2 acts as a pro-cancer enzyme. COX-2 is a stimulator for different types of cancer, which exerts multiple effects. COX-2, cyclooxygenase-2; MMP, matrix metalloproteinase; M2, macrophage type 2; EMT, epithelial-to-mesenchymal transition; CAF, cancer-associated fibroblast; CTL, cytotoxic T lymphocyte; IDO, indoleamine 2,3-dioxygenase; VEGF, vascular endothelial growth factor.

of cancer and is typically downregulated in tumor cells (52,53). However, some miRNAs are often cancer specific, whereby the miRNA is overexpressed in a specific type of tumor but is suppressed in other types of cancer (54).

Dysregulated expression of miRNAs is associated with increased cancer incidence, which are considered oncomiRs or anti-oncomiRs (48). Downregulated or upregulated expression of miRNAs can regulate carcinogenesis and affect cell proliferation by interfering with cell cycle regulators (48). During tumorigenesis, miRNAs control programmed cell death in cancer cells, which in turn affects the survival of these cells (7). It is speculated that upregulated expression of miRNAs may inhibit different tumor suppressor genes in cancer cells, while downregulated expression of miRNAs may suppress oncogenic transformation in healthy tissues. In addition, epigenetic mechanisms, such as DNA methylation and histone modifications, can modulate the expression of miRNAs (48). Loss of transcription factor, extragenic suppression and gene deletion can also inhibit the expression of tumor suppressive miRNAs in cancer cells (55). However, whether abnormal miRNA expression can induce the development of cancer, or whether it is a consequence of this pathological state remains largely unknown.

From the therapeutic point of view, miRNAs exhibit unique features of multi-target and effective regulation, which holds a great promise for the development of novel antitumor drugs. miRNAs are small and stable, and are not easily degradable by endogenous ribonuclease when extracted from blood and feces. This allows them to be used as promising biomarkers for early diagnosis and prognosis, with potential reflection of treatment outcome (56-58). miRNAs may be therapeutically targeted *in vivo* (56). For example, miR-9 serves as a promising non-invasive marker for patients with breast cancer, which is detectable in blood, urine and bile samples (57,58). A meta-analysis revealed that overexpression of miR-125b predicts poor prognosis in patients with non-small cell lung cancer (NSCLC) and prostate cancer (59), suggesting that miR-125b acts as a potential biomarker for predicting poor clinical outcomes in patients with cancer.

4. Post-transcriptional COX-2 regulation is mediated by miRNAs

Several intracellular pathways are responsible for the increase/decrease in COX-2 protein expression in cancer cells. For example, miR-101 negatively modulates COX-2 protein expression, which in turn decreases the proliferative ability of cancer cells (60). Studies have demonstrated that the COX-2 gene comprises several putative miRNA binding sites, and its expression is associated with miRNA-mediated translational repression (53,60) (Table I). Previous studies have reported that miRNAs can bind to the 3'-UTR of the COX-2 gene, which in turn decreases its expression (60). In addition, miR-101 exerts suppressive effects on different types of cancer cells, and its expression is downregulated in glioblastoma (61), esophageal squamous cell carcinoma (62), lung cancer (63) and gastric cancer (64). Similarly, miR-101 re-expression inhibits angiogenesis and cell proliferation of aggressive endometrial carcinoma via COX-2 activation (53). Given that miR-101 has low or null toxicity (60), it can serve as a novel class of COX-2 selective inhibitor for the treatment and prevention of cancer.

Gastrointestinal tumors. Increasing evidence suggest that COX-2 plays an important role in gastrointestinal tumors (65-72). miRNAs exert either oncogenic or tumor suppressive roles in gastrointestinal tumors by regulating their target genes (66,67). A previous study reported that miR-143 expression is markedly downregulated in gastric cancer (GC), which is positively associated with GC progression (68). Further analysis revealed that miR-143 can bind to the 3'-UTR of COX-2, and COX-2 protein expression was downregulated following transfection with miR-143 (69). Furthermore, the results of a dual-luciferase reporter assay demonstrated that miR-144 directly targets and suppresses COX-2 expression, thus inhibiting the proliferation of GC cells (70). Taken together, these findings suggest that miR-143 and miR-144 may serve as potential diagnostic biomarkers and therapeutic targets for patients with GC. In addition, both *in vivo* and *in vitro* experimental results have demonstrated that miR-30a-3p inhibits the proliferation and migration of *Helicobacter pylori*-infected GC cells by targeting COX-2 mRNA (71). Furthermore, miR-137 suppresses COX-2 expression, and upregulated expression may decrease the aggressive properties of cancer cells (72). Collectively, these findings suggest a strong association between miR-137, miR-143, miR-144, miR-101, miR-30a-3p and COX-2 expression in GC, which can help further understand the role of miRNAs in GC by targeting COX-2.

Colorectal cancer (CRC) is one of the most common human malignancies (73). miR-1297 has been demonstrated to downregulate COX-2 expression, and its expression is markedly lower in CRC tissues compared with normal adjacent tissues (73). miR-1297 directly binds to the 3'-UTR of COX-2, and decreased COX-2 expression has been observed in HCT116 and LOVO cells overexpressing miR-1297 (73). In addition, low miR-216a-3p expression markedly enhances the proliferation of CRC cells. Reverse transcription-quantitative PCR and western blot analyses and dual-luciferase reporter assays have demonstrated that miR-216a-3p regulates COX-2 expression by directly targeting its 3'-UTR (74). Further analysis revealed that miR-216a-3p can suppress COX-2 expression in CRC cells (74). A previous study has demonstrated that miR-155 promotes COX-2 expression during inflammation, whereas its downregulation diminishes carcinogenesis (75). Several miRNAs, such as miR-26, miR-155, miR-101 and miR-1297, are involved in the regulation of COX-2 during carcinogenesis (73-75). Thus, these miRNAs may serve as promising targets for inhibiting COX-2 expression in CRC.

In most cases, chronic liver inflammation and the inflammation-associated microenvironment can promote the initiation and progression of hepatocellular carcinoma (HCC) (76). The COX-2/PGE2 pathway plays an essential role in mediating the pathophysiology of liver diseases, including cirrhosis and HCC (76). A previous study demonstrated that miR-16 directly silences COX-2 expression in HCC cells and indirectly through downregulation of human antigen R (77). In addition, miR-16 suppresses cell proliferation and induces cell apoptosis in HCC cell lines by downregulating COX-2 expression (77). Notably, there is no significant association between miR-101 and COX-2 expression in HCC. This may be due to the tumor tissue-specific expression of miRNAs. The latest report indicates that miR-136 expression is markedly downregulated in HCC cells and tissues, and negatively associated with COX-2 mRNA expression (78). Taken together, these

Table I. COX-2 regulation mediated by miRNAs.

miRNA	Target gene/ pathway/protein	Regulation of COX-2	Types of cancer	Function	(Refs.)
miR-101	COX-2 mRNA	Downregulated	Prostate cancer	Proliferation (-) Growth (-)	(60)
			Endometrial carcinoma	Angiogenesis (-)	(53)
miR-143-5p	COX-2 mRNA	Downregulated	GC	Growth (-)	(69)
miR-144	COX-2 mRNA	Downregulated		Proliferation (-) Apoptosis (+)	(70)
miR-30a-5p	COX-2 mRNA	Downregulated		Growth (-) Migration (-)	(71)
miR-137	COX-2 mRNA	Downregulated		Proliferation (-) Migration (-)	(72)
miR-1297	COX-2 mRNA	Downregulated	CRC	Growth (-) Migration (-) Invasion (-)	(73)
miR-216a-3p	COX-2 mRNA	Downregulated		Growth (-) Proliferation (-)	(74)
miR16	COX-2 mRNA HUR	Downregulated	HCC	Proliferation (-) Apoptosis (+)	(77)
miR-136	COX-2 mRNA	Downregulated		Proliferation (-) Migration (-) Invasion (-)	(78)
miR-146a	COX-2	Downregulated	Lung cancer	-	(80)
miR-26b	COX-2 mRNA	Downregulated		Proliferation (-) Migration (-) Invasion (-)	(81)
miR-144-3p	WT1D	Downregulated		Proliferation (-)	(83)
miR-221/222	PTEN	Upregulated	Breast cancer	Proliferation (+) Migration (+) Invasion (+)	(84)
miR-27a	ZBTB10-protein pathway	Upregulated	Ovarian epithelial cancer	Angiogenesis (+)	(87)
miR-128	COX-2 mRNA	Downregulated	Glioma	Proliferation (-) Invasion (-)	(88)
miR-26b	COX-2 mRNA	Downregulated		Migration (-) Invasion (-)	(89)
miR-137	COX-2 mRNA	Downregulated	RB	Proliferation (-) Migration (-)	(91)
miR-143	COX-2 mRNA	Downregulated	Bladder cancer	Proliferation (-) Migration (-)	(92)
miR-203	COX-2 mRNA	Downregulated	Laryngeal carcinoma	Proliferation (-)	(93)

COX-2, cyclooxygenase-2; miRNA/miR, microRNA; HUR, Human Antigen R; WT1, Wilms' tumor 1; PTEN, phosphatase and tensin homolog; GC, gastric cancer; CRC, colorectal cancer; HCC, hepatocellular carcinoma; RB, retinoblastoma; -, unknown; (-), inhibition; (+), promotion.

results suggest that miR-136 plays a key role in regulating HCC cell proliferation and metastasis by targeting COX-2.

Lung cancer. Chronic inflammation serves a key role in the pathogenesis of lung cancer (79). It has been reported that overexpression of COX-2 promotes the initiation and progression of NSCLC and other types of lung tumors (79). A previous study has demonstrated that miR-146a negatively regulates the production of cytokines and chemokines from lung cancer cells, and downregulates COX-2 expression by destabilizing its mRNA (80). In addition, miR-26b can inhibit the proliferation, migration and invasion of lung cancer cells by directly targeting COX-2 (81,82). When one of the signaling pathways is truncated or suppressed, the others may enrich their functions to maintain a stable molecular dynamic. The latest research has demonstrated that COX-2 protein

Table II. Effect of COX-2 selective inhibitors in suppressing cancer by regulating miRNA expression.

COX-2 selective inhibitor	Model	Target miRNA	Regulation of miRNA	Effect	(Refs.)
Celecoxib	Bladder cancer cells	miR-145	Upregulated	Migration (-) Invasion (-)	(98)
	Mouse	miR-150	Upregulated	Tumor-associated inflammation (-)	(101)
	Gastric cancer cells	miR-29c	Upregulated	Apoptosis (+)	(102)
	Breast cancer cells	miR-256b miR-655	Downregulated	Migration (-) Invasion (-)	(104)
Parecoxib	Glioblastoma cells	miR-29c	Upregulated	Proliferation (-) Migration (-) Invasion (-)	(108)

miRNA/miR, microRNA; COX-2, cyclooxygenase-2; (-), inhibition; (+), promotion.

expression markedly increases following suppression of the IL-1β/miR-144-3p/WT1D signaling pathway via transfection with miR-144-3p mimic (83).

Gynecological cancer types. Aberrant angiogenesis is associated with cancer progression and metastasis, and is mediated by miR-101. Upregulated miR-101 expression can slow tumor growth, the effects of which are reversed following downregulation of miR-101 expression (53). A previous study reported that miR-101 regulates abnormal angiogenesis in endometrial cancer via COX-2 (53). COX-2 expression has been observed in nearly 40% of patients with primary breast cancer, at both pre-invasive and invasive stages of the disease. In addition, COX-2 expression is significantly associated with breast cancer progression (84,85). Through downregulation of phosphatase and tensin homolog deleted on chromosome 10, miR-221/222 induces AKT phosphorylation and subsequently activates the COX-2 gene, which increases COX-2 expression in cancer cells (84). Thus, miR-221/222 induces tumor growth and maintains breast cancer stem-like characteristics by upregulating COX-2 expression (84). Notably, overexpression of COX-2 upregulates the expression levels of miR-526b and miR-655 in breast cancer cell lines (85). Furthermore, miR-526b expression is upregulated via the COX-2 and EP4 pathways in high-grade primary breast tumors (39). According to the gonadotropin theory, ovarian cancer commonly occurs in postmenopausal women, mainly due to the high levels of follicle-stimulating hormone and luteinizing hormone resulting from the negative feedback of estrogen (86). Follicle-stimulating hormone increases miR-27a expression, which in turn increases the expression levels of COX-2, survivin and vascular endothelial growth factor via the ZBTB10-specificity protein pathway (87).

Other types of cancer. Glioma is the most common type of brain tumor. Downregulated miR-128/26b expression and upregulated COX-2 expression have been detected in glioma tissues (88,89). Transfection with miR-128 and miR-26b mimics decreases the luciferase activity associated with the 3'-UTR of COX-2, and miR-128 notably decreases the stability of COX-2 mRNA. Conversely, transfection with miR-128 inhibitor markedly increases COX-2 mRNA expression, as well as the protein expression levels of ki67 and MMP9, while promoting the growth of glioma tumors (88,89). The direct association between COX-2 and miR-128/26b has been verified by publicly available data (88,89). Retinoblastoma is the most common type of eye cancer, which accounts for high mortality rates in young children (90). Bioinformatic analysis has demonstrated that miR-137 negatively modulates COX-2 expression and PGE2 production in retinoblastoma cells (91). Targeted COX-2 knockdown inhibits the invasion and increases the proliferation of retinoblastoma cells, while inhibiting the synthesis of PGE2 (91). Bladder cancer is a common malignancy of the urinary tract and the fifth most diagnosed cancer type in Western countries (92). The latest report suggests that miR-143 negatively regulates COX-2 expression in bladder carcinoma T24 cells (93). In addition, it has been reported that the role of miR-143 in tumor growth and migration is mainly due to its involvement in the COX-2 pathway (93). Laryngeal cancer is the most common type of cancer in the head and neck area (94). A previous study revealed that miR-203 expression was notably downregulated in laryngeal squamous cell carcinoma tissues (94). Collectively, this finding suggest that miR-203 acts as a tumor suppressor in laryngeal squamous cell carcinoma, partially by regulating COX-2 expression.

5. Upregulated expression of miRNAs by COX-2 selective inhibitor

Currently, there are three methods used to inhibit COX-2 expression, post-transcriptional control, inhibitory transcription factors and COX-2 inhibitors. Celecoxib was the first COX-2 inhibitor approved by the FDA. This drug has been used for over 20 years as an anti-inflammatory, analgesic and antipyretic agent (95). Given the role of inflammation in carcinogenesis, celecoxib has gained a novel opportunity for its application (95). The antitumor and chemoprevention effects of celecoxib on colon carcinogenesis were first demonstrated in rats (96), and later in different *in vivo* experimental models (97).

Celecoxib inhibits the migration, invasion and EMT of bladder cancer cells, partially by regulating the miR-145/TGFBR2/Smad3 pathway (98). In addition, the concomitant use of celecoxib and miR-145 mimic notably

inhibits the migration and invasion of bladder cancer cells (98). The results of other experiments also suggest that celecoxib increases miR-146a expression in high-risk human papillomavirus (HPV) (99). Another miRNA investigated in this experiment was miR-150. miR-150 is positively mediated by NF-kB (99), a common transcription factor expressed in HPV-related cancer types (100). In this experiment, celecoxib also downregulated the NF-kB pathway via miR-150. Taken together, these findings suggest that the antitumor effect of celecoxib against HPV-induced lesions is partly mediated by upregulating miR-146a and miR-150 expression (101). Furthermore, miRNA microarray analysis has demonstrated that miR-29c expression is markedly higher in GC tissues compared with normal gastric mucosa, and celecoxib can promote miR-29c expression in GC cells (102). In addition, Mcl-1 is a target of miR-29, which encodes Bcl-2-like antiapoptotic proteins (103). A previous study reported that miR-29 regulates cell apoptosis by targeting Mcl-1 (103). Celecoxib increases miR-29c expression and inhibits its target oncogene, Mcl-1, resulting in the apoptosis of GC cells (102). In addition, miR526b/miR655 expression is significantly higher in breast tumors, and the interplay between COX-2 and hypoxia has been demonstrated to promote tumor aggression (104). Previous studies have demonstrated that celecoxib regulates hypoxia-enhanced function in breast cancer cells by downregulating miR526b/miR655 expression (104,105).

Parecoxib is another important selective COX-2 inhibitor, with high postoperative pain control and less side effects (106). Treatment with parecoxib has exhibited a promising anticancer role in different types of human cancer (106,107). The latest research suggests that parecoxib inhibits the proliferation, migration and invasion of glioblastoma cells by upregulating miR-29c expression (108).

Despite the extensive use of COX-2 inhibitors in the treatment of cancer, their application is limited due to the associated adverse events. The most reported side effect of celecoxib is the increased frequency of cardiovascular disorders following its long-term use (109). Considering that post-transcriptional control may exert a more appreciable effect, it has attracted great interest. Although the expression patterns of miRNAs are not yet fully understood in human cells, their functional roles represent one of the most exciting topics for elucidating the molecular mechanisms underlying the therapeutic effects of COX-2 inhibitors (Table II).

6. Conclusions

Based on the current literature regarding miRNA-mediated COX-2 regulation, a novel COX-2 selective inhibitor may be developed with miRNAs. It was suggested that anti-COX-2 miRNAs may serve as novel targets for the treatment of cancer. In addition, small interfering (si)RNAs, instead of miRNAs, may also be used to inhibit COX-2 expression via similar molecular mechanisms (97). However, off-target effects may exist due to mRNA destabilization by identical siRNA sequences, thus suppressing other mRNAs with partial complementarity (96). Taken together, the results discussed here suggest that miRNA-based strategies hold great promise for inhibiting COX-2 expression, and thus may be used to treat cancer types overexpressing COX-2.

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Authors' contributions

WGH and BYW conceived the present review. ZXG performed the literature review and revised the manuscript for important intellectual content. NL prepared the figures. SKL, WJL and QZ interpreted the table data. ZXG and BYW confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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