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REVIEW

COX-2 in lung cancer: Mechanisms, development, and targeted therapies

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Abstract

Lung cancer (LC) is the leading cause of cancer-related death worldwide, with non-small cell lung cancer (NSCLC) comprising 85% of all cases. COX-2, an enzyme induced significantly under stress conditions, catalyzes the conversion of free arachidonic acid into prostaglandins. It exhibits high expression in various tumors and is closely linked to LC progression. COX-2 functions as a pivotal driver in cancer pathogenesis by promoting prostaglandin E2 synthesis and facilitating tumor cell occurrence and development. Furthermore, COX-2 holds potential as a predictive marker for early-stage NSCLC, guiding targeted therapy in patients with early COX-2 overexpression. Additionally, combining COX-2 inhibitors with diverse treatment modalities enhances tumor therapeutic efficacy, minimizes adverse effects on healthy tissues, and improves overall patient survival rates posttreatment. In conclusion, combined therapy targeting COX-2 presents a promising novel strategy for NSCLC treatment, offering avenues for improving prognosis and effective tumor treatment. This review provides novel insights and ideas for developing new treatment strategies to improve the prognosis of NSCLC.

KEYWORDS

COX-2, lung cancer, PGE2, targeted therapy, tumor development

Key points

- COX-2 cross-interacts with a variety of signaling molecules, participating in multiple signaling pathways and in the development of tumors.
- Targeted COX-2 therapy can effectively inhibit the occurrence and development of non-small cell lung cancer.
- Potential future drug development, limitations, and prospects for targeted COX-2 therapy.

1 | INTRODUCTION

Lung cancer (LC) continues to be the foremost cause of cancer-related deaths both in the United States and globally.[1–3] It ranks as the second most common cancer type, following female breast cancer, with an estimated 20,000 new cases and 17,600 deaths per year.[2,4] LC can be classified into main types based on the cells of origin: small-cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC).[2] NSCLC constitutes approximately 85% of all LC cases.[2] The treatment options for NSCLC are diverse, such as surgery, chemotherapy, radiotherapy, and molecular targeted therapy (e.g., epidermal growth factor receptor [EGFR] or anaplastic lymphoma kinase [ALK] inhibitors and immunotherapy).[2,5] Despite these interventions, nearly 70% of diagnosed patients were

Xueqi Liu and Junli Zhang contributed equally to this study.

found to have advanced unresectable NSCLC, resulting in a discouraging 15% 5-year survival rate.[3,5,6] Therefore, gaining a comprehensive understanding of the pathogenesis of NSCLC holds paramount importance in developing innovative drugs, strategies, and therapies that can enhance treatment efficacy, minimize adverse effects on healthy tissues, and improve the overall patient survival rate posttreatment.

Regarding preclinical studies, studies demonstrated the pivotal role of cyclooxygenase-2 (COX-2) at the tumor level and its association with various pathological conditions.[6–9] This target molecule is involved in tumor proliferation, invasion, angiogenesis, and resistance to apoptosis.[6–9] The evidence continues to accumulate, underscoring the significance of COX-2 in NSCLC progression.[10,11] Therefore, a comprehensive understanding of the underlying molecular mechanisms can provide valuable predictive biomarkers and therapeutic targets in the treatment of NSCLC. In this review, we aimed to outline the molecular mechanisms, signaling pathways, development, and therapeutic strategies associated with COX-2. For this aggressive form of cancer, we intend to provide a potential COX-2-related framework that can be utilized for diagnostic, prognostic, and therapeutic.

2 | COX-2 AND TUMORIGENESIS

In the lung, tumorigenesis is influenced by a variety of nonmodifiable and modifiable factors of risk that lead to the shaping of a favorable tumor microenvironment.[5] Nonmodifiable risk factors encompass age, gender, race, and family history, while modifiable factors of risk include tobacco and cannabis smoking, asbestos exposure, radon exposure, air pollution, arsenic exposure, infections, and chronic obstructive pulmonary disease (COPD).[5] Both modifiable and nonmodifiable risk factors found in LC may have an impact on the expression of multiple molecular targets, including COX-2, EGFR, ALK, ROS1, BRAF, neurotrophic tropomyosin receptor tyrosine kinases (NTRK), MET, and RET, as well as emerging targets HER2, KRAS, and NRG (Figure 1).[2] The activation and mutation of specific molecular targets within the lung can lead to cell proliferation, antiapoptosis, invasion, metastasis, and angiogenesis, thereby driving the development of LC.[2,12] For example, MET protein overexpression was observed during 28.0%–33.5% of NSCLC patients, while COX-2 was found to be positively expressed in 71.6% of lung atypical adenomalike hyperplasia tissues.[13,14] These molecular targets were closely associated with tumorigenesis, with COX-2, in particular, having a strong relationship with the tumor microenvironment.[14] Additionally, certain cells within the tumor microenvironment, such as fibroblasts and type 2 macrophages, released COX-2-related prostaglandin E2 (PGE2), contributing to the formation of an oncogenic microenvironment.[11] Conversely, a pivotal role in creating an oncogenic milieu was played by the tumor microenvironment. Specifically, tumor cells within the microenvironment produce PGE2, which polarized tumor-associated macrophages (TAMs) into M2-like TAMs.[15] Furthermore, stromal cells within the tumor microenvironment made a contribution to the generation of COX-2 and PGE2. These factors recruited stromal fibroblasts and contribute to tumor stroma formation by activating the CXCL12-CXCR4 axis.[16] In LC cells, the production of PGE2 was promoted through the activation of the p38 pathway by Fas signaling, further supporting the recruitment of myeloid-derived suppressor cells (MDSC) to the tumor microenvironment.[17] Moreover, EGFR signaling pathway activation in LC cells created an immunosuppressive tumor microenvironment by recruiting tumor-associated macrophages (TAMs) and regulatory T cells (Tregs).[18] The interaction between EGFR and COX-2 was also significant in LC cells, as the activation of EGFR signaling enhanced mitogen-activated protein kinase (MAPK) activity, subsequently triggering activator protein-1 (AP-1)-mediated increased in COX-2 gene expression and generation of PGE2.[19] This PGE2, in turn, could activate EGFR, thereby stimulating cell proliferation.[19] These aforementioned molecular targets actively contributed to tumorigenesis and played critical roles in tumor progression, with particular emphasis on COX-2, which significantly supported the tumor microenvironment and EGFR interactions involving multiple signaling pathways (Figure 1).[19] Understanding the intricate relationships among these molecules is essential for unraveling the complexities of the tumor microenvironment and developing targeted therapeutic interventions.

3 | SIGNALING PATHWAYS OF COX-2 IN TUMORS

Prostaglandin synthase exhibits two distinct activities in the lung. First, its cyclooxygenase activity converts free arachidonic acid (AA) into preprostaglandin G2 (PGG2), and second, its hydroperoxidase activity converts PGG2 into PGH2.[20] The isomerization reaction of PGH2 to PGE2 is mediated by microsomal prostaglandin synthase-1 (MPGES-1).[21] PGE2, being a downstream product of COX-2, plays a vital role in cancer cell growth and survival, contributing to cancer cell proliferation, apoptosis resistance, restricted migration and invasion, angiogenesis, recruitment of myeloid suppressor cells to evade T-cell attack and chronic inflammation (Figure 2).[11,21] Cyclooxygenase is involved in various cellular events, including inflammation, fever, thrombosis, neurodegenerative diseases, and neoplastic diseases.[22] The COX enzyme family comprises three isomers: COX-1, COX-2, and COX-3.[20,23,24] COX-1 was constitutively expressed in the majority of cells and tissues, while COX-3 was primarily found in the central nervous system and showed minimal induction by acute inflammatory stimuli.[23–25] COX-2, an inducible enzyme, is minimally expressed in normal cells, except for the

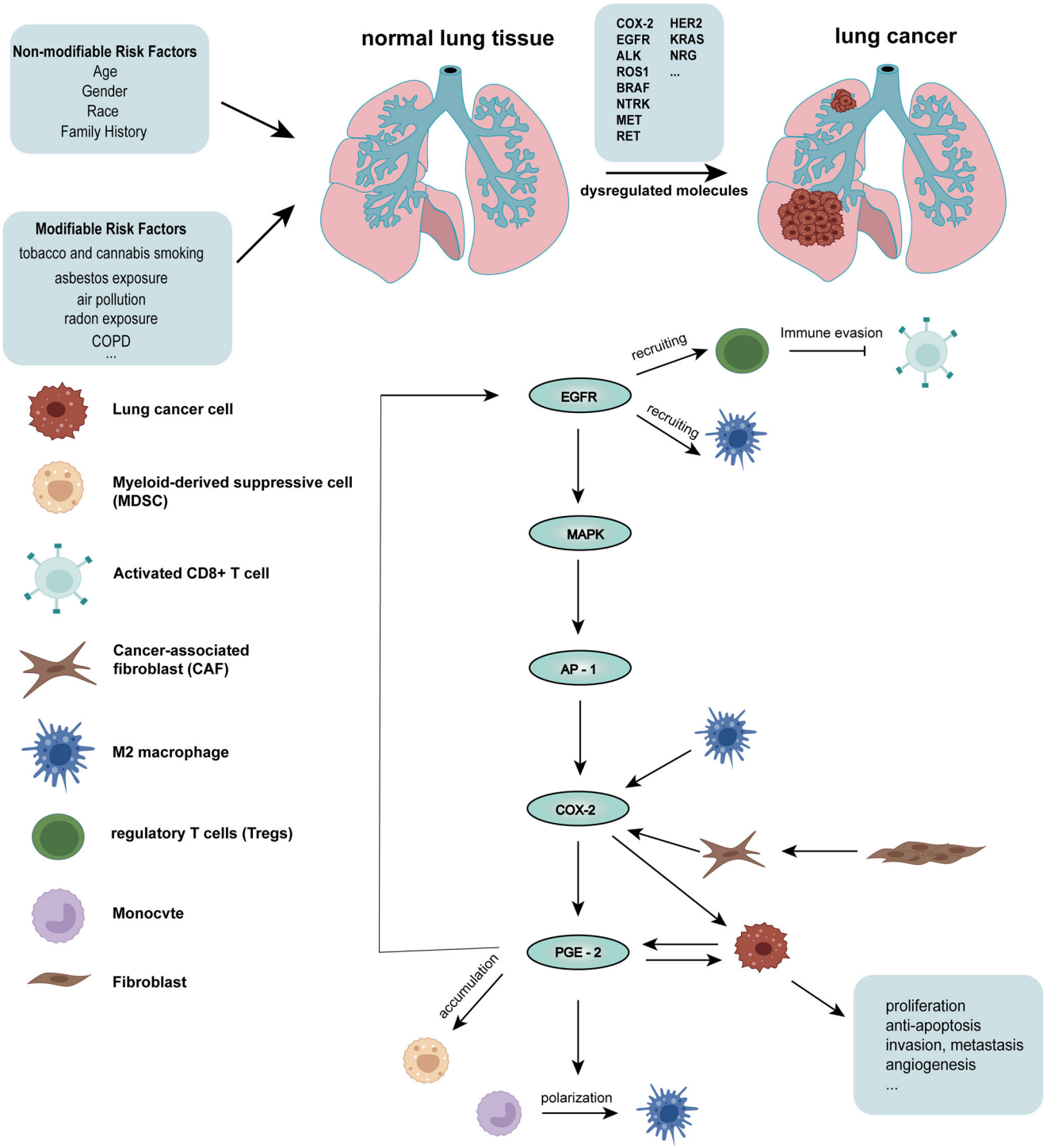

FIGURE 1 Cyclooxygenase-2 functions in the tumor microenvironment. COPD, chronic obstructive pulmonary disease.

stomach, kidney, female reproductive system, and central nervous system.[11] However, under conditions of cellular damage or exposure to various stressors such as endotoxins, mitogens, and cytokines, COX-2 can be significantly upregulated.[11] COX-2 expression was regulated by NF-κB, MAPK, and PI3K/Akt signaling pathways.[26] HER2 enhanced COX-2 expression through the MEK/ERK signaling pathway, while COX-2 activated the PI3K/AKT pathway, it facilitated the proliferation and invasion of NSCLC cells.[27] Transforming growth factor-β1 (TGF-β1)-induced downregulation of COX-2 expression can be blocked by TβRI inhibitors and Smad3-specific inhibitors, indicating the involvement of the TGF/Smad signaling pathway in COX-2 expression.[28] Furthermore, the persistent activation of the Wnt/β-catenin signaling pathway was associated with excessive activation of cold-inducible RNA binding protein

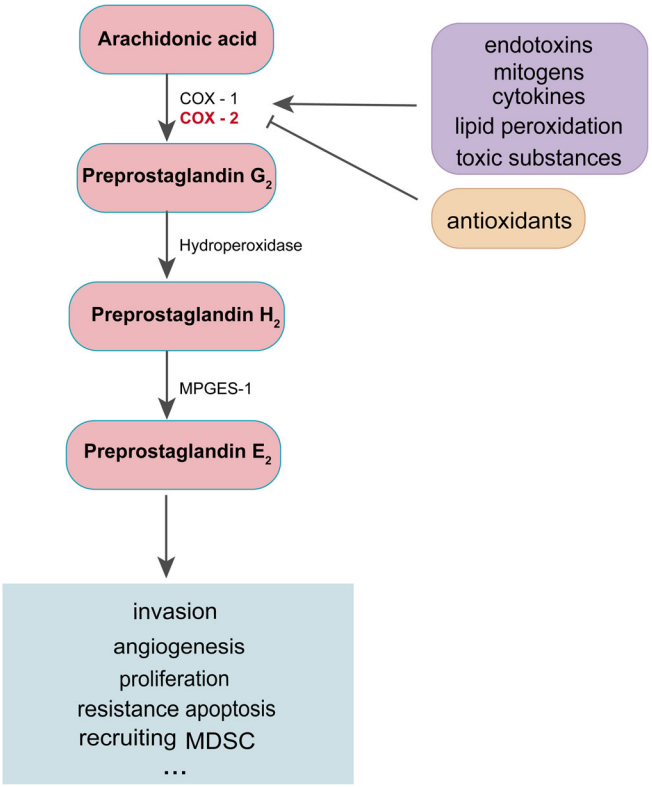

FIGURE 2 Factors affecting the expression of cyclooxygenase-2 (COX-2) and the synthesis pathway of COX-2. MDSC, myeloid-derived suppressor cells.

(CIRP), subsequently regulating the expression of important target genes, including COX-2 (Figure 3).[29] Recent studies indicated that COX-2 serves as a widely used biomarker for iron death in vivo or in vitro, although its role may vary depending on cell type and environmental conditions. Its upregulation was regulated by lipid peroxidation, while the effects of antioxidants and toxic substances could either decrease or increase its expression.[30] Furthermore, COX-2 is overexpressed in diverse cancer subtypes, including non-small cell lung, breast, pancreatic, and colon cancers, and it is primarily involved in promoting tumorigenesis and progression through its mediation of PGE2 production.[11] PGE2 activated protein kinase A (PKA), enhanced cAMP response element-binding protein (CREB) binding to the COX-2 promoter, and stimulated COX-2 expression.[31] Additionally, PGE2 exerted its tumorigenic and progressive effects through four G protein-coupled receptors (GPCRs) (EP1, EP2, EP3, and EP4).[32] In NSCLC cells, all four GPCRs participated in PGE2-induced COX-2 expression.[31] For instance, PGE2 activation of the EP1 receptor triggered the MAPK/ERK pathway via protein kinase C (PKC) activation, leading to ERK phosphorylation.[32] Similarly, PGE2 binding to the EP4 receptor in NSCLC cells mediated JUK, PI3K, and PKA signal activation, resulting in increased α7nAChR expression and enhanced cell growth.[33] In the LC microenvironment, PGE2 potentially regulated programmed cell death protein-1 (PD-1) levels in infiltrating $CD8^+$ T cellsby binding to EP2/EP4 receptors. Elevated expression of PGE2 may inhibit immune cell-mediated attack on tumor cells, thereby establishing immune tolerance to tumors.[34] Through EP2 and EP4 receptors, PGE2 activated the GSK3β/β-catenin pathway, resulting in the transcriptional upregulation of oncogenes, including c-myc, cyclin D1, and vascular endothelial growth factor (VEGF), ultimately promoting tumor cell growth and migration.[35] Similarly, in colonic tumor cells, PGE2 bound to the EP2 receptor to activate the Gs-axin-beta-catenin signaling axis, stimulating cell proliferation.[36] Furthermore, the activation of the PI3K/Akt signaling pathway occurred when PGE2 bound to the EP4 receptor, resulting in enhanced cell proliferation.[36] In MDSC, COX-2/EP2/EP4 was implicated in the regulation of CXCR4 expression, influencing its responsiveness to CXCL12 or ovarian ascites, which promoted tumor escape, growth, and the inhibition of immune response (Figure 4).[36] Previous studies demonstrated an intricate relationship between EGFR and COX-2 in LC, affecting crucial aspects such as tumor growth, angiogenesis, and metastasis.[29] Activation of EGFR signaling induced increased activity of the MAPK, leading to AP-1-mediated transcriptional upregulation of COX-2 and subsequent production of PGE2.[19,31] Remarkably, PGE2 could further stimulate cell proliferation by transactivating EGFR.[19,31] Additionally, EGFR signaling activation could trigger the PI3K/Akt pathway, which in turn activates the downstream molecular protein NF-κB, either directly or indirectly.[37,38] Consequently, this activation led to overexpression of COX-2.[39,40] Interestingly, PGE2, a product of COX-2, exhibited a surprising inhibitory effect on NF-κB activity through a negative feedback loop.[40] In the context of cancer, this bidirectional positive feedback loop between EGFR and COX-2 could significantly amplify the process of carcinogenesis (Figure 4).[19,41] Moreover, COX-2 regulated several downstream effectors, such as IL1β, IL6, TNF-α, CXCL5, EZR, FN1, and CCND1, to maintain tumor progression.[10,42]

In conclusion, COX-2 plays a critical mediating function in tumorigenesis and cancer progression. It can be activated by tumor effector molecules, and in turn, it activates downstream effectors. Additionally, COX-2 synergistically interacts with other target molecules to promote cancer development and progression.

4 | MOLECULAR MECHANISM OF COX-2 IN LC

COX-2 overexpression was linked to various oncogenic processes, including cell proliferation, apoptosis down-regulation, angiogenesis, metastasis, and drug resistance.[7,43] Epithelial–mesenchymal transition (EMT) played a critical role in cancer metastasis and drug resistance, facilitated by transcription factors like Twist, Snail, Slug, and ZEB1.[5,44] In lung carcinogenesis, COX-2 was pivotal in maintaining EMT-induced changes, and

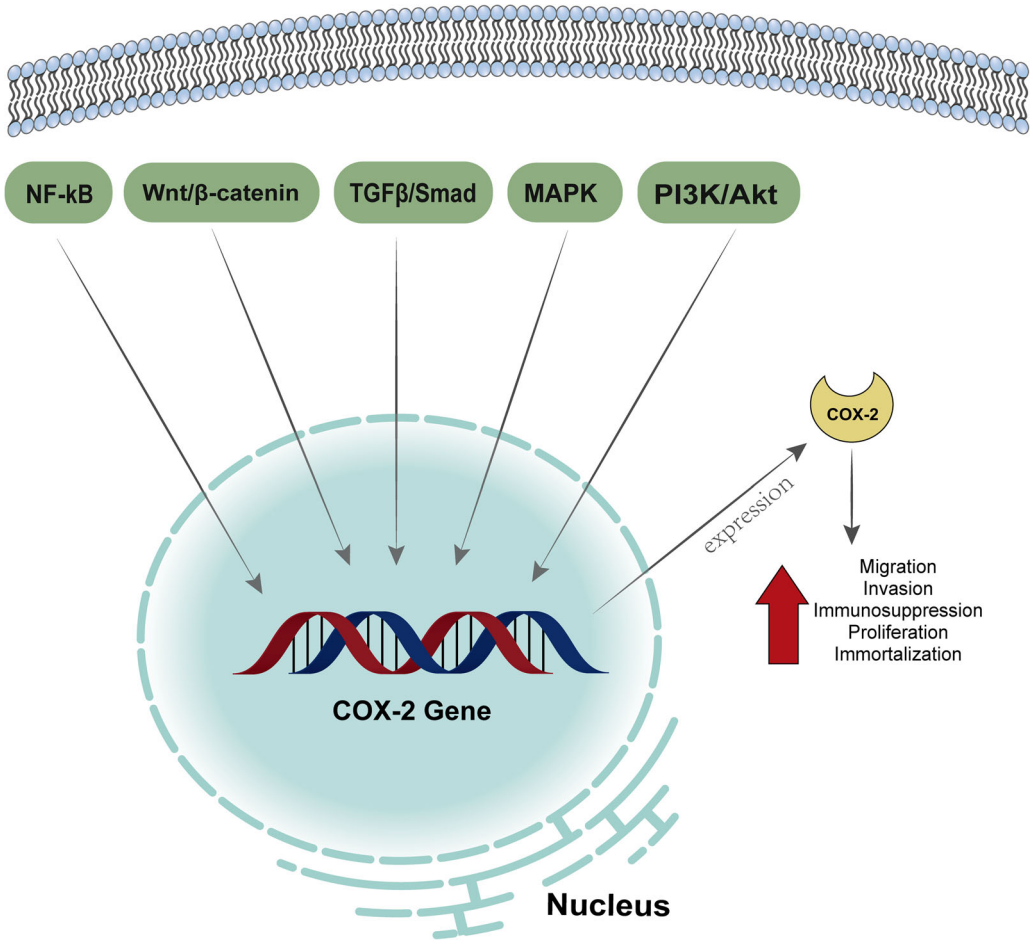

FIGURE 3 Upstream signaling pathway mediating cyclooxygenase-2 expression. MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-κB; PI3K, phosphoinositide 3-kinases; TGF, transforming growth factor.

its inhibition had the potential to reverse these changes, inhibiting LC progression and metastasis.[45] However, it was observed that EMT can be induced by celecoxib, a COX-2 inhibitor, via the MEK-ERK pathway, increasing the risk of metastasis and chemoresistance.[46]

Tumor angiogenesis, facilitated by COX-2 overexpression, was strongly associated with the proangiogenic factor VEGF.[47] Interestingly, VEGF upregulation in LC was believed to be dependent on downstream metabolites of COX-2 rather than COX-2 protein itself.[8] Elevated COX-2 messenger RNA expression enhanced angiogenesis, cell migration, and invasion by promoting thromboxane A2 (TXA2) synthesis, activating the PI3K/Akt pathway.[8,9] Moreover, COX-2 maintained high levels of VEGF in NSCLC tissues through the PKA pathway, contributing to tumor-induced angiogenesis.[8] Additionally, COX-2 and the resulting substance, PGE2, upregulated CXCR4 expression in microvascular endothelial cells, enhancing the proangiogenic effects of bFGF and VEGF.[16] Notably, naproxen inhibited CXCR4 expression through COX-2/PGE2 inhibition, suppressing lung tumor growth.[48]

Concomitant dysregulation of c-MET and COX-2 significantly promoted LC proliferation, survival, invasion, metastasis, and resistance.[10] COX-2, acting as a downstream mediator of the HGF/c-MET signaling pathway, regulated c-MET and phosphorylates its Y74 site, as well as activating T-lymphokine-activated killer cell-derived protein kinases (TOPK).[10] In NSCLC, HGF increased transcription and expression of the COX-2 gene by activating Erk1/2 and p38 pathways, ultimately leading to the activation of transcription factors such as AP-1, C/EBP, and CREB.[49] Furthermore, COX-2 overexpression in NSCLC promoted IGF-IR autophosphorylation, activated the Class IA PI3K signaling pathway, reduced IGFBP-3 expression, and enhanced IGF-I and IGF-II activity, promoting cell mitosis and survival.[50] Surprisingly, COX-2 could directly catalyze DGLA to form the anticancer byproduct 8-HOA, inducing apoptosis through downregulation of the YAP1/TAZ pathway and activation of the p53-dependent endogenous apoptotic pathway, while enhancing LC sensitivity to chemotherapy.[51] Additionally, COX-2 contributed to radioresistance in LC cells by activating the JNK/Sp1 signaling pathway.[52] Moreover, COX-2 promoted EMT, adhesion, and metastasis of Lewis Lung carcinoma (LLC) cells by upregulating ELMO3 protein expression (Figure 5).[51] In a coculture environment comprising neutrophils and LC cells, PGE2

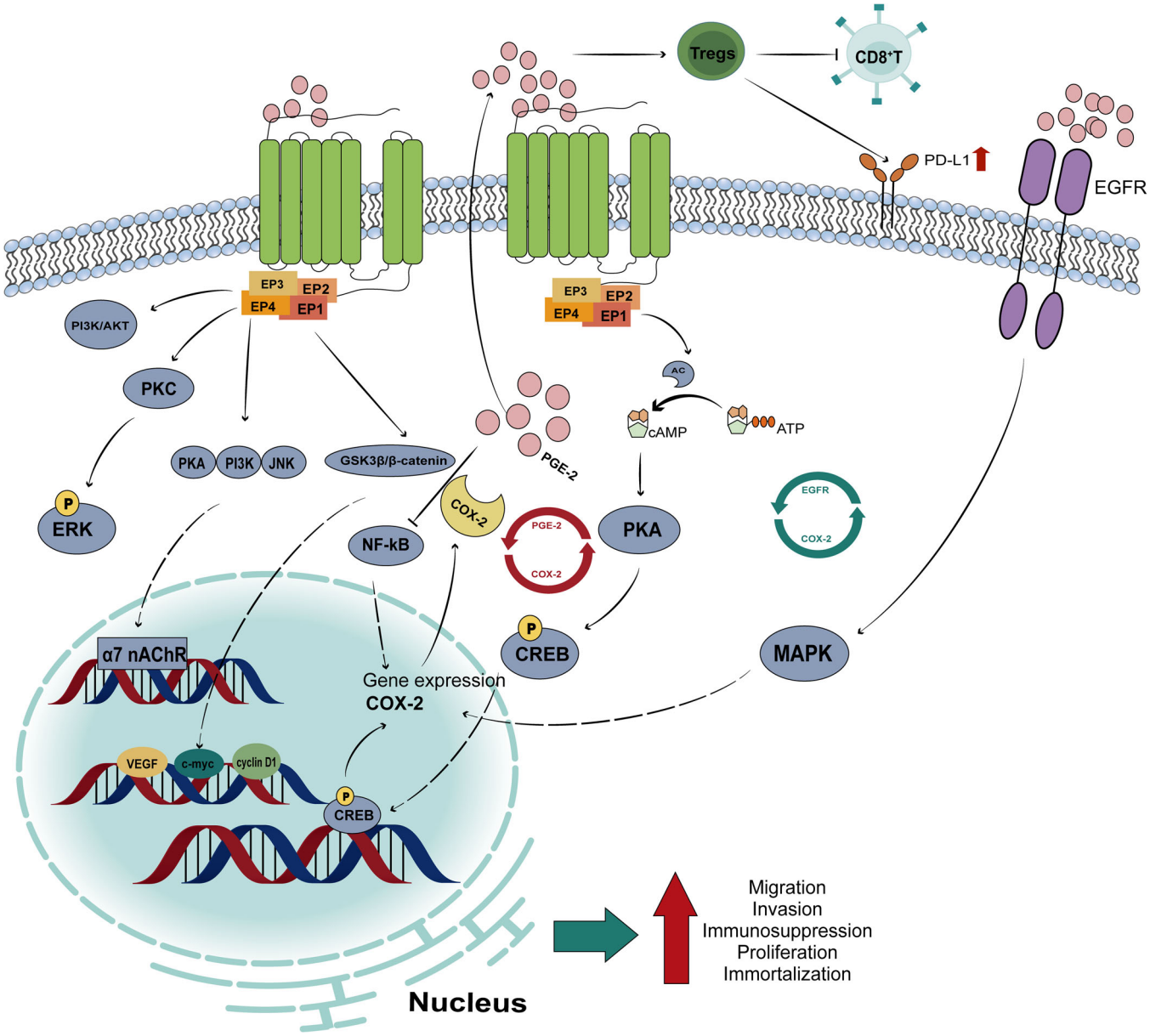

FIGURE 4 The role of the cyclooxygenase-2 and its downstream product prostaglandin E2 signaling pathway in tumorigenesis and cancer development. CREB, cAMP response element-binding protein; EGFR, estimated glomerular filtration rate; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-κB; PI3K, phosphoinositide 3-kinases; PKA, protein kinase A.

produced by the synergistic action of elastase and COX-2 released from neutrophils played a crucial role in facilitating lung tumor cell proliferation.[53]

5 | THE FUNCTION OF COX-2 IN THE PROGRESSION OF NSCLC

Several studies explored the presence of active COX-2 in NSCLC. Initially, Huang et al.[54] assessed the COX-2 expression in NSCLC using immunohistochemical assessment of tumor specimens and adjacent affected tissues. In the evaluation of 15 tumor specimens, which comprised eight adenocarcinomas and seven squamous cell carcinomas, all showed positive cytoplasmic staining for COX-2. Subsequently, Wolff et al.[55] presented further findings on the expression of COX-2 in the lungs from 21 adenocarcinoma and 11 squamous carcinoma patients using immunohistochemistry. COX-2 expression was observed in lung tissue from 19 adenocarcinomas and all squamous cell carcinomas. Particularly, highly differentiated adenocarcinomas exhibited a significantly higher COX-2 positive expression rate compared to poorly differentiated adenocarcinomas, squamous carcinomas, and small cell lung carcinomas, with small cell lung carcinomas showing the weakest staining intensity.[55]

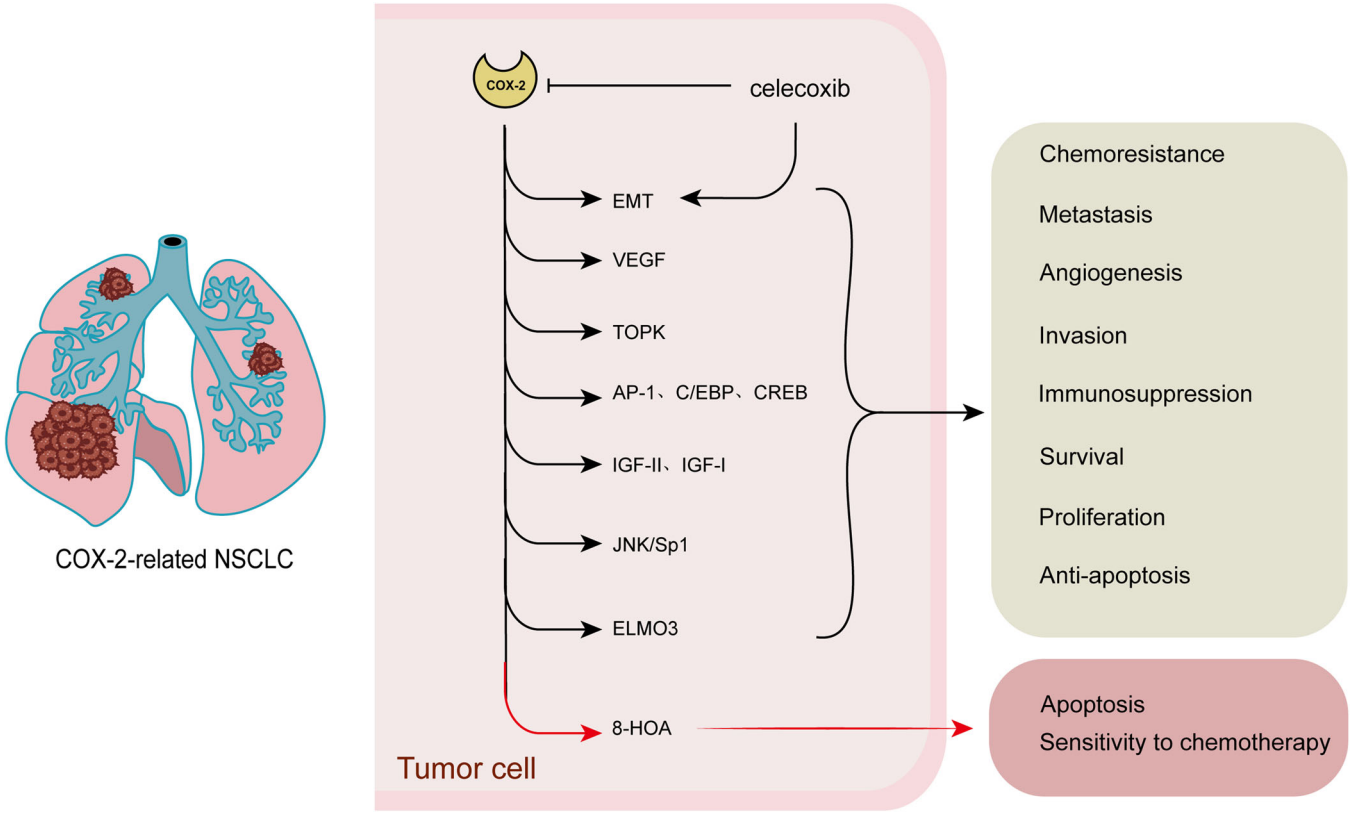

FIGURE 5 Cyclooxygenase-2 signaling pathway in non-small cell lung cancer occurrence and development. 8-HOA, 8-hydroxyoctanoic acid; EMT, epithelial–mesenchymal transition; IGF-I, insulin-like growth factor 1 NSCLC, non-small cell lung cancer; TOPK, T-lymphokine-activated killer cell-derived protein kinases; VEGF, vascular endothelial growth factor.

Moreover, COX-2 protein expression was also detected in atypical alveolar epithelium, considered a precursor lesion for LC, and correlated with asbestosis and idiopathic fibrous alveolitis.[55] In additional studies, Hosomi et al.[14] showed positive COX-2 expression in 71.6% of lung atypical adenomatous hyperplasia tissues, a precursor to adenocarcinoma. Zhao et al and Song et al.[56,57] also found an increasing expression level of COX-2 with higher differentiation of LC. Song et al.[57] evaluated COX-2 expression in 101 LC tissues and seven normal tissues using immuno-histochemistry and image analysis. They observed higher COX-2 expression in peripheral LC compared to central LC, which may be attributed to the prevalence of peripheral lesions in lung adenocarcinomas, thus confirming the close association between COX-2 and lung adenocarcinoma.[57] The study also reported significantly higher COX-2 expression in advanced LC and the lymph node metastasis-positive group compared to the negative group.[57] Zhang et al.[58] examined COX-2 expression using immuno-histochemistry in 52 NSCLC patients and found a positive COX-2 expression rate of 83.3% in patients with lymph node metastasis, higher expression in T3–T4 stage (92.3%) compared to T1–T2 stage (33.3%), and significantly higher expression in clinical stage 3–4 (80%) compared to clinical stage 1–2 (28.1%).

Several studies investigated the prognostic importance of COX-2 expression in lung adenocarcinoma and NSCLC patients. Achiwa et al.[59] evaluated a cohort of 130 lung adenocarcinoma patients and found that elevated COX-2 expression was not significantly associated with clinical prognosis, except in the subgroup of stage I patients who underwent surgical resection. Similarly, in a study by Khuri et al.,[60] 160 specimens from patients with stage I NSCLC were examined. The results revealed that higher COX-2 expression intensity was linked to worse overall survival and disease-free survival, indicating an unfavorable prognosis.[60] In a subsequent cohort study of 259 NSCLC cases, Laga et al.[61] observed that increased COX-2 expression was associated with shorter patient survival, particularly in stage I and II NSCLC. However, the prognostic impact of COX-2 expression in NSCLC remains inconsistent among different studies. Mattsson et al.[62] assessed the relationship between COX-2 transcript levels in LC cells and clinical parameters or overall survival of NSCLC patients using nine publicly available gene expression data sets. The study did not discover any correlation between COX-2 expression in LC cells and clinical parameters or the overall survival of patients. However, high protein expression of COX-2 in stromal cells was greatly connected with longer survival, although not

with clinical parameters.[62] Moreover, Nan et al.[63] investigated the relationship between COX-2 gene polymorphisms and survival in 136 patients with unresectable stage IIIA-B NSCLC. The results suggested that specific COX-2 gene polymorphisms were linked to improved overall survival and extended progression-free survival.[63] However, a Brazilian cohort study with 104 NSCLC patients did not find a correlation between COX-2 gene polymorphisms and overall survival.[64]

In summary, COX-2 expression was detected early in LC, particularly in highly differentiated adenocarcinomas and lymph node metastases. However, the prognostic significance of COX-2 expression in LC remains controversial. While some studies suggested an association between high COX-2 expression and poor prognosis, particularly in early-stage NSCLC, others did not find a correlation. Additionally, COX-2 gene polymorphisms may play a role in the development and prognosis of LC, although the findings are inconsistent. These variations in results may be influenced by factors such as sample size, study design, different ethnicities, and treatment approaches. Therefore, further studies are necessary to validate and elucidate the role and potential mechanisms of COX-2 in LC.

6 | TARGETING COX-2 APPROACHES IN LC

6.1 | COX-2 as a predictor of LC

Although current methods have been utilized for LC treatment, the identification of new predictive markers is crucial for achieving early diagnosis and providing improved prognostic information for patients. While COX-2 alone may not serve as an independent predictor of LC, several molecules up and downstream of COX-2 have been considered potential markers for LC prognosis. For instance, in a recent study, it was observed that high expression of PGI2, a product of COX-2, was associated with a lower 5-year survival rate compared to the low PGI2 expression group, indicating its significance in predicting the prognosis of LC.[65] Additionally, co-expression of BPTF (COX-2 promoter binding protein) and COX-2 was linked to poor prognosis in LC patients.[66] The overexpression of Ku80, a novel binding protein of the COX-2 gene promoter, was shown to upregulate COX-2 expression in LC cells and was associated with a poorer prognosis in LC patients.[67] Furthermore, Cox regression analyses indicated that Ku80 overexpression and the expression of mPGES and PGI2 were statistically significant in predicting LC prognosis.[65,67] Significant COX-2 expression in bronchial precursor cells of squamous cell carcinoma was also demonstrated by Mascaux et al.,[68] suggesting the potential of COX-2 as an early marker for this type of carcinoma. Additionally, the COX-2 −1195G>A (rs689466) polymorphism was found to be associated with LC susceptibility in different ethnic groups.[45] A study in a Japanese population revealed that the pure COX-2 −1195A genotype increased the risk of lung squamous cell carcinoma.[45]

In conclusion, while COX-2 alone may not be an independent predictor of LC, significant potential exists in utilizing COX-2 upstream and downstream molecules as predictive markers to enhance the diagnosis and prognosis of LC. Studies demonstrated the prognostic value of PGI2, BPTF, Ku80, and COX-2 expression in LC patients, along with the association of COX-2 polymorphisms with LC susceptibility. These findings suggested the importance of exploring and validating the role of these molecules in clinical settings to improve patient outcomes.

6.2 | COX-2 as a pharmacological target in LC

LC presents significant challenges in terms of treatment efficacy due to its resistance to immunotherapy, targeted therapies, and cytotoxic treatments.[5] Several selective COX-2 inhibitors have seen clinical use but were withdrawn from the market due to severe cardiotoxicity.[69] Presently, Celecoxib (Celebrex) stands as the sole Food and Drug Administration (FDA)-approved selective COX-2 inhibitor, demonstrating efficacy with minimal toxicity in treating inflammatory diseases.[70] Clinical trials involving Celecoxib in conjunction with radiotherapy for unresectable stage I NSCLC indicate the feasibility of concurrent administration with thoracic radiotherapy at the FDA-approved maximum dosage of 800 mg/day. Even when not reaching the maximum dose, the progression-free survival rates at 1 and 2 years were 66.0% and 42.2%, respectively, signifying a notable improvement in survival rates.[71] Following these findings, a subsequent clinical trial investigated the efficacy of Celecoxib combined with paclitaxel, carboplatin, and radiotherapy in patients with inoperable stage IIIA/B NSCLC. However, the addition of Celecoxib to concurrent chemoradiotherapy did not yield survival benefits in inoperable IIIA/B NSCLC cases.[72,73] Despite less promising experimental outcomes, early administration of Celecoxib in combination with chemoradiotherapy in NSCLC patients demonstrated improved survival rates. This underscores the therapeutic potential of targeted COX-2 inhibition in NSCLC, prompting further exploration and development of novel therapeutic strategies and drugs for NSCLC treatment. In this context, several effective strategies could be considered:

(1) Nonspecific COX-2 inhibitors, such as ibuprofen, sulforaphane, nimesulide, diclofenac, indomethacin, and aspirin, showed COX-2 inhibition in cancer cells, potentially attributed to elevated ROS concentrations. However, it is important to note that these inhibitors may stimulate the upper gastrointestinal system.[41]

(2) Selective COX-2 inhibitors, such as celecoxib, etodolac, and NS-398, offered a lower rate of gastrointestinal damage compared to nonspecific inhibitors.[41]
(3) Targeting microRNAs involved in COX-2-mediated LC progression has shown promise. For example, the compound orientin, a bioflavonoid from *Trigonella hamosa* L, reduced COX-2 expression by upregulating miR-26b and miR-146a, providing a potential strategy for NSCLC treatment.[74]
(4) Utilizing vectors to deliver small interfering RNA (siRNA) for COX-2 can be an effective strategy. For instance, 3WJ-EpCAM-D5D siRNA nanoparticles have shown high affinity and penetration in LC cells, reducing PGE2 production by altering the peroxidation pattern of COX-2 catalyzed ω-6 fatty acids (e.g., DGLA).[75]
(5) Multifunctional COX-2 ligand traps, such as the quinazolinone-based stay-phenyluronium derivative (6a-p), which targeted the double mutant EGFRL858R/T790M, COX-2, and 15-LOX, offer a promising approach.[76]
(6) Blocking COX-2 production through indirect inhibition could be achieved by compounds like imino dibenzyl, which disrupted the conversion of dihomo-γ-linolenic acid (DGLA) to AA in cancer cells by decreasing δ-5-desaturase (D5 D).[51]
(7) Regulation of T-cell immune response, such as the use of cd47-CAR-T cells, genetically modified T cells regulated by COX-2 protein, showed potential.[77]
(8) Combining COX-2 inhibitors with other targeted inhibitors has shown enhanced anticancer effects. For example, the combination of the COX-2 inhibitor celecoxib and the EGFR inhibitor afatinib enhanced the anticancer effect of radiation on NSCLC cells.[78] PPAR-γ agonists and COX-2 inhibitors exerted synergistic effects by inhibiting COX gene expression and inactivating COX-2 enzymes, respectively.[9]

In summary, targeted therapies against COX-2 offer a promising future in oncology treatment, considering its involvement in multiple signaling pathways in tumor development. There is substantial evidence supporting the potential of natural derivatives in chemoprevention and their ability to antagonize COX-2 expression in LC. For example, melafolone, one of the pharmacologically active flavonoids derived from Polygonum lapathifolium, showed promising effects in improving the efficacy of tumor anti-PD-1 immunotherapy.[12] It achieved this by dual inhibition of COX-2 and EGFR in both in vivo and in vitro LC cells, leading to downregulation of PD-L1 expression and increased proliferation of $CD8^+$ T cells.[12] Furthermore, melafolone promoted normalization of the tumor vascular system by downregulating VEGF or TGF-b in nontumor cells within the tumor microenvironment.[12] In addition to melafolone, Korean Red Ginseng treatment of A549 cells coincubated with BPA was found to inhibit BPA-induced production of reactive oxygen species (ROS), subsequently suppressing MMP-9 and COX-2 expression.[79] Similarly, sesamin, a type of lignan compound, exerted positive effects on cell cycle organization and apoptosis in A549 cells by inhibiting the Akt-PI3K signaling pathway through COX-2 downregulation.[42] Curcumin, in a study with NSCLC P14 cells, demonstrated downregulation of COX-2 and EGFR expression by inhibiting NF-κB activation and inducing p65 nuclear translocation.[40] Additionally, BEL forms hydrogen bonded with Tyr385 and Ser530 in the COX-2 receptor, leading to the inhibition of COX-2 expression.[34] β-Elemene significantly reduced COX-2 expression through the silencing of C3orf21.[80] Another natural compound, Chai Cao Saponin D, a triterpene saponin, was shown to inhibit COX-2 expression possibly by downregulating phosphorylated STAT3 and C/EBP-β.[34]

In conclusion, these studies provide evidence for natural COX-2-blocking products and encourage further exploration to discover new products for the treatment of LC. Targeted therapies against COX-2 hold significant potential to improve treatment outcomes and warrant further investigation.

7 | LIMITATIONS AND PROSPECTS OF TARGETED COX-2 THERAPY

Although COX-2 has been implicated in NSCLC development, its therapeutic targeting remains a challenge. Presently, COX-2 therapy is not mainstream in LC treatment for several reasons: First, numerous COX-2 inhibitors, such as rofecoxib, valdecoxib, and parecoxib, have been associated with an elevated risk of cardiovascular events, leading to their withdrawal or rejection by the FDA.[69,70] Second, the correlation between COX-2 expression and survival varies among NSCLC patients, hindering the establishment of definitive treatment guidelines for COX-2 inhibitors in LC management.[61–64] Last, clinical trial outcomes have been inconclusive. Some studies suggested the potential efficacy of celecoxib, a COX-2 inhibitor, in LC treatment, while others failed to confirm significant therapeutic benefits, resulting in controversy over its clinical utility.[71–73,81–83]

Given the current limitations of COX-2 inhibitors in LC treatment, future research should focus on: (1) Developing COX-2 inhibitors with reduced cardiotoxicity. (2) Investigating the interplay between COX-2 and key signaling pathways, aiming to develop dual or multi-target inhibitors. (3) Employing precision medicine approaches to deliver individualized treatment, enhancing treatment relevance and efficacy while minimizing adverse reactions. (4) Exploring combination therapies involving COX-2 inhibition.

COX-2 identification as a potential marker and therapeutic target for NSCLC has garnered significant interest in the field. Assessing COX-2 expression profiles, particularly in early NSCLC stages, holds promise for guiding targeted therapeutic selection. With NSCLC being a prevalent tumor lacking effective treatment options, there is an urgent need for new biomarkers to aid in diagnosis and personalized treatment, ultimately aiming to improve patient outcomes and survival rates. Improving overall survival in LC patients necessitates exploring novel approaches to COX-2 targeting therapy, providing potential for more effective intervention in this challenging malignancy.

8 | CONCLUSION

Collectively, targeting COX-2 inhibition represents a promising therapeutic approach in NSCLC. Identifying regulators of COX-2 expression may serve as valuable markers for LC. Combining COX-2 inhibitors with multiple treatment modalities holds the potential to enhance the prognosis of LC, particularly in NSCLC patients. Furthermore, the combination of COX-2 inhibitors with conventional therapies such as chemotherapy and radiotherapy offers a promising strategy to overcome drug resistance in LC.[43] These approaches pave the way for novel and effective strategies in combating this aggressive cancer.

AUTHOR CONTRIBUTIONS

Zhuang Ma: Conceptualization. **Wenwu Sun**: Resources. **Xueqi Liu**, **Junli Zhang**, **Wenwu Sun**, **Zhuang Ma**: Writing—original draft preparation. **Xueqi Liu**, **Jianping Cao**: Writing—review and editing. **Xueqi Liu** and **Junli Zhang**: Visualization. **Zhuang Ma**: Supervision. All authors contributed to the article and approved the submitted version.

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The authors have nothing to report.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

None.

ETHICS STATEMENT

None.

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