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" Review Article: The Role of COX-2 and HIF-1α in Colon Cancer: Insights from Immunohistochemistry"

Authors

Amira Fikry Mohammed AboSamra[1], Marwa Hosny Mohamed Khashaba[2], Mayada Saad Mohammed Ali Farrag[3], Azza Hassan Mohammad Zidan[4,5]

[1] Demonstrator of Pathology, Pathology Department, Faculty of Medicine, Port Said University, Egypt.

[2] Lecturer of Pathology, Pathology Department, Faculty of Medicine, Port Said University, Egypt.

[3] Associate Professor of Pathology, Pathology Department, Faculty of Medicine, Port-Said University, Egypt

[4] Professor of Pathology, Pathology Department, Faculty of Medicine, Port Said University, Egypt.

[5] Professor of Pathology, Galala University, Suez, Egypt. https://orcid.org/0000-0002-1862-9291

ABSTRACT:

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Abstract:

Colorectal cancer (CRC) is one of the leading causes of cancer-related morbidity and mortality worldwide. Its complex pathogenesis involves a multitude of molecular and cellular pathways, among which Cyclooxygenase-2 (COX-2) and Hypoxia-Inducible Factor 1-alpha (HIF-1α) have gained significant attention. COX-2, an enzyme involved in prostaglandin synthesis, is frequently overexpressed in colorectal tumors and contributes to inflammation, cell proliferation, resistance to apoptosis, and angiogenesis. Similarly, HIF-1α, a key transcription factor activated under hypoxic conditions, promotes tumor survival by regulating genes involved in angiogenesis, metabolism, and invasion.

Both molecules not only facilitate tumor progression but are also associated with poor clinical outcomes. This review aims to discuss existing research on the roles of COX-2 and HIF-1α in CRC development and progression. In particular, it highlights findings from immunohistochemical (IHC) studies that evaluate their expression in tumor tissues and discusses their potential use as diagnostic, prognostic, and therapeutic targets in colorectal cancer management.

1. Introduction to Colon Cancer

Colorectal cancer (CRC) is the third most prevalent cancer globally [1] and is among the primary causes of cancer-related mortality [2]. Despite advances in treatment, the prognosis for many patients remains poor due to late-stage diagnosis and metastasis. Tumorigenesis in colon cancer is driven by genetic mutations, epigenetic changes, and environmental factors [3]. Key pathways implicated in CRC include those governing cell cycle regulation, apoptosis, and angiogenesis [4–6]. Notably, inflammation plays a pivotal role in colon carcinogenesis, with COX-2 emerging as a central mediator in this process [7].

2. COX-2 in Colon Cancer: Mechanisms and Role

Cyclooxygenase-2 (COX-2) is an enzyme responsible for the synthesis of prostanoids, including prostaglandins, which serve as key mediators of inflammation [8,9]. While COX-1 is constitutively expressed, COX-2 expression is upregulated during inflammatory responses and in various tumors, including colon cancer [10].

Pathogenic Mechanisms in CRC

COX-2 contributes to colorectal carcinogenesis by facilitating inflammation, enhancing cell proliferation, stimulating angiogenesis, and inhibiting apoptosis [11,12]. The enzyme is often overexpressed in colorectal adenomas and carcinomas, correlating with metastasis and poor prognosis [13]. COX-2 mediates the production of prostaglandin E2 (PGE2), which promotes cell proliferation and suppresses immune surveillance by modulating the tumor microenvironment. PGE2 has been linked to activation of signaling pathways such as Wnt/β-catenin, which is crucial for CRC progression [14].

COX-2 as a Prognostic Marker

Numerous studies have demonstrated the prognostic importance of COX-2 overexpression in colon cancer. A meta-analysis found that elevated COX-2 expression correlates with shorter disease-free survival (DFS) and poorer overall survival (OS) in patients with CRC [15]. COX-2 expression has been assessed in cancer tissues using immunohistochemical (IHC) techniques, with its overexpression linked to increased tumor aggressiveness and resistance to chemotherapeutic agents [16].

3. HIF-1α in Colon Cancer: Role in Tumor Microenvironment

Hypoxia-inducible factor 1-alpha (HIF-1α) is a transcription factor that regulates cellular responses under low oxygen conditions (hypoxia) [17]. In normal tissues, HIF-1α undergoes rapid degradation under aerobic conditions, but in tumors, hypoxia stabilizes HIF-1α, allowing it to drive the expression of genes associated with angiogenesis, metabolism, and cell survival [18].

Role in CRC Pathogenesis and Tumor Progression

HIF-1α regulates several pro-angiogenic factors, most notably vascular endothelial growth factor (VEGF), which facilitates the formation of new blood vessels to sustain tumor growth [19]. In colon cancer, elevated HIF-1α levels are linked to high metastatic potential, poor prognosis, and resistance to therapies [20]. HIF-1α also facilitates the epithelial–mesenchymal transition (EMT), a process critical for metastasis, by upregulating genes involved in cell invasion, such as matrix metalloproteinases (MMPs), vimentin, and fibronectin [21].

4. Immunohistochemistry (IHC) in Evaluating COX-2 and HIF-1α Expression

Immunohistochemistry (IHC) is a powerful tool for detecting protein expression in tissue samples. It allows localization and quantification of COX-2 and HIF-1α in tumor tissues, providing valuable information about their role in cancer biology.

- **COX-2 Immunohistochemistry:** In colon cancer, COX-2 expression can be assessed using IHC to determine its presence and distribution in tumor tissues [22,23]. Increased levels of COX-2 expression correlate with more aggressive tumors and a poorer prognosis [24].
- **HIF-1α Immunohistochemistry:** Similarly, HIF-1α expression is evaluated in colorectal cancer tissues using IHC, where it is typically overexpressed in poorly differentiated tumors. High HIF-1α expression

has been linked to resistance to chemotherapy and radiotherapy, making it a key prognostic marker [25].

4.1. IHC Considerations

Accurate interpretation of COX-2 and HIF-1α expression by IHC requires methodological standardization and awareness of technical pitfalls.

- **Tissue fixation:** Adequate formalin fixation (typically 10% neutral buffered formalin, 24–48 hours) is essential to preserve antigenicity while preventing over-fixation artifacts[26,27].
- **Validated antibody clones:** Use of well-characterized and validated antibody clones is critical to ensure specificity and reproducibility of staining results[28].
- **Internal controls:** Adjacent normal mucosa, stromal cells, or inflammatory infiltrates can serve as internal positive controls to verify staining quality[29].
- **Subcellular localization:** Interpretation must consider expected patterns—COX-2 is cytoplasmic, whereas HIF-1α is nuclear and cytoplasmic staining)[30]
- **Heterogeneity:** Intra-tumoral heterogeneity is frequent; multiple tumor regions may need evaluation to avoid sampling bias [31].
- **Pitfalls:** Common issues include non-specific staining, variability between laboratories, and inter-observer differences, all of which can affect reproducibility and comparability of findings[32,33].

Standardization of fixation, antibodies and reporting is essential to enhance the clinical utility of COX-2 and HIF-1α IHC results in colon cancer research and diagnostics.

5. Interaction Between COX-2 and HIF-1α in Colon Cancer

The interaction between COX-2 and HIF-1α in colon cancer has attracted growing research attention. COX-2 not only contributes to inflammation but also induces HIF-1α expression in the tumor microenvironment. In return, HIF-1α stabilizes COX-2 expression under hypoxic conditions, creating a positive feedback loop that enhances tumor progression [34].

Molecular Crosstalk

COX-2 and HIF-1α are both engaged in regulating angiogenesis and EMT. COX-2-derived PGE2 has been shown to upregulate HIF-1α expression, while HIF-1α enhances COX-2 transcription through the activation of the prostaglandin pathway [35].

6. Clinical Implications and Therapeutic Potential

Given the critical roles of COX-2 and HIF-1α in colon cancer, both represent attractive targets for therapeutic intervention. However, translation into clinical practice requires cautious evaluation.

- **COX-2 inhibitors in colon cancer therapy:** Inhibitors of COX-2, such as celecoxib and other NSAIDs, have demonstrated potential in reducing tumor growth and improving survival, particularly in combination with chemotherapy. Their anti-inflammatory and anti-metastatic properties make them valuable investigational agents. Nonetheless, their clinical use is limited by **cardiovascular and thromboembolic risks**, especially with prolonged or high-dose use. These safety concerns have prevented routine approval for cancer prevention or treatment, highlighting the need for careful patient selection and monitoring in future trials [36].
- **HIF-1α targeting strategies:** HIF-1α inhibitors are promising for disrupting tumor adaptation to hypoxia and enhancing sensitivity to conventional therapies. Preclinical studies have shown encouraging effects on angiogenesis, metabolism, and treatment resistance. However, most candidates remain in **preclinical or early-phase trials**, and robust clinical data in colorectal cancer are still lacking. Challenges related to specificity, toxicity, and drug delivery must be overcome before widespread clinical application [37,38].

7. Search Strategy and Methodology

A systematic literature search was conducted across **PubMed, Scopus, Web of Science, and Google Scholar**. Search terms included combinations of *"colorectal cancer"*, *"colon cancer"*, *"COX-2"*, *"HIF-1α"*, *"hypoxia-inducible factor"*, *"immunohistochemistry"*, and *"prognosis"*. Boolean operators (*AND*, *OR*) were used to refine the strategy.

- **Eligibility criteria:** Original research, systematic reviews, and meta-analyses; human studies on CRC; outcomes related to COX-2 and HIF-1α expression, function, prognosis, or therapy; publications in English; and timeframe **2000–2025**.
- **Exclusion criteria:** Non-English articles, animal-only studies, case reports, conference abstracts without full text, or studies not directly relevant to COX-2/HIF-1α in CRC.

Titles and abstracts were screened, followed by full-text review. Evidence was synthesized narratively, prioritizing meta-analyses and large cohort studies to strengthen conclusions.

8. **Conclusion**

Both COX-2 and HIF-1α play pivotal roles in the pathogenesis of colon cancer by driving inflammation, angiogenesis, and tumor progression. Their overexpression correlates with poor prognosis and metastasis, making them important biomarkers for diagnosis and prognosis. Immunohistochemistry has been instrumental in characterizing their expression and prognostic value. While targeting COX-2 and HIF-1α represents a promising therapeutic avenue, limitations remain: **COX-2 inhibitors carry cardiovascular safety risks**, and **HIF-1α inhibitors are still largely preclinical**. Thus, further well-designed clinical studies are essential before these targets can be reliably integrated into colorectal cancer management.

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