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REVIEW ARTICLE

Current Therapeutic Strategies Targeting Tyrosine Kinase Receptor in Colon Cancer

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ABSTRACT

Colon cancer represents a significant global health burden characterized by heterogeneous molecular profiles that influence disease progression and treatment outcomes. Tyrosine kinase receptors (TKRs), including epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor (VEGFR), play a pivotal role in its pathogenesis by initiating oncogenic signaling pathways that are crucial for tumor growth, angiogenesis, and metastasis. The use of inhibitors, including monoclonal antibodies and tyrosine kinase inhibitors, to target TKRs has transformed the treatment of metastatic colorectal cancer (mCRC), leading to enhanced clinical outcomes, especially when used alongside conventional chemotherapy protocols. However, challenges like therapeutic resistance and adverse effects underscore the need for continued research into novel agents, biomarker development for patient stratification, and combination therapies integrating TKR inhibitors with immunotherapies. This review offers a detailed summary of existing treatment approaches that target TKRs in colon cancer, focusing on how they work their effectiveness in clinical settings, associated challenges, and future prospects for improving treatment outcomes and patient care.

KEYWORDS

• VEGFR • Metastaticcolorectal cancer (mCRC) • Immunotherapies and next-generation TKIs

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Implication for health policy/practice/ research/medical education:

Understanding the role of TKRs in colon cancer highlights the importance of targeted therapies in improving patient outcomes. Health policies should support access to molecular diagnostics and personalized treatments. Clinical practice must adopt biomarker-driven approaches for effective patient stratification. Continued research is essential to overcome resistance and enhance therapeutic efficacy. Medical education should emphasize molecular oncology to prepare professionals for precision medicine.

INTRODUCTION

According to the World Health Organization (WHO), cancer was a leading cause of death worldwide in 2020, responsible for nearly 10 million deaths about one in six. The most commonly diagnosed cancers that year were breast cancer (2.26 million cases), lung cancer (2.21 million cases), and colorectal cancer (1.93 million cases). WHO, 2022 has reported the most common causes of cancer death in 2020 were: lung (1.80 million deaths) and colon and rectum (916 000 deaths).[1] The World Health Organization (WHO) estimates that by 2040, the number of new cancer cases will rise to approximately 29.5 million.[2] The increasing cancer burden is largely influenced by demographic changes and population shifts, as the global population, estimated at around 8 billion in 2022, is projected to reach 9.7 billion by 2050.[3]

Colon cancer remains a major global public health concern, causing considerable illness and death, even with progress in early diagnosis and therapeutic approaches. Colon cancer is a complex and heterogeneous disease marked by a variety of molecular changes, including disruptions in signaling pathways essential for cell growth and survival. Due to this complexity, effective treatment requires a comprehensive, multi-targeted strategy. One of the central molecular contributors to colon cancer progression is the family of tyrosine kinase receptors (TKRs), which are crucial for activating oncogenic signaling pathways that regulate cell division, blood vessel formation, and metastasis.[4]

The dysregulated activation of tyrosine kinase receptors (TKRs), such as epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), and mesenchymal-epithelial transition factor (MET), has become a defining characteristic of colon cancer development. These receptors drive tumor growth, invasion, and resistance to conventional therapies through their downstream signaling pathways, posing formidable challenges to effective treatment strategies. Consequently, developing targeted therapies against TKRs has garnered considerable attention in the quest for more precise and efficacious interventions for colon cancer patients.[5]

In recent years, substantial progress has been achieved in understanding the complex signaling pathways regulated by tyrosine kinase receptors (TKRs) in colon cancer cells. This has facilitated the discovery of new therapeutic targets and the development of targeted therapies with greater precision. As a result, several tyrosine kinase inhibitors (TKIs) have gained clinical approval for treating advanced or metastatic colon cancer, either as standalone treatments or in combination with other therapies.[6] These TKIs, selectively inhibiting the catalytic activity of dysregulated TKRs, promise improved clinical outcomes and prolonged survival for patients with refractory disease.

However, despite the initial success of TKI-based therapies, challenges such as intrinsic and acquired resistance, off-target toxicities, and limited patient stratification persist, underscoring the need for continued research efforts to optimize treatment efficacy and patient selection. Additionally, the discovery of new TKRs and resistance mechanisms adds both promise and complexity to the clinical management of colon cancer, emphasizing the importance of a deeper understanding of tumor biology and resistance pathways.[7] Considering these factors, this review aims to provide a clear and comprehensive summary of current therapeutic Strategies Tyrosine Kinase receptors in colon cancer, along with an overview of resistance mechanisms and future prospects.

Colorectal cancer (CRC):

In the field of oncology, colorectal cancer (CRC) remains a significant challenge, as it is one of the leading causes of cancer-related mortality worldwide.[8] Thepathogenesis of colorectal cancer (CRC) is multifaceted, involving

a multifaceted interplay of genetic and environmental factors that disrupt molecular pathways regulating cellular functions. Central to this intricate network are tyrosine kinase receptors (TKRs), which significantly contribute to controlling fundamental cellular processes, including proliferation, differentiation, and survival.[9] These receptors, finely tuned in healthy physiology, become protagonists in the narrative of cancer when their signalling cascades veer off course. Aberrant activation of TKRs is a common thread in the development of several malignancies, including colorectal cancer (CRC), where their dysregulated signalling fuels tumorigenesis, fosters tumour progression, and confers resistance to therapeutic interventions.[10] Thus, understanding the intricate interplay between TKRs and CRC pathophysiology unveils promising avenues for targeted therapeutic interventions aimed at disrupting the oncogenic signalling networks driving disease progression.[11-13]

Role of Tyrosine Kinase Receptors in Colon Cancer:

TKRs are transmembrane proteins vital in orchestrating cellular responses by initiating intracellular signalling cascades upon binding with specific ligands. Tyrosine kinase receptors (TKRs) are a class of cell surface receptors that are activated when specific ligands (like growth factors) bind to them. This binding triggers a cascade of intracellular signaling pathways, allowing the cell to respond appropriately to changes in its external environment. These responses are essential for maintaining normal cellular behavior, and any dysfunction in these receptors can lead to abnormal cell growth and cancer development specifically in colorectal cancer (CRC), aberrant activation of TKRs emerges as a central feature driving tumorigenesis and disease progression. Key among the TKRs implicated in CRC pathogenesis are the Epidermal Growth Factor Receptor (EGFR), Vascular Endothelial Growth Factor Receptor (VEGFR), Platelet-Derived Growth Factor Receptor (PDGFR), and Insulin-Like Growth Factor 1 Receptor (IGF-1R).[14-17] EGFR, for instance, undergoes frequent overexpression or mutational changes in colorectal cancer, facilitating abnormal cell proliferation and tumorigenesis.[18] Similarly, VEGFR plays a fundamental role in promoting angiogenesis, Enhancing vascular development within the tumor, and supporting metastatic spread.[19] PDGFR and IGF-1R also contribute to CRC Contributing to cancer advancement by influencing cellular proliferation, survival, and migration.[20-21]

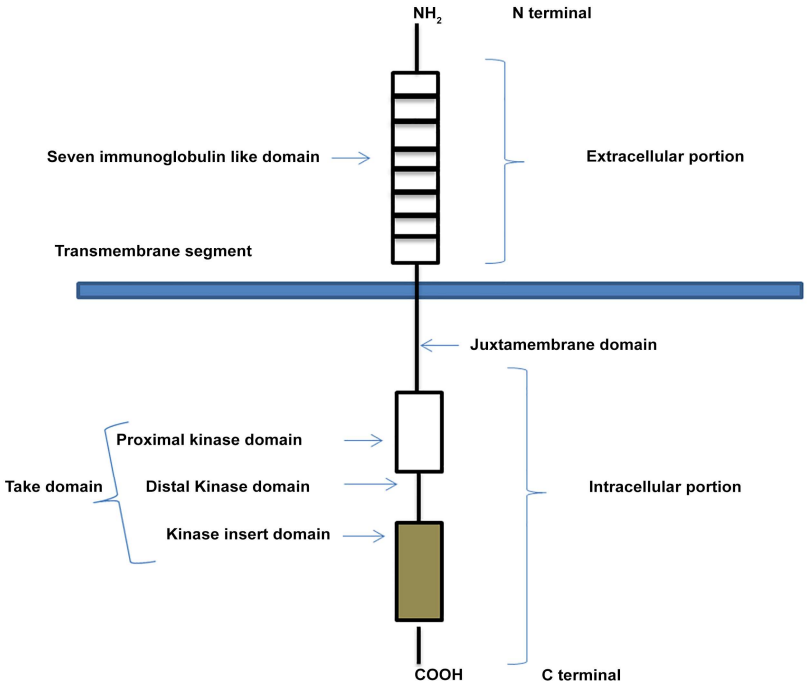

Figure 1: Structure of vascular endothelial growth factor receptor –2 (VEGFR-2)

Mechanisms of TKR Involvement:

EGFR (Epidermal Growth Factor Receptor): In colorectal cancer (CRC), EGFR is frequently overexpressed or mutated, resulting in unchecked cellular proliferation. As part of the ErbB receptor family, EGFR triggers downstream signaling cascades including the Ras/Raf/MEK/ERK and PI3K/Akt/mTOR pathways that promote cell growth, survival, and metastasis.[22-23]

VEGFR (Vascular Endothelial Growth Factor Receptor): Promotes angiogenesis, vital for tumour growth and metastasis. VEGFR signalling drives the proliferation of endothelial cells, migration, and survival, fostering the formation of new blood vessels that nourish the tumour microenvironment and facilitate metastatic dissemination.[24]

PDGFR (Platelet-Derived Growth Factor Receptor): Involved in cell proliferation and angiogenesis regulation. PDGFR activation triggers downstream signalling cascades implicated in Cancer cell growth, movement into surrounding tissues, and blood vessel growth promoting CRC progression and metastasis.[25]

IGF-1R (Insulin-Like Growth Factor 1 Receptor): Stimulates cell growth and survival, contributing to tumorigenesis. Activation of IGF-1R signalling pathways stimulates progression through the cell cycle and inhibits cell death mechanisms and enhances cell motility, facilitating CRC development and progression.[26]

Current Therapeutic Agents Targeting TKRs:

EGFR Inhibitors: Cetuximab and Panitumumab: Monoclonal antibodies that block extracellular ligand-binding domain of the epidermal growth factor receptor, preventing ligand binding and receptor activation. These agents are used in combination with chemotherapy for metastatic CRC (mCRC).[27] Tyrosine Kinase Inhibitors (TKIs) such as gefitinib and erlotinib inhibit the cytoplasmic catalytic domain of the epidermal growth factor receptor, although their use in CRC is less common compared to monoclonal antibodies.[28]

VEGFR Inhibitors: Bevacizumab: A monoclonal antibody that targets VEGF, blocking its interaction with VEGF receptors (VEGFR). Integrated into chemotherapeutic protocols for mCRC.[29] Aflibercept: acts as a soluble decoy receptor, binding VEGF and preventing its interaction with VEGFR, inhibiting its interaction with VEGFR. It is administered alongside chemotherapy for the treatment of metastatic colorectal cancer (mCRC).[30] Regorafenib and Ramucirumab: Small molecule TKIs and monoclonal antibodies targeting VEGFR and other angiogenic receptors. These agents are utilized in refractory mCRC.[31-32]

PDGFR and Multi-TKR Inhibitors: Imatinib: Primarily used in gastrointestinal stromal tumours (GISTs), imatinib targets PDGFR and is being explored for potential use in CRC.[33] Regorafenib: A multikinase inhibitor targeting VEGFR, PDGFR, and other kinases. Approved for refractory mCRC treatment.[33]

IGF-1R Inhibitors:

Figitumumab: A monoclonal antibody targeting IGF-1R, although its clinical development in CRC has faced challenges due to limited efficacy and toxicity issues.[34]

Table 1: Overview of VEGF/VEGFR-Targeting Drugs with Clinical Indications

Category	Drug Name (Brand)	Target(s)	Approved Indications	Reference
Monoclonal Antibodies				
Anti-VEGF Antibodies	Bevacizumab (Avastin)	VEGF-A	Colorectal cancer, NSCLC, RCC, glioblastoma, others	[35]
Anti-VEGFR2 Antibodies	Ramucirumab (Cyramza)	VEGFR2	Gastric cancer, colorectal cancer, NSCLC, HCC	[36]
Small-Molecule TKIs				
Multi-Targeted TKIs	Sunitinib (Sutent)	VEGFR1, VEGFR2, VEGFR3, PDGFR, c-KIT	RCC, pNET, GIST	[37]
	Sorafenib (Nexavar)	VEGFR2, VEGFR3, PDGFR, RAF	HCC, RCC, thyroid cancer	[38]

table cont....

Category	Drug Name (Brand)	Target(s)	Approved Indications	Reference
	Pazopanib (Votrient)	VEGFR1, VEGFR2, VEGFR3, PDGFR, c-KIT	RCC, soft tissue sarcoma	39
	Axitinib (Inlyta)	VEGFR1, VEGFR2, VEGFR3	RCC	40
	Lenvatinib (Lenvima)	VEGFR1, VEGFR2, VEGFR3, FGFR, PDGFR, RET	Thyroid cancer, RCC, HCC	41
	Cabozantinib (Cabometyx, Cometriq)	VEGFR2, MET, AXL	RCC, HCC, medullary thyroid cancer	42
	Regorafenib (Stivarga)	VEGFR1, VEGFR2, VEGFR3, TIE2	Colorectal cancer, GIST, HCC	43
Selective VEGFR2 Inhibitors	Fruquintinib (Elunate)	VEGFR1, VEGFR2, VEGFR3	Metastatic colorectal cancer (China)	44
	Apatinib (Rivoceranib)	VEGFR2	Gastric cancer, HCC (China)	45
Fusion Proteins	Aflibercept (Zaltrap)	VEGF-A, VEGF-B, PlGF	Metastatic colorectal cancer	46
Emerging VEGFR Inhibitors	Tivozanib (Fotivda)	VEGFR1, VEGFR2, VEGFR3	Advanced RCC (Europe)	47
	Anlotinib	VEGFR2, FGFR, PDGFR, c-KIT	NSCLC, soft tissue sarcoma (China)	48
	Sitravatinib	VEGFR2, MET, TAM kinases	NSCLC (clinical trials)	49

Clinical Efficacy and Challenges:

EGFR Inhibitors:

EGFR-targeting agents like cetuximab and panitumumab have shown therapeutic effectiveness in treating metastatic colorectal cancer (mCRC), especially in individuals with KRAS wild-type tumors.These monoclonal antibodies block EGFR's extracellular domain, inhibiting downstream signalling pathways crucial for tumour growth and survival.[50] However, resistance mechanisms significantly limit their effectiveness, including mutations in downstream signaling molecules like KRAS, NRAS, and BRAF.[51] Ongoing research explores combination therapies and biomarker-driven approaches to circumvent resistance and enhance treatment outcomes in EGFR inhibitor therapy.

VEGFR Inhibitors:

VEGFR inhibitors, like bevacizumab and aflibercept, improve survival in mCRC when combined with chemotherapy by aiming to prevent the growth of new blood vessels, a critical process for tumour growth and metastasis.[52-53] Despite their efficacy, resistance to VEGFR inhibitors and adverse effects such as hypertension and proteinuria remain substantial challenges in clinical practice.[54] Current investigations focus on elucidating resistance mechanisms and developing predictive biomarkers to optimize patient selection and therapeutic efficacy.

Multi-TKR Inhibitors:

Agents such as regorafenib, a multikinase inhibitor targeting VEGFR, PDGFR, and other kinases, provide a viable treatment option for refractory mCRC patients who haveexhausted standard therapies.[55] However, their use is often limited by notable characterized by side effects including skin irritation on hands and feet, exhaustion, and systemic hypertension.[56] Ongoing investigations seek to manage side effects effectively while maintaining the drug's potency.

Emerging Therapies and Future Directions:

Combination Therapies: Integrating TKR inhibitors with immunotherapies (e.g., checkpoint inhibitors) and other molecularly targeted agents hold promising strategy to enhance treatment responses and overcome resistance mechanisms.[57]

Biomarker Development: Advancing research in predictive biomarkers facilitates better patient stratification, allowing for personalized treatment approaches tailored to individual molecular profiles.[58]

Novel Agents: Developing next-generation TKIs with enhanced specificity and reduced toxicity profiles can potentially improve treatment outcomes and patient quality of life.[59]

CONCLUSION

The therapeutic landscape targeting tyrosine kinase receptors (TKRs) in colon cancer has witnessed significant advancements, underscoring the pivotal role of TKRs in driving oncogenic signalling cascades critical for tumour growth and progression. As evidenced by the clinical efficacy of EGFR and VEGFR inhibitors, among others, the integration of targeted therapies with conventional chemotherapy has led to improved outcomes in metastatic colorectal cancer (mCRC) patients. However, challenges such as intrinsic and acquired resistance, along with associated toxicities, necessitate ongoing research efforts to optimize treatment strategies and patient outcomes.

Future directions in TKR-targeted therapy involve exploring novel agents with enhanced specificity and reduced adverse effects and integrating TKR inhibitors with emerging immunotherapies and other targeted approaches. Biomarker development holds promise for refining patient selection criteria, enabling personalized treatment regimens tailored to individual molecular profiles. Additionally, more profound insights into resistance mechanisms and the tumour microenvironment will be crucial for overcoming therapeutic hurdles and improving long-term survival rates.

In conclusion, the evolving field of TKR-targeted therapy in colon cancer reflects a paradigm shift towards precision medicine, where understanding the intricate molecular landscape of tumor's paves the way for more effective, personalized treatment approaches. Continued collaboration between researchers, clinicians, and pharmaceutical developers will be instrumental in advancing these therapeutic strategies and ultimately enhancing the quality of care for colon cancer patients worldwide.

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