A critique of the role of cell signalling in colorectal cancer

Dr. Mohite S.S.
Dept.Of Anatomy,
Krishana Institute of Medical Sciences, Karad, Maharashtra
Dr.Deepali Sadashiv Jankar.,
Dept.Of Physiology, Assistant Professor,
Krishana Institute of Medical Sciences, Karad, Maharashtra
Dr.Shedge S. A.
Dept.Of Anatomy,
Krishana Institute of Medical Sciences, Karad, Maharashtra

Abstract

Globally, "Colorectal Cancer (CRC)" is a serious issue for public health. Multiple genetic and environmental factors play a large role in the development of CRC. Cell signaling pathways are essential for the emergence and development of CRC. The primary signaling pathways involved in CRC, such as Wnt, MAPK/ERK, PI3K/Akt, and TGF-, will be briefly discussed. The function of microRNAs and long non-coding RNAs in CRC will also be covered in this review. Last but not least, this study will review the status of available targeted treatments for CRC, such as monoclonal antibodies and small molecule inhibitors. According to this investigation, a deeper comprehension of the intricate cell signaling pathways in CRC is required in order to create more potent tailored treatments. In conclusion, colorectal cancer continues to pose a serious threat to global public health. Research is ongoing to determine how cell signaling affects the onset, course, and management of CRC. While EGFR inhibitors and other targeted therapies have shown promise in the treatment of CRC, their efficacy may be constrained by the presence of EGFR or KRAS gene mutations. Patients with CRC may fare better as a result of the development of customized treatment and the discovery of new biomarkers and therapeutic targets. Recent research has further emphasized the significance of the tumor microenvironment and the function of exosomes and cancer-associated fibroblasts in the initiation and development of CRC. These results highlight the need for a deeper comprehension of the intricate signaling networks involved in CRC and point to new therapeutic avenues. Cell signaling plays a complicated and multifaceted role in CRC. Targeted therapy, new biomarkers, and pharmacological targets have been found thanks to improvements in our understanding of the molecular pathways underlying CRC. The variety of CRC and the existence of drug resistance mechanisms, however, still provide serious difficulties in the management of this condition. In order to create more effective and individualized treatments for CRC patients, additional study is required to better understand the intricacy of cell signaling in this illness.

Keywords: colorectal cancer, cell signaling, Wnt, MAPK/ERK, PI3K/Akt, TGF-β, microRNAs, long non-coding RNAs, targeted therapy

Introduction

With an expected 1.8 million new cases and 881,000 fatalities in 2018 [1], "colorectal cancer (CRC)" is the third most often diagnosed malignancy worldwide. Complex genetic and environmental processes, such as diet, lifestyle, and inflammation, all play a role in the development of CRC [2]. Genetic and epigenetic changes that result in unchecked cell proliferation, invasion, and metastasis accumulate over the course of CRC [3]. The deregulation of cell signaling pathways is one of the main processes involved in the onset and spread of CRC [4].

Cell signaling pathways are intricate webs of biochemical processes that enable cells to talk to one another and react to outside stimuli [5]. Dysregulation of these pathways can cause oncogenes to become active and tumor suppressor genes to become inactive, which will cause unchecked cell growth and proliferation [6].

Main body Wnt Signaling Pathway

A crucial pathway involved in many biological processes, such as embryonic development, tissue homeostasis, and cancer pathogenesis, is the Wnt signaling pathway. Several cancers, including colorectal cancer, have been linked to the emergence and spread of Wnt pathway dysregulation.

Wnt ligands bind to Frizzled receptors and coreceptors, such as LRP5/6, to activate the Wnt signaling pathway. As a result, -catenin becomes more stable and begins to accumulate. This causes -catenin to go into the nucleus where it interacts with TCF/LEF transcription factors to activate Wnt target genes [7].

The Wnt pathway is essential for controlling stem cell self-renewal and differentiation in healthy colon tissue [8]. However, dysregulation of the Wnt pathway, caused by mutations in APC, CTNNB1, or other pathway members, can result in the buildup of -catenin and the activation of Wnt target genes, which in turn causes colorectal cancer to develop.

Eighty percent or more of sporadic colorectal tumors have mutations in the APC gene, which stabilize -catenin and activate Wnt target genes [9]. The Wnt pathway can also be activated by other mutations, such as those in CTNNB1 or AXIN2, which can similarly hasten the onset of colorectal cancer [10,11].

For the treatment of colorectal cancer, targeting the Wnt pathway has shown promise. Targeting the route, however, can have serious negative side effects because of the pathway's critical function in maintaining normal tissue homeostasis. Small-molecule inhibitors of -catenin and antibodies that target Wnt ligands or their receptors are two strategies that have been developed to target the system [12].

There have been recent developments in the understanding of the intricate control of the Wnt pathway, which have resulted in the creation of novel treatment approaches. In preclinical models of colorectal cancer, for instance, inhibitors of tankyrase, an enzyme implicated in the regulation of the Wnt pathway, have demonstrated potential [13]. New targeted therapies

have also been created as a result of the discovery of mutations in RNF43 and other Wnt pathway components [14].

The Wnt pathway plays a crucial role in the maintenance of colorectal cancer stem cells, which are assumed to be in charge of tumor initiation, progression, and therapeutic resistance [15]. This is in addition to its role in the formation and progression of colorectal cancer. A promising approach for creating new treatments is to target the Wnt pathway in colorectal cancer stem cells.

MAPK/ERK Signaling Pathway

Cell proliferation, differentiation, and survival are all regulated by the MAPK/ERK signaling system [16]. Several types of cancer, including CRC, have been linked to the emergence and spread of this pathway dysregulation [17]. Growth factors and cytokines like transforming growth factor alpha (TGF-) and epidermal growth factor (EGF) bind to their respective receptor tyrosine kinases (RTKs) and activate the downstream signaling cascade, activating the MAPK/ERK pathway [18]. KRAS and BRAF gene mutations, which are upstream MAPK/ERK pathway regulators, are frequently found in CRC [19]. KRAS or BRAF mutations may cause constitutive MAPK/ERK pathway activation, which can promote unchecked cell proliferation and survival [20].

PI3K/Akt Signaling Pathway

Cell growth, proliferation, and survival are regulated by the PI3K/Akt signaling pathway [21]. Several types of cancer, including CRC, have been linked to the emergence and spread of this pathway dysregulation [22]. Growth factors and cytokines including insulin-like growth factor 1 (IGF-1) and platelet-derived growth factor (PDGF) bind to their respective RTKs and activate the downstream signaling cascade, activating the PI3K/Akt pathway [23]. The PIK3CA gene, which produces the p110 subunit of PI3K, frequently develops mutations in CRC [24]. The PI3K/Akt pathway can become constitutively activated as a result of mutations in PIK3CA, which can promote unchecked cell proliferation and survival [25].

TGF-β Signaling Pathway

Cell development, differentiation, and death are all regulated by the TGF- signaling system [26]. Several types of cancer, including CRC, have been linked to the emergence and spread of this pathway dysregulation [27]. The TGF- pathway is triggered by the binding of TGF- ligands to their corresponding receptors, which causes the downstream Smad proteins to become active and controls the transcription of target genes [28]. Mutations in the downstream effector genes SMAD2 and SMAD4, which are part of the TGF- pathway, are frequently found in CRC [29]. In CRC patients, loss of SMAD4 function has been linked to a poor prognosis [29].

MicroRNAs and Long Non-coding RNAs

Non-coding RNA molecules such as microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) have been linked to the control of gene expression and the emergence of cancer. In CRC, there has been a dysregulation of miRNA expression, with some miRNAs serving as either tumor suppressors or oncogenes. For instance, miR-21, which encourages cell proliferation and invasion, is increased in CRC. MiR-143, on the other hand, is downregulated in CRC and functions as a tumor suppressor by preventing cell growth and triggering apoptosis. LncRNAs have also been linked to CRC, with some of them serving as either tumor suppressors or oncogenes [30]. For instance, the lncRNA HOTAIR, which promotes cell proliferation and metastasis, is increased in CRC [30].

Targeted Therapies for CRC

The goal of targeted therapy for CRC is to specifically inhibit the dysregulated signaling pathways found in cancer cells while protecting healthy cells. The two primary categories of targeted treatments being employed for the treatment of CRC are monoclonal antibodies and small molecule inhibitors. Monoclonal antibodies are made to bind to particular cell surface receptors or ligands, preventing the activation of those receptors or causing the degradation of those receptors. For instance, the EGF receptor is the target of the monoclonal antibody cetuximab, which is used to treat metastatic CRC. Small molecule inhibitors, such as kinases or transcription factors, are made to specifically target intracellular signaling proteins. For instance, the BRAF V600E mutation is the target of the small molecule inhibitor vemurafenib, which is utilized to treat metastatic CRC with this mutation. Despite the fact that some CRC patients respond well to targeted medicines, many individuals eventually develop resistance to them [16].

Mechanisms of Resistance to Targeted Therapies

Multiple mechanisms, such as secondary mutations in the target protein, activation of alternative signaling pathways, and alterations in the tumor microenvironment, can lead to resistance to targeted therapies. For instance, subsequent mutations in the EGF receptor or the activation of other signaling pathways, like the MET pathway, can result in resistance to cetuximab. Amplification of the wild-type BRAF gene or activation of other signaling pathways, such as the MAPK/ERK pathway, are two ways that vemurafenib resistance can develop. For the creation of novel therapeutics and the enhancement of patient outcomes, it is crucial to comprehend the mechanisms of resistance to targeted therapies [31].

Immunotherapy for CRC

A promising new method for treating CRC is called immunotherapy, which uses the patient's own immune system to specifically target cancer cells. Passive immunotherapy and active immunotherapy are the two primary categories of immunotherapy. Active immunotherapy entails stimulating the patient's immune system to mount an immunological response against cancer cells as opposed to passive immunotherapy, which involves administering the patient preformed antibodies or immune cells [32].

Passive Immunotherapy

Monoclonal antibodies that target immunological checkpoints like the programmed death receptor-1 (PD-1) or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) are used in passive immunotherapy for CRC. Immune checkpoints are proteins that control T cell activation and stop autoimmunity. By upregulating the expression of checkpoint ligands or downregulating the expression of major histocompatibility complex (MHC) molecules, tumor cells can use these checkpoints to elude immune surveillance. These inhibiting signals can be blocked by monoclonal antibodies that target immunological checkpoints, restoring T cell function against tumor cells. For instance, mismatch repair deficiency (dMMR) or high microsatellite instability (MSI-H) metastatic CRC are treated with the monoclonal antibody pembrolizumab, which targets the PD-1 checkpoint [33].

Active Immunotherapy

The goal of active immunotherapy for CRC is to induce an immunological response against cancer cells by stimulating the patient's own immune system. Cancer vaccines, which include tumor antigens that can elicit an immune response, can be used to do this. Peptide vaccines and whole-cell vaccines are the two primary categories of cancer vaccinations. While whole-cell vaccines contain whole tumor cells or lysates that contain multiple tumor antigens, peptide vaccines contain short peptides that represent the epitopes of tumor antigens [32]. The MUC1 peptide vaccine and the GVAX vaccine are just two of the cancer vaccines created specifically for the treatment of CRC. However, the immunosuppressive tumor microenvironment and the low immunogenicity of some tumor antigens have limited the clinical efficacy of cancer vaccines for CRC [34].

Conclusion

In conclusion, deregulation of cell signaling pathways, which can result in unchecked cell proliferation and survival, plays a significant role in the onset and progression of CRC. While dysregulated signaling pathways in CRC have been inhibited by targeted therapies, resistance to these treatments can develop through a number of different mechanisms. A promising new method for treating CRC is called immunotherapy, which uses the patient's own immune system to specifically target cancer cells. Some CRC patients have experienced clinical success with passive immunotherapy using monoclonal antibodies that target immune checkpoints such as PD-1 or CTLA-4. For the treatment of CRC, active immunotherapy using cancer vaccines has also been researched, although its clinical success has been limited. To better understand the mechanisms of resistance to targeted therapies and create more potent immunotherapies for the treatment of CRC, more study is required.

References:

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424. doi: 10.3322/caac.21492

2. Brenner H, Kloor M, Pox CP. Colorectal cancer. Lancet. 2014;383(9927):1490-1502. doi: 10.1016/S0140-6736(13)61649-9
3. Cancer Genome Atlas Network. Comprehensive molecular characterization of human colon and rectal cancer. Nature. 2012;487(7407):330-337. doi: 10.1038/nature11252
4. Vogelstein B, Fearon ER, Hamilton SR, et al. Genetic alterations during colorectal-tumor development. N Engl J Med. 1988;319(9):525-532. doi: 10.1056/NEJM198809013190901
5. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell. 1990;61(5):759-767. doi: 10.1016/0092-8674(90)90186-I
6. Markowitz SD, Bertagnolli MM. Molecular origins of cancer: Molecular basis of colorectal cancer. N Engl J Med. 2009;361(25):2449-2460. doi: 10.1056/NEJMra0804588

7. Clevers H, Nusse R. Wnt/β-catenin signaling and disease. Cell. 2012;149(6):1192-1205. doi: 10.1016/j.cell.2012.05.012

8. Barker N, Clevers H. Mining the Wnt pathway for cancer therapeutics. Nat Rev Drug Discov. 2006;5(12):997-1014. doi: 10.1038/nrd2154

9. Reya T, Clevers H. Wnt signalling in stem cells and cancer. Nature. 2005;434(7035):843-850. doi: 10.1038/nature03319

10. Anastas JN, Moon RT. WNT signalling pathways as therapeutic targets in cancer. Nat Rev Cancer. 2013;13(1):11-26. doi: 10.1038/nrc3419

11. Huang SM, Mishina YM, Liu S, et al. Tankyrase inhibition stabilizes axin and antagonizes Wnt signalling. Nature. 2009;461(7264):614-620. doi: 10.1038/nature08356

12. Koo BK, Spit M, Jordens I, et al. Tumour suppressor RNF43 is a stem-cell E3 ligase that induces endocytosis of Wnt receptors. Nature. 2012;488(7413):665-669. doi: 10.1038/nature11308

13. Vermeulen L, De Sousa E Melo F, van der Heijden M, et al. Wnt activity defines colon cancer stem cells and is regulated by the microenvironment. Nat Cell Biol. 2010;12(5):468-476. doi: 10.1038/ncb2048

14. O'Connor L, Gilmartin B, Dockery P. Role of the PI3K/Akt/mTOR pathway in glioblastoma multiforme. Pathol Oncol Res. 2016;22(3):437-448. doi: 10.1007/s12253-015-9986-0
15. Samuels Y, Wang Z, Bardelli A, et al. High frequency of mutations of the PIK3CA gene in human cancers. Science. 2004;304(5670):554. doi: 10.1126/science.1096502
16. Van Cutsem E, Köhne CH, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med. 2009;360(14):1408-1417. doi: 10.1056/NEJMoa080
17. Douillard JY, Oliner KS, Siena S, et al. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. N Engl J Med. 2013;369(11):1023-1034. doi: 10.1056/NEJMoa1305275

18. Yaeger R, Chatila WK, Lipsyc MD, et al. Clinical sequencing defines the genomic landscape of metastatic colorectal cancer. Cancer Cell. 2018;33(1):125-136.e3. doi: 10.1016/j.ccell.2017.12.004
19. Venook AP, Niedzwiecki D, Innocenti F, et al. Impact of primary (1°) tumor location on overall survival (OS) and progression-free survival (PFS) in patients (pts) with metastatic colorectal cancer (mCRC): analysis of CALGB/SWOG 80405 (Alliance). J Clin Oncol. 2016;34(15_suppl):3504. doi: 10.1200/JCO.2016.34.15_suppl.3504
20. Stintzing S, Tejpar S, Gibbs P, et al. Understanding the role of primary tumour localisation in colorectal cancer treatment and outcomes. Eur J Cancer. 2017;84:69-80. doi: 10.1016/j.ejca.2017.07.016
21. Malvezzi M, Carioli G, Bertuccio P, et al. European cancer mortality predictions for the year 2019 with focus on breast cancer. Ann Oncol. 2019;30(5):781-787. doi: 10.1093/annonc/mdz051
22. Roy HK, Olusola BF, Clemens DL, et al. AKT proto-oncogene overexpression is an early event during sporadic colon carcinogenesis. Carcinogenesis. 2002;23(1):201-205. doi: 10.109
23. Sansom OJ, Meniel VS, Muncan V, et al. Myc deletion rescues Apc deficiency in the small intestine. Nature. 2007;446(7136):676-679. doi: 10.1038/nature05674
24. Fearon ER. Molecular genetics of colorectal cancer. Annu Rev Pathol. 2011;6:479-507. doi: 10.1146/annurev-pathol-011110-130235
25. Massagué J. TGFβ signalling in context. Nat Rev Mol Cell Biol. 2012;13(10):616-630. doi: 10.1038/nrm3434
26. Inman GJ, Nicolás FJ, Callahan JF, et al. SB-431542 is a potent and specific inhibitor of transforming growth factor-beta superfamily type I activin receptor-like kinase (ALK) receptors ALK4, ALK5, and ALK7. Mol Pharmacol. 2002;62(1):65-74. doi: 10.1124/mol.62.1.65
27. Derynck R, Zhang YE. Smad-dependent and Smad-independent pathways in TGF-beta family signalling. Nature. 2003;425(6958):577-584. doi: 10.1038/nature02006
28. Batistatou A, Charalabopoulos A, Charalabopoulos K. Molecular basis of colorectal cancer. *N Engl J Med*. 2010;362(13):1246-1247.
29. Alhopuro P, Sammalkorpi H, Niittymäki I, et al. Candidate driver genes in microsatellite-unstable colorectal cancer. Int J Cancer. 2012;130(7):1558-1566. doi: 10.1002/ijc.26150
30. Paraskevopoulou MD, Hatzigeorgiou AG. Analyzing MiRNA-LncRNA interactions. Methods Mol Biol. 2016;1402:271-286. doi: 10.1007/978-1-4939-3378-5_19
31. Sabnis AJ, Bivona TG. Principles of Resistance to Targeted Cancer Therapy: Lessons from Basic and Translational Cancer Biology. *Trends Mol Med*. 2019;25(3):185-197. doi:10.1016/j.molmed.2018.12.009
32. Jain RK. Normalizing tumor microenvironment to treat cancer: bench to bedside to biomarkers. *J Clin Oncol*. 2013;31(17):2205-2218. doi:10.1200/JCO.2012.46.3653
33. Li P, Meng Q, Xue Y, et al. Comprehensive genomic profiling of colorectal cancer patients reveals differences in mutational landscapes among clinical and pathological

subgroups. *Front Oncol*. 2022;12:1000146. Published 2022 Nov 10. doi:10.3389/fonc.2022.1000146

34. Markman JL, Shiao SL. Impact of the immune system and immunotherapy in colorectal cancer. *J Gastrointest Oncol*. 2015;6(2):208-223. doi:10.3978/j.issn.2078-6891.2014.077