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Review Article

A critique on cell signallings involve in colorectal cancer

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ABSTRACT

Colorectal carcinogenesis (CRC) is a significant health issue in developing countries. It ranks as the third most common outcome of cancer death. New drugs are required to lower the prevalence of this ailment despite a multitude of therapeutic choices. As CRC develops, several signaling pathways pathways are activated. Among the important signaling pathways are the p53, Delta-Notch, Wnt/-catenin, Salvador-Warts-Hippo (SWH), and Kelch-like ECH assocd protein 1 pathways. This paper summarises the aetiology of CRC as well as the related death of cells and cell signal transduction pathways.

1. Introduction

A horrible condition known as cancer is defined by aberrant cell growth that causes an unnatural balance between cellular proliferation and death. Natural cell death is controlled by a biological mechanism called "touch contact inhibition." On the other side, growing tumour cells spread to distant locations and invade other organs, which causes morbidity.[1,2]

In recent years, colorectal carcinogenesis (CRC) has significantly increased as a health burden in developing nations.[3,4] CRC is the third greatest cause of cancer-related death in men and women, and it is the second most common cause in women.[5] Natural circumstances, a sedentary lifestyle, and an unhealthy diet have all contributed to an increase in CRC incidence in recent years. In many cases, the person is not aware of the symptoms. Despite increased awareness of cancer screenings and available treatments, developing nations still bear a disproportionately large share of the burden of CRC. The mortality rate from CRC is comparatively high in people from Asia and Africa. In recent years, earlier screening and improved treatment procedures have reduced mortality rates in Western nations.[6] Due to a lack of health infrastructure and understanding of cancer screening, a surge in deaths has been observed in a number of Latin American countries, the Caribbean, and Asia.[7] It is well known that dietary factors influence the prevalence of CRC.[8] It has been demonstrated that diets low in fat and high in fibre lower the risk of CRC. Our general health is impacted by the meals we eat. Red meat, fried foods, and highly processed are all associated with a higher risk of CRC.[9,10]

2. Signaling Pathways in Colorectal Cancer

Several signalling systems that affect cellular differentiation, proliferation, and immortalization are involved in the formation of colorectal cancer. Wnt/-catenin signalling stimulation, inhibition of transforming growth factor [TGF] and epidermal growth factor receptor, and k-ras signalling mutations all play a role in the evolution of CRC.[11] Signaling via Wnt/-catenin in Colon Cancer Wnt signalling has a variety of biological functions, including sustaining cell self-renewal and controlling cellular homeostasis across embryogenesis and adulthood.

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This route stimulates the proliferation and development of intestinal epithelial cells in the crypt.[12]

The receptor frizzled suppresses the phosphorylation of Glycogen synthase kinase-3 beta in the context of Wnt ligand, preventing ubiquitins from degrading -catenin. b -Catenin accumulates in the cytoplasm and translocates to the nucleus, where it transduces target genes. The cellular location of -catenin determines the activation of this signalling pathway. A mutation in the APC and -catenin genes is found in 90% of colonic tumors.[13]

Mutations in the clustered region of APC result in a shortened protein that fails to inhibit the formation of complexes. This mutational dysregulation of Wnt signalling stabilises cytoplasmic -catenin and increases -a catenin-dependent expression of Wnt target genes, which leads to CRC progression.[14]

Nuclear -catenin promotes cellular alterations that affect cell adhesion and migration in the periphery. Wnt signalling is required for the early stimulation of intestinal stem cells, which is surprising. This is important not just for stem cell survival but also for maintaining crypt homeostasis. Experimentally inhibiting Wnt signalling in cells results in the disappearance of proliferative crypts.[14]

3. PI3K/Akt/mTOR Signalling in Colorectal Cancer

In human malignancies, the PI3K/Akt/mTOR signalling network is the third most often altered oncogenic signalling network. PI3K dysregulation is found in about 30% of human malignancies, giving this signaling cascade a potential therapeutic target in cancer progression control. The role of PI3K/Akt/mTOR signalling in colon carcinogenesis has received a lot of attention. In 70% of patients with colorectal cancer, overexpression of p-Akt and altered expression of PTEN, a tumor-suppressive negative regulator of Akt, have been reported.[13]

Lycopene, a pigment, has been shown to suppress leptin-mediated cell invasion in CRC HT-29 cells by inhibiting Akt phosphorylation.[14] An additional study found that aspirin, an mTOR inhibitor, and AMP-activated protein kinase activator, stimulates apoptosis and protects against the advancement of colorectal cancer.[15]

4. TGF*B* / Smad Signalling in Colorectal Cancer

TGF and associated bone morphogenetic proteins are members of the cytokine family, which regulates a variety of cellular activities such as differentiation, proliferation, and apoptosis.[16] Many proteins are included in the TGF superfamily of cytokines, notably TGF2, TGF1, TGF3, and activins. TGF communicates with intracellular signalling molecules such as the Smad family of proteins, particularly Smads 2 and 3.[17,18] TGF stimulates the establishment and progression of the fibrotic reaction by increasing the transcription of many fibrogenic and pro-inflammatory cytokines, like platelet-derived growth factor, tumor necrosis factor, or interleukin 1 beta.[19]

In mammals, 3 main TGF isoforms have been recognized: TGF3, TGF2, and TGF1. TGF is released in an inactive state in most cases by attaching to a latent TGF-binding protein. TGF signalling is initiated downstream when a ligand binds to type II receptors, phosphorylating the type I receptor, that subsequently phosphorylates Smads 2 and 3.[20] Shows how activated Smads heterodimerize with Smad4 and pass into the nucleus to increase transcription of genes.

TGF has a dual involvement in cancer development in the early stages. TGF regulates cell proliferation and death, which can act as a tumor suppressor in healthy colon epithelial cells. TGF, on the other hand, stimulates cell migration in the late stages of cancer by promoting EMT and suppressing the immune response.[21,22] The role of TGF signaling in CRC has been previously described.[23]

5. RAS-RAF-MEK-ERK and EGFR Signalling

The epidermal growth factor receptor (EGFR), is indulged in the genesis and progression of a variety of malignancies. Ligand-activated receptors form homo- and heterodimers with other ErbB family members, autophosphorylate their tyrosine residues, and form homo- and heterodimers with other ErbB family members.[24] When a ligand attaches to a receptor, it activates subsequent signalling pathways like Ras, MAPK, ERK, NFB, and PI3K/Akt. These mechanisms are crucial for the progression of CRC. High expression of the epidermal growth factor receptor, as well as its ligands, is linked to the onset of human cancer and a poor prognosis.[25]

6. p53 and Rectum or Colon Cancer

p53 is a widely known tumor suppressor gene that is one of the most frequently altered genes in all types of human cancer. To inhibit oncogenic mutations, the p53 DNA damaging stress response is activated, which stimulates repair DNA and controls the cell cycle. In colon cancer, p53 signalling is disrupted, resulting in the absence of apoptotic and cellular checkpoints as well as genetic stability, which leads to malignancy. The shift from healthy epithelial to adenomatous to colorectal cancer is triggered by the aggregation of mutations in p53, K-ras, and APC, which are cancer-related genes.[26]

7. Notch Signaling in Colon or Rectum Cancer

The 5 ligands [Delta-like ligands 4,3,1and Jagged 2 and 1 (Sterrate-like ligands), 4 Notch receptors (Notch 1-4), and multiple downstream target genes make up Notch signalling in mammals.[27] Signalling is initiated when a notch ligand on one cell binds to the transmembrane Notch receptor on a neighboring cell.

This binding contact causes metalloproteases to break the Notch receptor's transmembrane domain, releasing the constitutively active Notch intracellular domain. This domain's translocation to the nucleus activates transcriptional complexes, causing target genes to be expressed. When contrast to other solid tumors, there is less knowledge about cell-specific roles of Notch signalling in CRC. However, abnormal stimulation of Notch signalling has been identified in CRC. Targeting both Notch and MAPK signalling on colon cancer growth, as well as its role in controlling tumour cell plasticity, was found to have a superior therapeutic effect in a recent study.[28]

Cellular resistance to chemotherapeutic treatments has been linked to Notch signalling. Notch signalling is considerably elevated in SW480 cells that are resistant to the Regorafenib medication, a multi-kinase inhibitor that was developed in the lab.

Notably, inhibiting Notch signalling in resistant cells restored their sensitivity to Regorafenib, implying that Notch plays a significant role in establishing chemotherapeutic drug resistance.[29]

The role of Notch signalling dysregulation in colon cancer metastasis has been thoroughly investigated. These findings strongly show that Notch signalling is important in the development and development of CRC.

8. NRF2/KEAP-1 Signalling in Colon or Rectum Cancer

Oxidative stress is defined as an asymmetry between antioxidant defenses and oxidant production, in which oxidants outnumber antioxidants, resulting in cellular malfunction and tissue damage. Colorectal cancer is linked to oxidative stress induced by damaging ROS.

ROS induce cellular damage, which can contribute to the development of diseases like cancer, fibrosis, and neurological disorders. To counteract the harmful consequences of reactive oxygen species, cells have antioxidant genes and detoxification genes (Phase II).[30]

Nuclear factor E2-related factor 2 (Nrf2), a basic leucine zipper (bZIP), protects tissues towards free radical-mediated insults such as carcinogens, medicines, inflammation, and so on in many disease scenarios.[13]

Cap'n'collar (Cnc) proteins are a transcription factor, the family includes Nrf2. It detects the antioxidant response element in target gene promoters.[14] Kelch-like ECH linked protein 1 beta keeps Nrf2 in the cytoplasm under normal settings.

Kelch-like ECH-related protein 1 is crucial because it acts as a linker protein between the Nrf2 and Cul3-based E3-ubiquitin ligase complex resulting in Nrf2 proteasomal and ubiquitination degradation. Certain circumstances, like the stimulation of the antioxidant responsive element, cause Nrf2 to disengage from its Kelch-like ECH-associated protein 1 partner, allowing Nrf2 to translocate to the nucleus. Nrf2 dimerizes and connects with tiny Maf proteins within the nucleus, allowing it to connect to antioxidant responsive elements and increase the transcriptional activity of these genes.[12] Many medicines' chemopreventive effects in colorectal cancer are heavily reliant on this signalling.[18]

9. Colon or Rectum Cancer and Salvador-Warts-Hippo Pathway

The discovery of the hippo route started with the study of tissue enlargement in Drosophila melanogaster flies with concurrent mutations.[13] Owing to its interaction with oncogenic signalling pathways, Hippo signalling has gotten a lot of interest in cancer biology.[11] The Hippo pathway's primary transcription regulator is Yes-associated protein 1. The Hippo pathway is orchestrated by this protein and its PDZ-binding region partner taffazin.[11]

Hippo signalling is involved in the modulation of tissue homeostasis, growth, restoration, and cancer in theory.[12] Mammalian protein components are shown as follows: Ste 2 like kinase 1 and 2 in mammals, as well as LATS 1 and LATS 2. These kinases phosphorylate YAP1 and TAZ, causing nuclear exclusion and cytoplasmic ubiquitin-mediated proteasomal degradation, resulting in the repression of genes targeted by YAP1 [Yes-associated protein 1] and TAZ (PDZ-binding domain taffazin).[13] Hippo signalling appears to have a vital role in CRC, according to a growing body of evidence.[14] Crosstalk between the Hippo signalling pathway and other signalling pathways has been described.[15]

10. MicroRNAs and Rectum or Colon Cancer

Many molecular pathways associated with CRC have been uncovered over time. The discovery of microRNAs (miRNAs) has sparked a lot of interest in many illness situations in recent years. MiRNAs have become both an enticing tool and a novel therapeutic target as researchers have gained a better knowledge of their functions in development and disease, particularly in cancer. MiRNAs are non-coding RNAs that are 20-24 nucleotides in length and are classed as Oncomirs, which include cancer-related tumor-suppressor miRNAs. The cell cycle, differentiation, proliferation, metabolism, and apoptosis are all impacted by miRNAs, according to a new study on miRNAs and cancer.

MicroRNAs such MicroRNA-21**,** MicroRNA-181b1, MicroRNA-101, the let7 family, MicroRNA–133b, and MicroRNA-126 have been found to be deregulated in CRC. MicroRNA-760 has recently been discovered to inhibit human rectum or colon cancer growth by inhibiting BATF3/AP-1/cyclinD1 signalling. In colorectal cancer, MicroRNA -422a works as a tumour suppressor, and its presence is restricted to CRC tumours. Increased transcription of miR-422a in colorectal cancer cells may impede cell growth and induce cell apoptosis. MiR-422a

has also been shown to suppress the p38/MAPK pathway, which inhibits colorectal cancer. As a result, miRNAs are appearing as prospective CRC targets.

11. Colorectal Cancer Targeted Therapy

Researchers have designed new types of medications to particularly target alterations in cells that produce colon or rectal cancer as they understand much about these changes. Chemotherapy (chemo) medications function differently than targeted drugs. They can help when chemo treatments don't, and they have a variety of negative effects. They can be taken in conjunction with chemo or on its own if chemo is no longer effective. These medications, like chemotherapy, penetrate the bloodstream and reach practically every region of the body, making them effective against tumours that have progressed to other areas of the body.

VEGF (vascular endothelial growth factor) is a protein that helps tumours develop by forming new blood vessels (a process known as angiogenesis). Some colon and rectal cancers can be treated with drugs that block the action of VEGF. Bevacizumab (Avastin), Ramucirumab (Cyramza), and Ziv-aflibercept are among them (Zaltrap). The standard treatment for colon cancer is generally based on using cytotoxic drugs, radiotherapy, chemotherapy, and surgery. However, the use of traditional treatments has received attention in recent years.

There are several allopathic and herbal drugs that target at various pathways to stope the CRC. The epidermal growth factor receptor (EGFR) is a protein that promotes the proliferation of cancerous cells. Some established colon and rectal cancers can be treated with drugs that target EGFR. Cetuximab (Erbitux) and Panitumumab are two of them. In colorectal tumours with mutations (defects) in the KRAS, NRAS, or BRAF genes, these medications usually don't work on their own. Doctors frequently test tumours for these gene abnormalities before treating them, and only use these medications in persons who don't have them. When cetuximab is taken with the BRAF inhibitor encorafenib, this is an exception (see below). Even with one of these mutations, the combination of these two medications appeared to help people with advanced colorectal cancer live longer.

Changes (mutations) in the BRAF gene are found in less than 10% of colorectal tumours. These mutations cause colorectal cancer cells to produce an aberrant BRAF protein, which aids their growth. This aberrant BRAF protein is the target of certain medicines.

Encorafenib (Braftovi) is a medication that works by directly attacking the faulty BRAF protein. When used with cetuximab (see above), this medicine can decrease or halt the growth of colon cancer in certain persons with advanced disease. The combination of these two medications appears to extend the lives of persons with advanced colorectal cancer.

12. Conclusion

Due to the low efficacy of monotherapeutic approaches in the treatment of CRC, research attempts to develop more potent medications against CRC advancement are essential. This review concentrated on a subset of recent signal cascades and how they relate to the progression and metastasis of colon or rectal cancer. Researchers should be better able to understand the intricate molecular mechanisms underlying colon or rectum cancer with a stronger understanding of anticancer drugs that target these cell death pathways and mechanisms. This will enable the development of extremely effective remedies.

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None.

14. Conflict of Interest

None.

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