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Review

A review on role of oncogene (KRAS) & tumor suppressor gene (TP53) in colorectal cancer

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Abstract

Multiple oncogenic mutations and the cross stalk between normal pathways are the sources of the complexity involved in Colorectal Cancer (CRC) therapy. Mutated from of a type of gene called protooncogenes, which is involved in normal cell growth and disunion. A tumor suppressor gene, also known as an antioncogene, controls a cell's division and replication. Activation of different protooncogenes can lead to the carcinogenesis of colorectal cancer. Despite important progress attained in the symptomatic and therapeutic management of patients with colorectal cancer, there has been newly a significant growth in the prevalence of large intestine cancer in individuals below the age of 50 years. Primal inception of colorectal cancer has a complex incidence of mucinous histology, a more remote site, a different deoxyribonucleic acid (DNA) methylation profile, and a reduced survival rate. Understanding the pathophysiological mechanisms underlying this oncogenesis process may also make it easier to identify new targets for treatment.

Keywords: Oncogene, Tumor suppressor gene, Colorectal cancer, Protooncogene.

INTRODUCTION

Colo rectal cancer also known as large bowl cancer or colon cancer, is described as a malignant growth in the colon, rectum, and appendix. One of the disease that arises and spreads when a living system controls a system and turns faulty is called cancer.[1] The identification of protooncogenes has led to progressions in our knowledge of the molecular genetics of polyp growth.[2] Reliability for protooncogenes to have a role in the pathophysiology of human and animal cells. Oncoprotein results in altered regulation, higher concentration, or enhanced protein activity compared to normal proteins. Protooncogenes are normal genes that have the potential to become oncogenes due to mutation.[3] According to the international classification of diseases for oncology, CRC cases were categorized as either rectum (C19.9&C20.9) or colon (C18.0-C18.9&C26.0).[4] Ras protein, a

protooncogenis most often metamorphosed in human cancer. The oncogenes Ras, EGFR (Erb-B1), Erb-B2, TGFalfa, and TGF-Beta1 have been shown to play a role in colorectal cancer. Oncogene was first identified in some RNA viruses. RAS protein is a type of oncogene formed from three genes. More than two decades ago two genes were discovered as retroviral oncogenes within two viruses KRAS (Kristen rat sarcoma virus) and HRS(Harvey rat sarcoma virus.[5] Tumor suppressors are indolent in case of development of CRC. The existence and development of malignant tumors mainly by the stimulation of oncogene and deactivation of tumor suppressor gene. Deactivation and development of metastatic colorectal cancer occur when the tumor suppressor gene activates.[6] Commonly mutated gene in human malignancies including colon cancer is RAS oncogene.

Oncogenes

The identification of protoncogenes has advanced our knowledge of the molecular genetics of human development.[7] Human and animal cancer is involved in pathogenesis when the proto-oncogenes are altered.[8] Oncogene has the potential to cause cancer. In colorectal cancer several genes mutated commonly they are KRAS (Kristen rat sarcoma virus), BRAF (N-rat murine sarcoma viral oncogene homo log-B), PIK3CA (Phosphatidylinositol-4,5-bisphosphate 3-kinase subunit alpha), MYC (Myelocytomatosis oncogene), SRC (Serine protein kinase), ERBB2 ((v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2), MET (Mesenchymal Epithelial Transition). The most mutated oncogene in CRC is KRAS, a family member of RAS in CRC.[9] HRAS and KRAS were identified from the Harvey sarcoma virus and Kristen sarcoma virus these two genes belong to the RAS family, discovered by Jennifer Harvey and Werner Kristen.[10]

RAS Mutations in CRC

Through the induction of a variety of inflammatory cytokines, RAS mutations have been linked to aberrant cell signaling that promotes tumor-promising inflammation, enhances tumorigenesis, and increases invasiveness. RAS mutations are common in CRC (45%), with KRAS being the most rampant (85%), followed by NRAS (15%) and HRAS (1%). The majority of KRAS mutations in KRAS mutations in the CRC are located in codons 12 and 13 of exon 2 (80% are G12A, G12C, G12D, G12S, G12V, G13C, G13D), and less frequently in codon 61 of exon 3 (5% are Q61H, Q61L, and Q61R) and codon 146 of exon 4 (2% are A146T and A146V). Any codon pseudo mutation promoted faster nucleotide exchange and reduced GAP binding. Both of these result in increased KRAS activation and GTP binding. KRAS mutations also have a poor prognostic effect since they predict that metastatic CRC patients will respond to anti-EGFR therapy.[11] With GTP hydrolase (GTPase) firmly situated on the cell membrane, RAS is an abundant guanylate-binding protein that is inactive when it binds to GDP.

KRAS Oncogene

KRAS oncogene acts as a molecular switch that cycles between a GDP-bound active state and an inactive GDP-bound state. Among all cancers, KRAS is one of the oncogenes with the highest frequency of mutations. In CRC cases, the frequency of KRAS mutations is almost 40%.[12] Once KRAS mutation occurs, the hydrolysis of GTP disturbed and/or nucleotide exchange is enhanced, and then KRAS accumulates in an active state, causative to continuous activation of downstream signaling pathways, thereby promoting tumor cell proliferation. Their bearing KRAS mutations are associated with advanced disease states, poor tumor differentiation, distinct metastasis, and their interior survival in patients.[12] In CRC, KRAS mutations are most associated with right-sided colon tumors and approximately 85% of KRAS mutations occur in one of the three major hotspots (codon 12,13&61).[13] According to this, codon 12 mutations are dominant in approximately 65% of KRAS alles.[14]

Tumor suppressors

A tumor suppressor gene or antioncogene is a gene that controls a cell during cell division and replication. If the cell grows uncontrollably, it will result in cancer. When a tumor suppressor gene is mutated, it results in a loss or reduction in its function. These tumor suppressor genes act as “double agents” that both positively and negatively regulate transcription. The tumor suppressor gene acts as a caretaker gene, gatekeeper gene.[15] Adenomatous polyposis coil gene (APC) and TP53 are two of the most frequently mutated tumor suppressor genes TSGs in colorectal cancer (CRC), and several other tumor suppressor genes have also been connected to the carcinogenic process of CRC. The progression of colorectal cancer is a multistage process that involves the activation of a tumor suppressor gene and the activation of an oncogene.[16] Numerous studies have concluded that P53 plays a major role in defending our body from the development of cancer. The present research demonstrates that mutations at the level of the APC gene commence the process of colon tumor development.

TP53 tumor suppressor gene

TP53 is a tumor suppressor gene in this P53 is protein product. A frequently known tumor suppressor gene in colorectal cancer is TP53. Its oncogenic property is due to P53 mutation. The role of TP53 in bringing caspase-mediated cell death, it also plays a key role in cell cycle regulation, Cellular senescence, chromosomal

segregation, and cell division controls and is regulated by TP53. Because of this, it is named as "guardian of the genome". P53 protein is a nuclear phosphoprotein. The progression of colorectal cancer is a multistage process that comprises the inactivation of tumor suppressor gene activation of oncogene.[17] Retinoblastoma protein gene was first revealed suppressor gene, and it is classified as a classic suppressor. In most of the cancers, the classic loss of the RB1 gene is observed, and thus the reduction or loss of expression of its protein product. Gene metamorphosis can cause continuous cell replication, despite DNA impairment and an accomplishment of mutation P53 protein action.[18] Realms of P53 protein are imperiled to post-translational adaptions and this allows P53 stabilization, oligomerization, and transactivation. TP53 protein is a transcription factor that switches the output of numerous biological processes according to the biotic progression class of cellular signal participation. Stress signals are known to stimulate P53 incorporating oncogene triggering, DNA destruction, and replication stress. The main biological function of P53 is to appear to fight in the defense of the DNA integrity of the cell.TP53 plays additional roles in development, aging, and cell differentiation.[19]

Several TSGs have been linked to the colorectal carcinogenic process During this process adenomatous polyposis coil gene (APC) and TP53 being two of the most commonly mutated TSGs play a major role in CRC.[20] CRC may develop due to various etiological factors like familial adenomatous polyposis (FAP) which accounts for around 1% of CRC cases going to occur in the early stage of life.[21] The main common changes of P53 in human cancers are missense mutations within the gene's coding sequence. Such mutations are found in major histogenitic groups comprising cancers of the colon (60%), breast (20%), lung(70%), brain(40%) and esophagus(60%).[22]

It is not astonishing that due to the nature of all procedure that P53 contribute in, its activity is closely controlled.[23] P53 definitive biological response is not persuaded by the cellular type, and stress but also by the defense modifiers/cofactors that bind to P53 protein before performing the transactivational mechanism of P53 target genes.[24] Additionally, P53 not only exerts its tumor suppressive functions during transactivational mechanisms but also by protein-protein interactions, where protein also varies across cell types.[25]

Abbreviations

Colorectal Cancer (CRC), Deoxyribonucleic Acid (DNA), Epidermal growth factor receptor (EGFR), KRAS (Kristen rat sarcoma virus), BRAF (N-rat murine sarcoma viral oncogene homo log-B), PIK3CA (Phosphatidylinositol-4,5-bisphosphate 3-kinase subunit alpha), MYC (Myelocytomatosis oncogene), SRC (Tyrosine-protein kinase) ERBB2 (v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2), MET (Mesenchymal Epithelial Transition), GTP Hydrolase (GTPase), Adenomatous Polyposis Coil Gene (APC), Familial Adenomatous Polyposis (FAP), Tumor Suppressor Gene (TSG).

CONCLUSION

Mutations in RAS oncogene, particularly KRAS, are common in colorectal cancer. These mutations leads to the stimulation of signaling pathways that drive uncontrolled cell proliferation and tumor growth. KRAS mutations are associated with resistance to certain therapies, making their identification important for treatment planning. The P53 protein is encoded by the TP53 gene, which is crucial for controlling the cell cycle and triggering apoptosis in reaction to damage to DNA.TP53 mutations are prevalent in colorectal cancer and often lead to the loss of these functions, contributing to tumor progression and genomic instability.KRAS mutations drive tumorigenesis through aberrant signaling, while TP53 mutations result in the loss of critical tumor-suppressing functions both genetic alterations participate in the growth and advancement of colorectal cancer and have implications for treatment strategies and prognosis.

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