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Extended Abstract

A Simple Outline of the Genetic Cross Talk and the Mutations in Colorectal Cancer That Could Be a Potential Cure in Future

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Abstract

One of the leading non – communicable disease that has inflicted devastative effects on millions of lives can well be pointed into the direction of cancer and out of which, the frontier in line is the colorectal cancer (CRC) affecting both gender with women showing the higher mortality in comparison to men for the age group of 65 and above. There are multiple sources including both epigenetic as well genetic mutations that may divert normal metabolic pathway to the formation of colorectal carcinoma. This very short review underlines our current knowledge on the CRC pathogenesis through genetic level along with the summarization of the role of genetic and epigenetic changes in the origin and progression of the multiple CRC pathways. Indeed, our understanding of the effect of colorectal carcinoma through molecular level and its transition from colorectal adenoma to carcinoma can be segregated into three specific pathways: (1) microsatellite instability (MSI) which is linked to the loss of DNA mismatch repair activity; (2) chromosomal instability (CIN) that results from the imperfections in the chromosomal segregation, the telomere firmness, and the biochemical/ metabolic responses against DNA damage; and finally (3) the CpG island methylator phenotype (CIMP); i.e., the global genome hypermethylation which turns off the tumour suppressor genes. However, it is important to note that although the understanding of CRC have progressed steeply in recent years but we are yet to identify the exact molecular signal transduction mechanism of colorectal cancer development as the identification of candidate genes are still in progress yet so far an array of the differentially expressed genes (DEGs) functionally involved in cell cycle and cell proliferation as well as in the mitotic cell cycle, the cell-cell signalling pathways, hormone activities, drug metabolism, androgen and estrogen metabolism, neuroactive ligand-receptor interaction; and in the cytokine and chemokine activity (including the cytokine-cytokine receptor interaction) has been identified basically through Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis. Several hub genes possessing significant roles in the protein-protein interaction (PPI) have also been identified whose deletions were noticed to be associated with the fatal impact on the integrity of the biological network thereby indicating their necessity for the survival from CRC. Genomic changes due to chromosome instability cause the inactivation of the tumour suppressor gene adenomatous polyposis coli (APC gene), whose mutations have been reported to impart colon cancers in approximately 80% cases within human. This inactivation leads to the constant expression of β-Catenin/Wnt signalling pathway which is one of the pivotal propulsion of colorectal carcinogenesis. In addition, the Mitogen-Activated Protein Kinase/Extracellular Signal-Regulated Kinase pathway (MAPK/ERK pathway) is another pathway that plays crucial role in the development of colorectal carcinoma. It occurs in two ways, one through the upregulation of Epidermal growth factor receptor (EGFR receptor) and the other through the mutation of proto-oncogenes - *ras* gene, encoding K-RAS, the GTP/GDP-binding signal transducing molecules from the cell surface to the nucleus and hence acting as a link in the signal transduction triggered by binding of the growth factors to cell membrane receptors facilitating the cell survival; and the *raf* gene encoding B-RAF (a protein from kinase family) to which GTP-bound RAS protein binds and interacts. Both RAS and RAF are known to be the desperate mediators of the MAPK pathway controlling the cellular homeostasis; and therefore the mutations of *ras* and *raf* genes are highly allied to the development of colorectal cancer. While the renowned oncogenes triggering the colorectal cancer are most widely known to be *ras*, transforming growth factor TGF-□ and □1,

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*erb*B-1, encoding the epidermal growth factor receptor (EGFR); the suppressor genes or gene products have been identified as the APC, p53, p27 and interestingly the deletion of the 5q allele as well as the hyper methylation. Indeed, the mutation of the guardian 4555 genome -TP53 is known to be highly associated with progression of CRC from adenoma to carcinoma. The TP53 gene in normal condition plays significantly role in cell cycle arrest, apoptosis and DNA damaged repair. This mechanism is turned off by mutation leading to loss of regulated cell death, thus causing prolonged cell growth and entering carcinoma. This is to be noted that under the stressed condition p53 mediates the DNA damage, hypoxia, or oncogene activation, etc. Besides, the *ras* genes also perform molecular crosstalk with phosphatidylinositol 3-kinase (PI3K)/ AKT (Protein Kinase B)/ mammalian target of Rapamycin (mTOR) pathway, promoting the survival and growth in response to the extracellular signals. Activation of PI3K–Akt signalling pathway leads to the induction of the coordinated expression of cyclin D1 (for the G1 phase progression), cyclin E (transition between G1 to S phase before DNA replication) and the oncogene CDK4 (gene knockdown by the small RNA or siRNA have shown inhibition of cellular proliferation and cell-cycle progression, promotion of cellular apoptosis). The activation of this pathway thus causes the contribution to the malignancy of the benign lesions. This either occurs through the mutation in the PIK3 genes (the phosphatidylinositol-4,5-bisphosphate 3-kinase that is one of the most commonly mutated genes in CRC) in the subunits CA and CB, or through the amplification of AKT pathway. Besides, loss of the function of PTEN, which maintains the cellular stability through the direct interaction with TP53, and is known to be the negative regulator PI3K–Akt signalling pathway as well as the hyper-activation of the mTOR gene further activates two distinct genes: carbamoyl-phosphate synthetase 2, aspartate transcarbamylase, and dihydroorotase (CAD) gene for pyrimidine synthesis, and the p70 ribosomal protein S6 kinase β-1 (p70S6K) for protein synthesis that finally lead to the activation of PI3K–AKT signalling pathway where an increase in cellular carcinoma occurs. AKT, RAS and Smad7 genes (TGF signal inhibitor) help to impede the destruction complex protein which normally degrades the beta catenin protein. The inhibition of the destruction complex protein causes beta- catenin to be upregulated thus allowing the progression of colorectal tumorigenesis. Furthermore, R-smad Co-smad complex also enhances the β-catenin activity by binding to β-catenin and its transcription factor, TCF, hence activating the proto-oncogenes C-myc, C-jun, cyclin D, EGFR, TGF1, CD44. Microsatellite instability inactivates many crucial mismatched repair (MMR) genes along with aberrant DNA methylation leading to the silencing of tumour suppressor genes leading to oncogenic mutation. Germline mutation of mismatch repair (*MMR*) genes (*MLH*1, *MSH*2 *MSH*6, *PMS*2) and epigenetic silencing of the promoter region of *MLH*1 by Cpg Island Methylator Phenotype (CIMP) in somatic CRC is highly susceptible to DNA replication error resulting in inactivated tumour suppressor proteins contributing to tumorigenesis. Lots of literatures have been published with the emphasis on the signal transduction pathway involved in the development of the CRC. Present write up further elucidated on the cross talk of the signalling pathways that lead to dysregulation of many proto-oncogenes as reported previously. Furthermore, it is stipulated that targeting the genes participating in the cross talks of possible intertwining pathways would be a potential therapeutic tool as well.