

Colorectal Carcinogenesis: A Complex Malignancy of Multiple Pathways

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Colorectal tumorigenesis, a multistep process that leads to deregulation of a various critical molecular pathways as a result of genetic alterations of oncogenes and tumor suppressor genes. Cellular changes at molecular level involving the different pathways leading to colorectal carcinogenesis (CRC) mostly begins with the classical adenoma-carcinoma sequence of the large bowel as a gradual series of pathological neoplastic alterations that are associated with accumulation of genetic and epigenetic molecular switches.

The pathways to CRC initiate either because of one or combination of various molecular pathways, viz; chromosomal instability (CIN), CpG island methylator phenotype (CIMP), and microsatellite instability (MSI) [1]. With the initiation of CIN pathway, the alteration in the APC gene begins at first instant followed by the activation of KRAS, an oncogene and inactivation of tumor suppressor TP53 [1]. The characteristic of CIMP pathway is mostly promoter hypermethylation of tumor suppressors, likely methylguanine DNA methyltransferase (MGMT) and MutL homolog 1 (MLH1). Microsatellite instability is also associated with hypermethylation [2].

Most of the reported studies have conserved the adenoma→carcinoma sequence and points out the presence of mutations in adenomas, which is a precursor lesion that finally develops to carcinoma. But Malhotra P, *et al.* in 2013 and 2014, showed that the lack of multiple mutations in tumors demonstrates that the genetic alterations might have independent influences on CRC development and possibility of various alternative genetic pathways to CRC [3,4]. Though the mutational frequency of APC and KRAS gene were similar to other studies in Europe and US, but there was no association between the mutations and its percentage. With this hypothesis, we worked on the alternative pathways to CRC in Indian population and explored the APC/β-Catenin/TCF-4 signaling pathway. In case of β-catenin gene, we observed various point mutations in humans with a frequency of 21.66% at different codons [5,6]. The frequency of mutations in case of APC was 45% in tumorous tissue [7]. DNA sequencing revealed 3, 4 and 3 point mutations in different tumor samples in GSK-3β exons 1, 10 and 11 respectively [8]. In addition, regardless the absence of mutations in exon 17 of TCF-4 gene and the decrease in the expression in tumor samples points the crucial role of TCF-4 gene in colorectal carcinogenesis [9]. Besides this, the role of miR 135 family in regulating APC function perse describes an independent role of miRNA dependent pathways to colorectal carcinogenesis [10].

Thus, these results suggest that CRC is the cumulative effect of many genetic and epigenetic pathways. And the current editorial provides an insight into various signalling pathways to colorectal tumorigenesis.

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