

JOINT EVENT ON

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Gut microbiome regulation of cancer stem cells and colon carcinogenesisAdhip P N Majumdar, Lulu Farhana, Fadi Antaki, Stephanie Judd, Pratima Nangia Makker, Sarah Sarkar, Timothy Hadden, Yingjie Yu and Edi Levi
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Colorectal cancer (CRC), whose incidence increases markedly after the age of 50 years, is a multi-step process resulting from accumulation of mutations during progression from normal epithelium to carcinoma. Loss or inactivation of the tumor suppressor gene in adenomatous polyposis coli (Apc) initiates genomic instability that is thought to produce the phenotypic appearance of an adenoma. Increasing evidence suggests that pluripotent cancer stem cells (CSCs) are involved in the development and progression of many types of malignancies, including CRC. Earlier, we reported that patients with ≥ 3 adenomas (High-risk for CRC) exhibit a marked increase in CSCs in the colon than those without adenomas. Although the regulatory mechanisms for this increase in CSCs are poorly understood, we have suggested a role for secondary bile acids in the intestine, specifically deoxycholic (DCA) and lithocholic (LCA) acids, bio-transformed by gut microbiota, in regulating this process. Indeed, we observed a marked rise in *Fusobacterium nucleatum* and *Enterobacterium* (in High-risk CRC patients). An opposite phenomenon was noted both are associated with CRC) for the anti-inflammatory *Bifidobacteria* and for probiotic *Lactobacillus acidophilus*. Among the secondary bile acids, DCA and LCA are thought to be the most significant with respect to the development of CRC. Interestingly, we found the levels of DCA and LCA in the colon of High-risk (HR) CRC patients to be markedly higher than those at lower risk (LR) for CRC. Interestingly, we found DCA and/or LCA to induce not only mutations of CRC initiating genes such as β -catenin but also CSCs in normal human colonic epithelial cells, as evidenced by increased colon sphere formation and elevated expression of several CSC markers as well as MMP-2, accompanied by an induction in drug exclusion and increased expression of multiple drug resistance (MDR) transporters ABCB1 and ABCG2. Our observations suggest that alterations in specific gut micro-organisms resulting in increase in DCA and LCA that induce stemness in colonic mucosal cells where CRC-initiating genes are mutated are responsible for the development of sporadic CRC.

Biography

Adhip P N Majumdar received his MS and PhD degrees from the University of London, England, and DSc (Doctor of Science) degree in Gastroenterology from the University of Aarhus, Denmark. He has been a Professor at Wayne State University since 1992. He also holds the post of Senior Research Career Scientist at the Detroit VA Medical Center. Over the past several years his work has been streamlined to uncover the biochemical and physiological pathways governing the growth of gastrointestinal (GI) tract. He has published 200 original scientific articles in peer-reviewed journals and a multitude of book chapters and review articles. He is particularly interested in elucidating the patho-physiology of age-related changes in the GI mucosa, specifically those that lead to malignancy. To this end, he has begun to investigate the role of pluripotent, self-renewing CSCs in the development and progression of GI malignancies. He has been continually funded by the VA and NIH and is considered one of the nation's leading investigators in gastrointestinal aging and cancer.

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