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Genetic and epigenetic alterations during the development of chronic colitis and colitis-associated colorectal cancer

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Chronic colitis malignant transformation is one of major causes to colorectal cancer, but the mechanisms of colitis development and malignant transformation is largely unknown. Using a unique mouse model, we have demonstrated that the mice with targeted disruption of the intestinal mucin gene Muc2 spontaneously developed chronic inflammation at colon and rectum at early age, whose histopathology was similar to ulcerative colitis in human. In the aged mice, Muc2-/- mice developed colonic and rectal adenocarcinoma accompanying severe inflammation. To determine the mechanisms of the malignant transformation, we conducted miRNA array on the colonic epithelial cells from Muc2-/- and +/+ mice. MicroRNA profiling showed differential expression of miRNAs (i.e. lower or higher expression enrichments) in Muc2-/- mice. Based on relevance to cytokines and cancer, the miRNAs were validate and were found significantly downregulated or upregulated in human colitis and colorectal cancer tissues, respectively. The targets of the miRNAs were further characterized and their functions were investigated. More studies from the Muc2-/- mice showed disorder of gut microbiota. Moreover, a novel tumor suppressor PRSS8 also plays a critical role in colorectal carcinogenesis and progression, for instance, tissue-specific deletion of the PRSS8 gene resulted in intestinal inflammation and tumor formation in mice. Gene set enrichment analysis showed that the colitis and tumorigenesis were linked to the activation Wnt/beta-catenin, PI3K/AKT and EMT (epithelial-mesenchymal transition) signaling pathways. Taken above, the disorder of gut microbiota could result in genetic mutations, epigenetic alterations, leading to the activation of oncogenic signaling, in colorectal epithelial cells, and finally, to colitis development, promoting malignant transformation and mediating colorectal cancer metastasis.

Biography

Wancai Yang is the Dean of the Institute of Precision Medicine and School of Basic Medical Sciences, Jining Medical University, China, and a Professor of Pathology at University of Illinois at Chicago, USA. He is also an Adjunct Professor of Biological Sciences at University of Texas, El Paso, USA. He obtained his MD degree and was trained a Pathologist, and received Post-doctoral training from Rockefeller University and Albert Einstein Cancer Center. In 2006, he moved to the Department of Pathology, University of Illinois at Chicago. He is serving as Grant Reviewer for the National Institutes of Health (USA) and the National Nature Science Foundation of China. His research focuses on: (1) mechanisms of gastrointestinal carcinogenesis, (2) identification of biomarkers for cancer detection and patient selection for chemotherapy, (3) implication of precision medicine in cancers. He has published about 90 articles and has brought important impact in clinical significance.

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