Wancai Yang, J Mol Biomark Diagn 2016, 7:5(Suppl)
http://dx.doi.org/10.4172/2155-9929.C1.028

Malignant transforamtion: Epigenetic alterations in colitis-associated colorectal cancer

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Besides the canonical and non-canonical Wnt pathway to colorectal cancer, chronic colitis is strongly associated with colorectal cancer formation. However, the mechanisms of colitis develops and how chronic colitis progress to malignance is not clear. To determine the mechanisms of the malignant transformation, we conducted miRNA array on the colonic epithelial cells from the 3-month 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, some miRNAs were validate and were found significantly downregulated in human colitis and colorectal cancer tissues. Using a unique mouse model, we have demonstrated that the mice with targeted disruption of the intestinal mucin gene Muc2 spontaneously develop chronic inflammation at colon and rectum at early age, whose histopathology was similar to ulcerative colitis in human. After 3 months of age, the Muc2-/- mice develop colonic and rectal adenocarcinoma accompanying severe inflammation. We further characterized one of the most changed miRNA – miR-27a. We found that miR-27a was significantly reduced in colorectal cancer tissues and colorectal cancer cell lines, and that the reduced miR-27a was associated with distant metastasis and colorectal cancer clinical pathological stages. Functional studies showed that increasing miR-27a inhibited colon cancer cell proliferation, promoted apoptosis and attenuated cell migration, which were also linked to downregulation of p-STAT3 and upregulation of cleaved caspase 3. *In vivo*, miR-27a inhibited colon cancer cell growth in tumor-bearing mice. Bioinformatic and systemic biological analysis predicted several targets of miR-27a, among them SGPP1 and Smad2 were significantly affected, and interestedly, miRNA-associated cytokines were also significantly increased in Muc2-/-mice. SGPP1 and Smad2 were negatively correlated with miR-27a in human colorectal cancer tissues and cancer cell lines. More studies from the Muc2-/- mice showed disorder of gut microbiota. The disorder of gut microbiota could result in genetic mutations, epigenetic alterations, and activation of oncogenic signaling, in colorectal epithelial cells, leading to colitis development, promoting malignant transformation and mediating colorectal cancer metastasis.

Biography

Wancai Yang is a Professor of Pathology and Dean of the School of Basic Medical Sciences and Institue of Precision Medicine, Jining Medical University, China and an Adjunct Professor of University of Illinois at Chicago, Chicago, Illinois, USA. He was trained as a Pathologist in China and received Post-doctoral training in Rockefeller University and Albert Einstein Cancer Center, New York, USA. He has published more than 80 papers in high-impact journals about his research on colorectal and esophageal cancers. He has also been serving as Grant Reviewer, Article Reviewer and Editorial Board Members of reputed journals.

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