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Epigenetic alterations during chronic colitis malignant transformation

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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 develop and how chronic colitis progress to malignancy is not clear. 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 an early age, whose histopathology was like ulcerative colitis in human. In the aged mice, *Muc2*^{-/-} mice develop 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 validated 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. 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.

Recent Publications

1. Qian Z, Wu Z, Huang L, Wang L, Li L, Yao L, Kang K, Qu J, Wu Y, Luo J, Liu J, Yang W and Gou D (2015) Mulberry fruit prevents LPS-induced NF- κ B/p38MAPK signals and suppresses both acute colitis and colorectal tumorigenesis in DSS and *MUC2*^{-/-} mouse models. *Sci. Report* 5:17348.
2. Bao Y, Wang Q, Guo Y, Li, K, Yang Y, Chen Z, Zhang H, Dong H, Shen K and Yang W (2016) PRSS8 methylation and its significance in esophageal squamous cell carcinoma. *Oncotarget* 7(19):28540-55.
3. Bao Y, Li K, Guo Y, Wang Q, Li Z, Yang Y, Chen Z, Wang J, Zhao W, Zhang H, Chen J, Dong H, Shen K, Diamond AM and Yang W (2016) Tumor suppressor PRSS8 targets Sphk1/S1P/Stat3/Akt signaling in colorectal cancer. *Oncotarget* 7(18):26780–26792.
4. Bi X, Shi Q, Zhang H, Bao Y, Hu D, Pohl N, Fang W, Dong H, Xia X, Fan D and Yang W (2016) c-Jun NH2-terminal kinase 1 interacts with vitamin D receptor and affects vitamin D-mediated inhibition of cancer cell proliferation. *J Steroid Biochem Mol Biol.* 163:164-72.
5. Guo Y, Bao Y, Ma M and Yang W (2017) Identification of Key Candidate Genes and Pathways in Colorectal Cancer by Integrated Bioinformatical Analysis. *Int. J. Mol. Sci.* doi: 10.3390/ijms18040722.

Biography

Wancai Yang is the Dean of the Institute of Precision Medicine and School of Basic Medical Sciences, China; and a Professor of Pathology, University of Illinois at Chicago, USA. He is also an Adjunct Professor of Biological Sciences, University of Texas, El Paso, USA. He obtained his MD degree and was trained a Pathologist from China and received Post-doctoral training on Cancer Biology from Rockefeller University and Albert Einstein Cancer Center, and was promoted as Assistant Professor. In 2006, he moved to the Department of Pathology, UIC. He was serving as grant reviewer for the National Institutes of Health, USA and National Nature Science Foundation of China. His research focuses on: the determination of mechanisms of gastrointestinal carcinogenesis, identification of biomarkers for cancer detection and patient selection for chemotherapy and implication of precision medicine in cancers. He has published more than 80 articles and has brought important impact in clinical significance.

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