OMICS Group Conferences
Accelerating Scientific Discovery

2nd International Conference on
Gastroenterology & Urology
June 10-12, 2013 Hilton Chicago/Northbrook, USA

Cloning Barretts stem cells: Insights into patient stratification, tumorigenesis and strategies of preemptive therapy

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Upper gastrointestinal cancers, including esophageal and gastric adenocarcinoma, are among the most deadly of proliferative diseases. This poor prognosis is driving a fundamental reassessment of therapeutic strategies for these patients, in particular the possibility of treating the premalignant lesions that ultimately lead to these cancers. These precancerous lesions appear as "intestinal metaplasia"- tiny, intestine-like glands designated "Barrett's esophagus" and "gastric intestinal metaplasia", and are likely derived from minority, rogue cell populations in these epithelia. If these precursor lesions could be preemptively eradicated, the risk of developing untreatable UGI cancers might be greatly mitigated. Attempts to destroy these precursor lesions by radiofrequency ablation have been stymied by high rates of recurrence- likely due to a failure to kill the stem cells responsible for the renewal of Barrett's glands. We have developed robust strategies to clone stem cells from normal intestines and are adapting this technology to clone the stem cells of Barrett's glands from endoscopic biopsies. Preliminary studies indicate that we can differentiate these putative Barrett's stem cells to mature intestinal metaplasia. Early results from exome sequencing suggest the possibility that we can readily stratify Barrett's patients into low and high-risk categories on the basis of their stem cell mutation profiles. We anticipate that a novel focus on the Barrett's stem cell will transform strategies for addressing esophageal and related UGI tract cancers by preemptively assessing and targeting precancerous intestinal metaplasia. At the practical level the studies described should permit the risk stratification of Barrett's patients and generate robust therapeutic options for those likely to convert to untreatable esophageal adenocarcinoma. Finally, the similarity of Barrett's to the precursor lesion of gastric adenocarcinoma suggests collateral value of these studies for related UGI tract cancers.

Biography

Wa Xian was born in Tianjin and received her BA from Nankai University. She obtained a Ph.D. in Molecular Genetics from the University of Texas, M.D. Anderson Cancer Center and did her postdoctoral work on FGF signaling in early breast cancer with Prof. Jeffrey Rosen at the Baylor College of Medicine. In 2009, she joined Prof. Christopher Crum's laboratory in Brigham and Women¹s Hospital at the Harvard Medical School in Boston to investigate the cellular origins and progression of high-grade ovarian cancers. She was appointed Principal Investigator at the Institute of Medical Biology at A*STAR in Singapore in 2009.

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