OMICS International
conferenceseries.com

J Mol Biomark Diagn 2015, 6:4
http://dx.doi.org/10.4172/2155-9929.C1.026

Study of circulating levels of microRNAs as biomarkers of doxorubicin-induced cardiotoxicity in breast cancer patients

Vagner Oliveira Carvalho, Ludmila R P Ferreira, Danielle Pazzotti Borges and Edimar Alcides Bocchi
University of Sao Paulo, Brazil

Doxorubicin (DOX) is the first-line drug in the treatment of breast cancer. Despite its beneficial therapeutic effects, cardiomyopathy and heart failure are observed when DOX is chronically administered for several weeks. Therefore, the development of new approaches to detect the cardiotoxic effects of DOX in earlier stages is still required. In this study, we evaluated circulating levels of miR-1, miR-133b, miR-146a, miR-208a/b and miR-423-5p in 59 female patients with breast cancer along 3, 6, 9 and 12 weeks of chemotherapy with cumulative dose of 60 mg/m2 DOX. As result, miR-208a/b were undetectable in plasma from all samples even at the maximum dose of DOX (12 weeks). Circulating levels of miR-1, miR-133b, miR-146a and miR-423-5p increased along the treatment reaching its peak at 9 weeks with a an increase of 18.9-fold, 11.51-fold, 10.56-fold and 12.09-fold respectively ($P<0.01$ for all miRNAs). Seven patients (11.86%) developed cardiotoxicity showing a cTnI increase from 8.3 (±1.9) to 123.4 pg/ml (±10.0) whereas from 6.3 (±0.2) to 31 pg/ml (±3.2) in the non-cardiotoxicity patients ($P<0.001$). A decrease in the LVEF from 65.71 (±1.97) to 56.80 (±6.59) was also observed in cardiotoxicity patients whereas it was preserved in non-cardiotoxicity patients ($P<0.001$). Despite all miRNAs analyzed had been up-regulated along the treatment, only miR-1 and miR-133b were differentially expressed between the two groups (10.25-fold and 3.73-fold respectively; $P<0.05$) showing a positive correlation with cTnI ($P<0.05$). These findings may lead to the development of biomarkers of earlier events in DOX-induced cardiotoxicity that occur before the release of cardiac troponins.

vagnercarvalho@usp.br

Epigenetic alterations in colitis-associated colorectal cancer

Wancai Yang
University of Illinois at Chicago, USA

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. 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. 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. 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.

wyang06@uic.edu