Interrogating cancer transcriptome reprogramming

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Recent high throughput interrogations of cancer landscape through programs such as The Cancer Genome Atlas (TCGA) have gained deeper understanding of cancer as a disease of heterogeneity of different stages of cell fate evolution and dedifferentiation. Epithelial tumors often exhibit mesenchymal features as a result of epithelial to mesenchymal transition (EMT), a process that can be driven by both genetic and epigenetic alterations in a form of network regulation. In ovarian cancer, loss of epithelial features and gain of a mesenchymal phenotype is associated with more aggressive tumor features. We performed an integrated genomic analysis which revealed a miRNA-regulatory network that further defined a robust integrated mesenchymal subtype associated with poor overall survival in 459 cases of serous ovarian cancer from TCGA and 560 cases from independent cohorts. Eight key miRNAs including miR-506, miR-141 and miR-200a were predicted to regulate 89% of the targets in this network. Follow-up functional experiments illustrate that miR-506 inhibited EMT by targeting SNAI2, a transcriptional repressor of E-cadherin as well as mesenchymal regulators vimentin and N-cadherin. MiR-506 also induced senescence by blocking CDK4/6-FoxM1 axis.We used our well-characterized nanoparticle platforms for systemic delivery of miR-506 in orthotopic OvCa mouse models and found such delivery to be highly effective for reduced tumor growth. Interestingly, mesenchymal tumors such as leiomyosarcoma and synovial sarcoma often exhibit epithelial features in a process of mesenchymal to epithelial transition (MET). MET in sarcoma is associated with improved prognosis. Therefore, reprogramming is an intrinsic hallmark of cancer. Understanding of these reprogramming promises leads to intervention that program cancer into an attractor stage that is more similar to normal cells or a stage that leads to irreversible cell death.

Biography

Wei Zhang is a Professor in Pathology and Cancer Biology in the Department of Pathology and the director of the Cancer Genomics Laboratory at MD Anderson Cancer Center. He has published more than close to 300 peer-reviewed papers and 21 book chapters. He co-edited two books (*Statistical and Computational Approaches to Genomics*, 1st and 2nd edition, and *Genomic and Molecular Neuro-Oncology*) and co-authored one book (*Microarray Quality Control*). He is a co-director of one of seven Genome Data Analysis Centers (GDAC) under the Cancer Genome Atlas (TCGA) project funded by NCI.

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Transcriptomics 2015
ISSN: 2329-8936, TOA an open access journal

Transcriptomics-2015
July 27-29, 2015

Volume 2, Issue 2

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