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Regulatory network analysis reveals miR-146b-5p within BCR-ABL1-positive microvesicles promotes leukemic transformation of hematopoietic cells

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Evidence is accumulating that extracellular microvesicles (MV) facilitate progression and relapse in cancer. Using a model in which MVs derived from K562 chronic myelogenous leukemia (CML) cells transform normal hematopoietic transplants into leukemia-like cells, we defined the underlying mechanisms of this process through gene-expression studies and network analyses of transcription factors (TF) and miRNAs. We found that antitumor miRNAs were increased and several defense pathways were initiated during the early phases of oncogenic transformation. Later, oncomiRs and genes involved in cell cycle, DNA repair and energy metabolism pathways were upregulated. Regulatory network analyses revealed that a number of TFs and miRNAs were responsible for the pathway dysregulation and the oncogenic transformation. In particular, we found that miR-146b-5p, which was highly expressed in MVs, coordinated the regulation of cancer-related genes to promote cell-transforming processes. Notably, treatment of recipient cells with MV derived from K562 cells expressing mimics of miR-146b-5p revealed that it accelerated the transformation process in large part by silencing the tumor-suppressor *NUMB*. High levels of miR-146b-5p also enhanced reactive oxygen species levels and genome instability of recipient cells. Taken together, our findings showed how upregulation of oncogenic miRNAs in MVs promote hematopoietic cells to a leukemic state, as well as a demonstration for TF and miRNA coregulatory analysis in exploring the dysregulation of cancers and discovering key factors.

Biography

An Yuan Guo has completed his PhD from Peking University and Post-doctoral studies from VCU and Vanderbilt University. His research focuses on the transcription factor and ncRNA regulatory network in complex diseases with NGS data and bioinformatics database construction. He is an expert in bioinformatics database and developed a series of databases (AnimalTFDB, miRNASNP and lncRNASNP). He developed an approach to study the microRNA and TF co-regulatory network in complex diseases. He has published about 50 papers in Molecular Psychiatry, Cancer Research, NAR, Bioinformatics, Briefings in Bioinformatics, Human Mutation etc and served as an Editor of Scientific Reports.

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