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Predicting synergistic drug targets in cancer through molecular networks

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Abstract

Cancer is a complex disease generally caused by multiple factors, which hamper effective drug discovery. Drug combination provides an alternate way and is becoming a standard mode of treatment. Synergistic drug pairs have special potential for treatment since they allow a desired effect to be achieved with lower total dose of administered medicine and usually with fewer side effects. However, the major challenge has been the prediction of chemotherapeutic efficacy based on the biological profile of the tumor. Computational prediction of essential genes circumvents expensive and difficult experimental screens and will help anticancer drug development. Because of the lack of gene expression data treated with drug combinations, in this study, we present a computational approach to identify effective drug combinations by exploiting high throughput data. We constructed tissue specific networks based on correlation of gene expression signatures on cell lines from multiple tissue types and chemo sensitivity data on 130 drugs under clinical and preclinical investigation obtained from Sanger Institute (Genomics and Drug Sensitivity in Cancer; http://www.cncerRxgebe.org). We evaluated CNS cancer subset and identified 108 genes and 42 drugs with high correlations ($-0.5 > r < 0.5$). Network analysis identified several cancer specific pathways ($p < 0.001$), including Focal adhesion, PDGF signaling, and ECM remodeling. Employing topological features from the Focal adhesion gene networks, we predicted a set of 20 essential genes with most interactions. We estimated pair wise drug synergy scores for all the target genes in this pathway and identified several synergistic pairs with potential clinical relevance.

Biography

Uma Shankavaram completed her Ph.D in Human Genetics and postdoctoral training in molecular biology and bioinformatics at National Institutes of Health. She is currently working as Staff Scientist and technical lead for the microarray core facility at Radiation Oncology Branch in National Cancer Institute. She has published more than 30 papers in peer reviewed journals.