Cancer systems biology identifies diagnostic and therapeutic targets in melanoma

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Abstract

The combination of systems biology and omics data will bring about a revolution in biomedicine. Today’s routine use of metabolic multiplexing in the clinic will be enhanced by patient specific sequence information and network models. We characterized the genomic landscape of human skin cutaneous melanoma (SKCM) using data obtained from The Cancer Genome Atlas (TCGA) project. The integration of systems biology networks into diagnostic interpretation will naturally generate regimes for personalized medicine practice. In this sense, metabolomics and systems biology will fundamentally transform our approach to patient care, disease prevention, diagnostics, and therapy.

Our systems biology analysis identified two new master regulators in cancer metabolism and epigenetics:

1) The pyrimidine enzyme dihydropyrimidine dehydrogenase, DPYD, is the single most frequent metabolic enzyme to be mutated (>20%). In the context of personalized chemotherapy with the antimetabolite 5-fluorouracil, DPYD has strong predictive value and its prospective cancer genotyping will benefit patient care by decreasing toxicity and drug resistance, while maintaining efficacy. Gene expression signatures of cancer patients show that recurring somatic mutations of DPYD reconfigure and activate pyrimidine metabolism promoting rapid cellular proliferation and metastatic progression.

2) The epigenetic modifier EZH2 is in the center of a repressive complex controlling differentiation of normal cells. In cancer, somatic copy number amplification and hyperactivating somatic mutations of EZH2 correlate with DNA methylation and drive epigenetic silencing of genes involved in tumor suppression and immune responses in melanoma. Identified changes in target genes were validated by transcriptomic data following treatment with the EZH2 inhibitor GSK126. Gene enrichment analysis revealed genes associated with tumor suppression, cell differentiation, cell cycle inhibition and repression of metastases as well as antigen processing and presentation pathways. The identified changes in EZH2 were associated with an adverse prognosis in the TCGA dataset. These results suggest that inhibiting EZH2 is a promising therapeutic avenue for a substantial fraction of melanoma patients.