Molecular networks as determinants of response and outcome

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The exact mechanisms involved in tumor development and therapy response are still largely unclear. Here we report on two computational approaches we developed to systematically unravel these genetic interactions based on high throughput datasets and show these can be employed to predict response to anti-cancer agents.

In the first approach, we developed a computational approach to reliably detect molecular interactions (co-occurrences and mutually exclusivities) from somatic variant and copy number data. We show that the number of aberrations per gene and per sample have a major influence on the results and propose a null-model to correct for these effects. We demonstrate the approach on the TCGA and METABRIC breast cancer cohorts. We identify no co-occurring aberrations but multiple mutually exclusive interactions, that represent a global breast cancer interaction network, shedding new light on breast cancer development and subtyping. We also performed a pan-cancer interaction analysis which reveals cancer type independent interactions.

In the second approach we performed integration of multiple omics data sets to construct models of drug response in cancer cell lines. While many oncogenic drivers and drug resistance mechanisms have been discovered, it is generally unclear how these mechanisms interact to induce sensitivity or resistance in a cell line for a particular drug. We characterized 30 breast cancer cell lines at the DNA, RNA and protein level, and measured the response to various kinase inhibitors. We then constructed Bayesian models encompassing several of the important driver pathways and resistance mechanisms, and tested how well these models describe the available data. The models provide estimates of the relative contribution of each of the drivers and resistance mechanisms and allow estimation of latent variables such as ‘pathway activation’. We demonstrate the utility of the models by thoroughly analyzing which parts of the data cannot be explained even by fairly extensive models. This provides interesting new leads and narrows down which follow-up studies may be most fruitful to advance our understanding of drug response. The systematic, quantitative understanding of drug response gained from these models will contribute significantly towards precision medicine for individual cancer patients.