Dissecting gene-gene and gene-drug interactions on cell cycle phenotypes, and pharmacogenetics in lymphoproliferative cancer

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Abstract

Gene-gene interactions shape complex phenotypes and modify the effects of mutations during development and disease. The effects of pairwise gene-gene interactions on single phenotypes have been used to aggregate genes into functional modules. However, it has not been possible to derive directional epistatic relationships between genes that constitute regulatory networks. We used combinatorial RNA interference and automated, single-cell phenotyping to generate a large genetic interaction map for 21 different phenotypic features of Drosophila cells. We devised a method that combines data on multiple phenotypes to reveal directional relationships, and report a dense regulatory network covering 1367 genes. This network could reconstruct the sequence of protein activities in mitosis, and revealed that the Ras pathway interacts with the SWI/SNF chromatin-remodelling complex, which we show is conserved in human cancer cells. This presents a powerful approach for reconstructing directional regulatory networks, and provides a resource for the interpretation of functional consequences of genomic alterations in disease. In the second part of the talk, I will describe a translation of these ideas to the dissection of drug-sensitivity in large panels of primary, patient-derived lymphoproliferative tumours. We dissect the influence of cell lineage, acquired tumour mutations and other omic profiles on individual drug sensitivity, in particular targeted drugs ("pathway inhibitors"). These data provide increased biological understanding of inter-individual differences in response to cancer therapy, can be distilled into predictive models and can guide personalized treatment choices.