SBMC 2010 Conference on Systems Biology of Mammalian Cells
June 3rd-5th 2010 · Freiburg | Germany · Konzerthaus · www.sbmc2010.de

HOW DO CANCER CELLS ESCAPE FROM TARGETED INTERVENTION?

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In many tumours, signalling via the pathways downstream of the oncogene Ras drives cellular transformation and tumour growth. Consequently, many targeted therapies were designed to target this pathway, both at the receptor level and further downstream at different kinases. We investigate how tumour cells circumvent the effects of kinase inhibitors through the adaptation of their signalling network using phospho-proteomics measurements and mathematical modelling. We find two possible strategies for escaping treatment, namely redundancy and feedback regulation. Experiments and models show that the action of MEK inhibitors is counteracted by strong posttranslational feedback from ERK to Raf. Using large-scale perturbation studies we additionally identify strong cross-talks linking ERK, AKT and Wnt signalling in colon cancer cell lines, which can be explained by a network model.

Since it is likely that cells have not specifically evolved the networks to counteract drugs, the question arises from where this robustness originates. One can speculate that fluctuations in protein levels in single cells are the largest source of uncertainty in healthy cells. And indeed, mathematical analysis shows that the same mechanisms that lead to robustness against kinase inhibitors do also compensate fluctuations. We confirm these model predictions by targeted knock-downs. We find that in agreement with model predictions, cells harbouring wild-type Raf do show remarkable robustness of the phospho-ERK level when reducing the total ERK levels by even more than 80%. In contrast, cells where the pathway is driven by mutated b-Raf loose this robustness. An sh-RNA screen shows that this compensatory mechanism is not limited to the core of the MAPK pathway, but is likely to be a much more wide-spread phenomenon that confers robustness to cellular decision making. (Funding: BMBF Forsys Partner, Medsys project ColoNet)

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