Identifying synthetic lethal candidates to target Notch-driven cancers via quantitative proteomics

Beth Barnes, Simon Woodcock, Martin Baron, Simon Hubbard

Notch signalling controls numerous cellular processes across many developing tissues and is also important in regulating homeostasis, turnover and repair in adult tissues. The widespread functions of Notch are also reflected in pathogenic outcomes arising from its misregulation. In particular, Notch signalling has been found to be oncogenic in several different forms of cancer. While clinical trials have investigated direct targeting of Notch with gamma-secretase inhibitors and blocking antibodies, these approaches have to date produced limited success clinically. The widespread role of Notch in normal tissue turnover makes direct targeting problematic. We have instead investigated a synthetic lethality approach to targeting cells with aberrantly high Notch signalling using Drosophila S2 cells as a model system to establish proof of principle. A previous work using a whole genome RNAi revealed around 646 target genes whose knockdown resulted in low viability only when Notch was activated. To explore the mechanisms by which new cell vulnerabilities arise as consequences of Notch activation we have now used a proteomics approach to identify proteins whose expression is up or down regulated by high or low Notch signalling to assess differences in cell status. Bioinformatics analysis, functional enrichment and protein-protein interaction network generation were performed to identify clusters of functionally related genes and integrated with functional networks from viability target genes identified in the whole genome RNAi screen. The results point to changes in mitochondrial metabolism, the spliceosome, DNA damage repair and glutathione metabolism, amongst other processes, dependent on Notch signalling levels.