Using microarray data to elucidate the molecular phenotype of a novel oncogene and identify a therapeutic strategy

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Introduction The incidence of esophageal and junctional adenocarcinoma has increased sixfold in the past 30 years. Despite aggressive chemotherapy and attempts at curative surgery, the 5-year survival rate remains at 20%. Unlike other epithelial cancers, targeted therapy is limited. We have identified TRIM44 as a putative oncogene that is amplified in 8% of EA and 6% of breast cancers.

Methods The aims of this project were to elucidate the molecular phenotype underlying the oncogenic role of TRIM44 as well as suggest ways to therapeutically target TRIM44 dysregulation.

Results Using three microarray datasets representing EA (n=37, n=64) and breast (n=997) we performed gene set enrichment analysis to identify signalling pathways dysregulated with TRIM44 high expression (EA and breast) or amplification (breast only). High expression of TRIM44 was associated with over-enrichment of targets of the mTOR pathway consistent across all three data sets. This association was validated using expression microarrays in a cell line (HSC39) with amplification of TRIM44 treated with siRNA. Using phosphorylation of p70S6K as a readout of mTOR activity we validated the link between TRIM44 and the MTOR pathway; knockdown of TRIM44 using siRNA in HSC39 and a cell line with high expression of TRIM44 (JIMT-1) resulted in a decrease in pathway activity. The connectivity map (http://www.broad-institute.org/cmap/), a collection of expression array data derived from lines treated with bioactive small molecules was queried using signatures generated from the microarray data representing genes positively or negatively associated with TRIM44 (breast, EA, HSC39 +SiRNA datasets). The top consistent hits were sirolimus, an mTOR inhibitor and analogue of rapamycin and LY-294002, a PI3K inhibitor. These hits represent small molecules predicted to reverse the effects of high TRIM44 expression. Treatment with inhibitors in HSC39 and JIMT-1 demonstrated that these lines were highly sensitive (IC50<30 nM) to rapamycin, but less sensitive to PI3K inhibition (IC50>400 nM), consistent with a link at the level of mTOR.

Conclusion We have demonstrated the ability to identify a previously unknown association between TRIM44 and the mTOR pathway using expression and copy number data. This phenotype was validated in cell line experiments and highlighted a potential therapeutic strategy using analogues of rapamycin, a small molecule inhibitor of the mTOR pathway, which are currently in clinical use as immunosuppressants and in clinical trials for other cancer types.

Competing interests None declared.

Reference

Completion rates of palliative chemotherapy are low in patients with oesophago-gastric cancer: results from a national audit

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Introduction Palliative chemotherapy is routinely offered to patients diagnosed with locally advanced or metastatic oesophago-gastric cancer. Based on data from the National Oesophago-Gastric Cancer Audit (NOGCA), we describe the characteristics of patients being offered palliative chemotherapy, determine the proportion of patients completing treatment, and identify factors associated with treatment completion.

Methods The NOGCA prospectively collected data on patients diagnosed with invasive epithelial cancer of the oesophagus or...