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ENDOCYTOSIS

Increased trafficking

Genome-wide array-based comparative genome hybridization analysis of 83 human melanoma samples has revealed a focal amplification at 5p13, which was also frequently found in other solid tumours, such as colon adenocarcinoma and non-small-cell lung carcinoma (NSCLC). Further analyses by Lynda Chin and colleagues have identified *GOLPH3* as an oncogene encoded in this region.

Scott, Kabbarah and colleagues found that knockdown of *GOLPH3* inhibited anchorage-independent growth in human melanoma and NSCLC cell lines with 5p13 amplification. Consistent with this, they showed that ectopic expression of GOLPH3 cooperated with HRAS-V12 to increase focus formation of *Cdkn2a*-deficient mouse embryonic fibroblasts. Additionally, GOLPH3 cooperated with BRAF-V600E in immortalized human melanocytes to induce anchorage-independent growth in soft agar, and GOLPH3 expression increased the growth of melanoma (WM239A cells) and NSCLC (A549 cells) xenografts. Together, these data indicate that *GOLPH3* is an oncogene.

GOLPH3 was initially identified as a phosphorylated protein localizing on the peripheral membrane of the *trans*-Golgi network and it is thought to be involved in the endocytosis of transmembrane receptors. Indeed, after initially using the yeast two-hybrid system and then co-immunoprecipitation and co-immunofluorescence in human cells the authors found that GOLPH3 interacts with VPS35, which is a member of the retromer complex that is involved in protein trafficking from endosomes to the *trans*-Golgi network. Previous studies have also indicated that GOLPH3 modulates mTOR signalling. Supporting this, lung adenocarcinoma samples with 5p13 amplification were significantly associated with increased mTOR expression and phosphorylation of cytoplasmic S6 kinase, which is a target of mTOR complex 1 (mTORC1) that regulates cell size. Furthermore, knockdown of *GOLPH3* in A549 cells led to a decrease in cell size comparable with the reduction observed when treating these cells with rapamycin. In addition, the authors found that phosphorylation of Akt (a target of the mTORC2 complex) was increased in human melanocytes expressing GOLPH3, indicating that GOLPH3 expression leads to the activation of both the mTORC1 and the mTORC2 complexes. Finally, in orthotopic subcutaneous transplantation into immunodeficient mice, human melanoma cells expressing GOLPH3 exhibited increased sensitivity to rapamycin, indicating that GOLPH3-mediated activation of mTOR is crucial for its oncogenic function and that GOLPH3 status may be a positive predictor of response.

The authors suggest that GOLPH3 might activate mTOR signalling owing to its role in protein retrograde trafficking, and specifically receptor recycling, providing a new link between deregulated endocytosis and tumorigenesis.

Gemma K. Alderton

ORIGINAL RESEARCH PAPER Scott, K. L. *et al.* GOLPH3 modulates mTOR signalling and rapamycin sensitivity in cancer. *Nature* 25 Jun 2009 (doi:10.1038/nature08109)
FURTHER READING Mosesson, Y. *et al.* Derailed endocytosis: an emerging feature of cancer. *Nature Rev. Cancer* **8**, 835–850 (2008)