Nature Reviews Cancer | AOP, published online 6 December 2012 doi:10.1038/nrc3423

DRUG RESISTANCE

Time for mediation?

> Knockdown of MED12 induces specific changes in the expression of TGFβ target genes

Although targeted therapies have had a substantial impact in the clinic, resistance to these agents is common. Combining targeted therapies to try and minimize the routes to resistance is now a priority, but an understanding of resistance mechanisms is required before this can be effectively achieved. René Bernards and colleagues have identified the loss of a component of the transcriptional mediator complex MED12 as a mechanism through which several cancer types develop resistance to various targeted therapies.

Bernards and co-workers carried out an RNA interference (RNAi) screen to identify mechanisms of resistance to two anaplastic lymphoma kinase (ALK) inhibitors using a non-small-cell lung cancer (NSCLC) cell line that harbours an *EML4–ALK* translocation and that is sensitive to both drugs. They found that reduced expression of MED12 results in resistance to ALK inhibitors. Suppression of MED12 also results in resistance to epidermal growth factor receptor (EGFR) inhibitors in NSCLC cells. Activation of downstream signalling pathways is a known mechanism of resistance to tyrosine kinase inhibitors (TKIs). Consistent with this, the authors observed that MED12 knockdown increased MEK and ERK signalling and induced resistance to inhibitors of MEK, oncogenic BRAF and the multikinase inhibitor sorafenib, as well as to the standard chemotherapeutic drugs 5-fluorouracil and cisplatin.

How does loss of MED12 confer resistance to these different treatments? The authors carried out a drop out screen where they looked for kinases the loss of which prevented the resistance induced by MED12 knockdown and they identified transforming growth factor-β (TGFβ) receptor 2 (TGFBR2) as a potential culprit. Overexpression of TGFBR2 or the treatment of cells with TGFβ replicated the resistance spectrum that was induced by MED12 loss. As MED12 is a member of the mediator complex, the authors looked for an effect on *TGFBR2* transcription, but noted only a modest effect on *TGFBR2* mRNA levels. However, MED12-knockdown cells show a substantial increase in TGFBR2 protein expression, indicating a post-translational effect. Cell fractionation studies indicated that MED12 is present in both the nucleus and the cytoplasm, unlike other components of the mediator complex. Co-immunoprecipitation studies showed that MED12 and TGFBR2 interact, and additional experiments suggestedthat MED12 prevents the expression of a fully glycosylated form of TGFBR2 on the cell surface.

Knockdown of MED12 induces specific changes in the expression of TGFβ target genes, including those involved in regulating epithelial to mesenchymal transition (EMT). The authors found that a signature gene set from cells with MED12 knockdown was a predictor of poor prognosis in patients with colorectal cancer and also indicated patients that were likely to be resistant to 5-fluorouracil. The authors also found that the sensitivity of NSCLC cells to TKIs was increased by a TGFβ receptor inhibitor. Thus, tumours that show an increased TGFβ signalling profile might be more sensitive to TKIs and to some standard chemotherapeutic agents when these are used in combination with a TGFβ receptor inhibitor. Although mutations in MED12 have been found in some tumour types, whether loss of MED12 occurs often in human tumours is unclear. The authors note that a reduction in MED12 activity results in reduced proliferation in cancer cells, suggesting that any cells with reduced MED12 function are likely to be less fit than other clones within a tumour in the absence of selective pressure that is conferred by treatment with a TKI.

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ORIGINAL RESEARCH PAPER Huang, S. *et al.* MED12 controls the response to multiple cancer drugs through regulation of TGF-β receptor signalling. *Cell* **151**, 937–950 (2012)