SLITRK6 : new target for the treatment of BRAF-mutant metastatic melanoma?

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Purpose:
The development of drugs targeting RAS/ERK/MEK pathway such as BRAF and MEK inhibitors has been a major advance in the therapeutic management of metastatic melanomas. However, patients relapse in most of the case due to resistance of cancer cells to the treatment. We and others demonstrated that MAPK inhibitor (MAPKi)-induced expression and activation of c-Jun account for cell resistance to MAPKi (1,2,3). Furthermore, depletion of c-Jun sensitizes cells to MAPKi through apoptosis induction.

Experimental Design:
BRAF-mutant melanoma cell lines were depleted or not for c-Jun by siRNA and treated by a BRAF inhibitor (PLX4032). Whole genome expression was analysed by transcriptomic study to determine target genes of c-Jun that could be associated with antitumor pharmacological response to MAPKi. mRNA and protein levels of potential target genes were then analysed in BRAF-mutant melanoma cell lines after treatment by BRAF inhibitor (PLX4032) alone or in combination with MEK inhibitor (AZD6244). Finally, protein depletion by siRNA was made in order to find targets that induce synthetic lethality with MAPKi.

Results:
The transcriptomic study reveals that SLIT And NTRK Like Family Member 6 (SLITRK6) is a potential target gene of c-Jun that could be associated with antitumor pharmacological response to MAPKi. Indeed, SLITRK6 mRNA and protein are induced in BRAF-mutant melanoma cell lines after MAPKi treatment. Furthermore, this induction is dependent on c-Jun. Finally, our preliminary results show that SLITRK6 depletion by siRNA induces synthetic lethality in combination with MAPK pathway inhibitors in BRAF-mutant cells.

Conclusion:
These results suggest that SLITRK6 could be a new pharmacological target for the treatment of BRAF-mutant metastatic melanoma and a potential biomarker of resistant cells to MAPKi.

References:
(1) Delmas A. et al. Oncotarget 2015
(2) Fallahi-Sichani M. et al. Molecular Systems Biology 2015
(3) Ramsdale R. et al. Science Signaling 2015