Using Tipifarnib to prevent resistance to targeted therapies in oncogene-addicted tumors

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Background

Drug-tolerant “dormant” cells (DTC) have emerged as one of the major non-genetic mechanisms driving resistance to targeted therapy (TT) in non-small cell lung cancer (NSCLC)1,2, although the sequence of events leading to entry and exit from dormancy remains poorly described. We recently reported a step-by-step phenotypic and molecular characterization of the different processes involved during the adaptive response to osimertinib in EGFRI-mutant NSCLC (Figaro et al. bioRxiv 2020), and we extend our findings to other oncogenic drivers such as KRAS and BRAF-mutant or ALK-translocated tumors treated with their corresponding TT. We identified a common non-genetic path of drug adaptation through a sub-G1 apoptotic-like differentiation process, which involves type 1 differentiation processes that are not regularly involved Rho/ROCK-dependent actin cytoskeleton remodeling. Among a panel of Rho/ROCK pathway inhibitors, we identified the farnesyltransferase inhibitor (FTI) tipifarnib as the most efficient compound in preventing relapse to targeted therapies in EGFRI-mutant lung cancer cells, but also in KRAS-mutant and ALK-translocated NSCLC or BRAF-mutant melanoma.

Methods

We conducted a panel of oncogene-addicted tumors harboring different oncogenic drivers (i.e., KRAS, BRAF, ALK) with the FDCS (fluorescence-activated cell sorting) system, and we monitored cell cycle dynamics in response to their corresponding targeted therapies (i.e., EGFRi osimertinib, KRASi sotrasi, BRAFi dabrafenib, ALKi Erlotinib). We performed bulk and single-cell RNAseq experiments at different time points during the acquisition of resistances in EGFRI/mutant NSCLC lines, and we compare the transcriptomes with public data available in different oncoprotein settings. Finally, we performed in vitro drug screening to target the most relevant identified pathway of drug-tolerance and we validate the combination in vivo using dedicated NSCLC xenografts and PDO (Patient-Derived Xeno).

Conclusions

We report that adaptive response to targeted therapy (TT) in NSCLC is a highly dynamic process which invariably involves reprogramming through an alveolar-type phenotype with contractile features. Using a screen of Rho/ROCK pathway inhibitors, we found that tipifarnib, a clinically active farnesyltransferase inhibitor, efficiently and durably prevented relapse to TT in several oncogene-addicted tumors in vitro and displayed potent antitumor efficacy in vivo with no evidence of toxicity in mice. Collectively, our data strongly support clinical exploration of tipifarnib in combination with TT to effectively and durably prevent relapse.

References


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