NEK1 IS INVOLVED IN TUMOR GROWTH THROUGH ALTERED IMMUNE SIGNALING

I. INTRODUCTION

1. a. Turbine’s Simulated Cell™ platform

Turbine’s simulated Cell™ platform models cancer cell signaling to predict cell viability and to identify novel drug targets by simulating perturbations of the (anti-)response pathway, with an emphasis on a cancer dependency in certain molecular contexts. NEK1 is part of the NEK-related kinase family, involved in DDR, cell cycle, and mitosis, making it an interesting candidate for antitumor intervention.

1. b. Model building and training

Cell-specific, models generated from genomic data and experimental data

2. a. Simulation

System perturbations

3. a. Translation

A. Hypothesis generation

B. Biological decoration clinical positioning

4. a. Experimental validation

A. Invasion suppression experimental design

II. RESULTS

II. a. NEK1 KO in silico (1) suggests novel dependencies in selected cell lines

Differential sensitivity of cell lines to fictive in silico NEK1 inhibitor

Identification of biomarkers predictive for sensitivity to NEK1 inhibition

II. b. NEK1 KO in vitro validates Simulated Cell™ predictions on cell viability

Legend: A. A fictitious in silico NEK1 inhibitor was used to simulate NEK1 downregulation in a panel of 895 simulated cancer cell lines, allowing the identification of cell lines with high sensitivity to NEK1 inhibition. To investigate the role of our biomarkers that indicate sensitivity to NEK1 knockdown, the knockdown NEK1 inhibition in combination with miRNA on additional genes was simulated in a 1 to 1 way. Those mutations that produced a shift of NEK1 inhibitor (CI) towards sensitization in a sufficient number of cell lines were further investigated to understand their biografted function and relation to NEK1 biology.

II. c. NEK1 KO in vivo reduces head and neck carcinoma and medulloblastoma CDX growth

Legend: A. Heatmap representing fold change models.

II. e. NEK1 KO in vivo reveals immune signaling changes based on mRNAseq analysis of CDX tumors

Legend: A. Pathway enrichment analysis in RNAseq samples culminated from NEK1- and DAVY KO tumors and NEK1 CRISPR KO tumors respectively in CDX models. B. Heatmap representing fold change gene expression in NEK1 KO tumors with respect to NEK1+ tumors.

III. CONCLUSIONS

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