ID: 00966
Type: Oral Comunication
Topic: Tumor biology

The critical role of Inhibitor of differentiation-1 (Id1) sustains mutant KRAS-driven lung adenocarcinoma (LUAD).

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Introduction: KRAS oncogene is the most frequently mutated gene in lung adenocarcinoma. However there is no an effective therapies developed for KRAS LUAD patients. This fact highlights the need to intensify the search for new molecular targets for this subgroup of patients. It has been demonstrated that genes with a prognostic role in mutant KRAS LUAD patients have previously shown a significantly functional role, yielding potential molecular targets for therapy development. Our group has defined Id1 gene as an independent prognostic marker in LUAD patients and has shown its role in cell viability and migration of murine lung cancer cell lines with KRAS mutation.
Objective: The main objective of this work is to determine the clinical, functional and mechanistic role of Id1 in human mutant KRAS LUAD.
Methods: The TCGA and SPORE patient cohorts, which include KRAS status, gene expression and clinical information, as well as LUAD cell lines were deployed. The expression of Id1 was analyzed in a panel of human LUAD cell lines by qPCR and Western blot. Several human cell lines with known mutations (H1792-604, H2009, H358, A549, H23, H441, H1568, H1437 and H2126) were selected to deplete Id1 expression by doxycycline inducible-shRNA. *In vitro* we performed cell proliferation, cell cycle and apoptosis assays to elucidate the cellular mechanism underlying to study the cellular mechanism underlying the effect of Id1 deficiency. The role of Id1 was also study *in vivo* using three humanized models of KRAS-driven LUAD. On the one hand, two mouse xenograft models were generated by subcutaneous injection of KRAS-mutant LUAD cells (H1792-604 and H2009), both Id1sh and GFPsh cells, in flanks of immunodeficient mice treated with doxycycline in drinking water from the time of inoculation or once the tumors were established. On the other hand, a mouse model of liver colonization was used to study the effect of Id1 depletion in metastatic capacity of tumor cells. Finally, RNA sequencing was used to investigate the molecular mechanisms dependent on Id1 expression.
Results: Our results show that high Id1 expression is a marker of poor overall survival in LUAD patients harboring KRAS mutations but not in wild-type KRAS ones. Moreover, *in vitro,* Id1 depletion induces a G2/M arrest and increases apoptosis preferentially in mutant KRAS LUAD cells. *In vivo* experiments have shown that Id1 loss strongly impairs tumor growth and maintenance, as well as liver metastasis, resulting in survival improvement. Mechanistically, Id1 loss involves downregulation of elements of the mitotic machinery via inhibition of the transcription factor FOSL1, and of some kinases of the KRAS signaling network.
Conclusion: Our study provides clinical, functional and mechanistic evidence underscoring Id1 as a critical gene in mutant KRAS LUAD and warrants further studies on Id1 as a therapeutic target in this LUAD subgroup.

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