THE ROLE OF THE KRAS UBIQUITINATION IN LUNG CANCER HETEROGENEITY

Tonči Ivanišević[1], Raj Sewduth[1] , Peihua Zhao[1], Wout Magits[1], Carla Riera Domingo[2], Benoit Lechat[1], Massimiliano Mazzone[2], Anna Sablina[1]

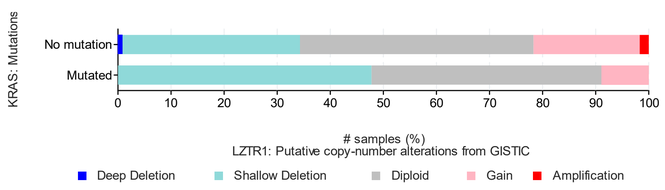
[1]*Laboratory for Mechanisms of Cell Transformation, Department of Oncology, VIB Center for Cancer Biology, KU Leuven, Leuven, Belgium*
[2]*Laboratory of Tumor Inflammation and Angiogenesis, Department of Oncology, VIB Center for Cancer Biology, KU Leuven, Leuven, Belgium*

Abstract

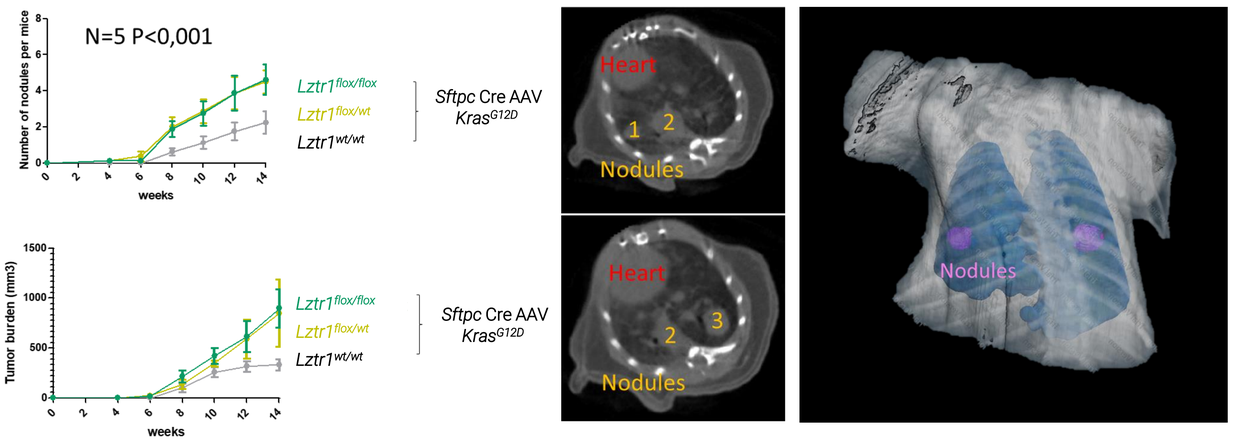
About 30% of NSCLC is driven by activating mutations in *KRAS*. KRAS signalling is tightly controlled through a series of post-transcriptional mechanisms, whereas dysregulation of KRAS activity is translated into heterogeneous clinical behaviour. Recently, leucine zipper-like transcriptional regulator 1 (LZTR1) was implicated, an adaptor of the CUL3-containing E3 ligase complex, in the control of RAS ubiquitination, suggesting that *LZTR1* loss could contribute to lung cancer by increasing the heterogeneity of KRAS signalling and affecting the drug response.

To assess the impact of LZTR1 on KRAS-driven lung cancer, we used the Kras^{G12D} mouse model.

LZTR1 loss of heterozygosity is found in one-third of lung adenocarcinomas and co-occurs with *KRAS* mutations

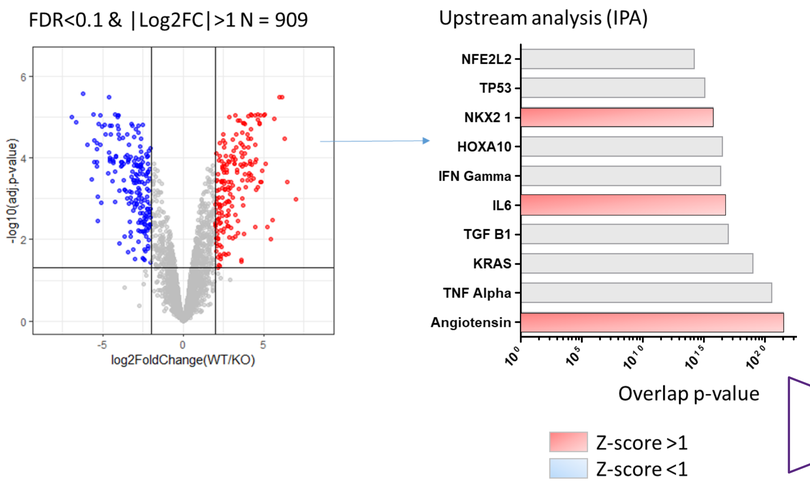


Knockout of *Lztr1* co-operates with oncogenic Kras and promotes tumor initiation and progression

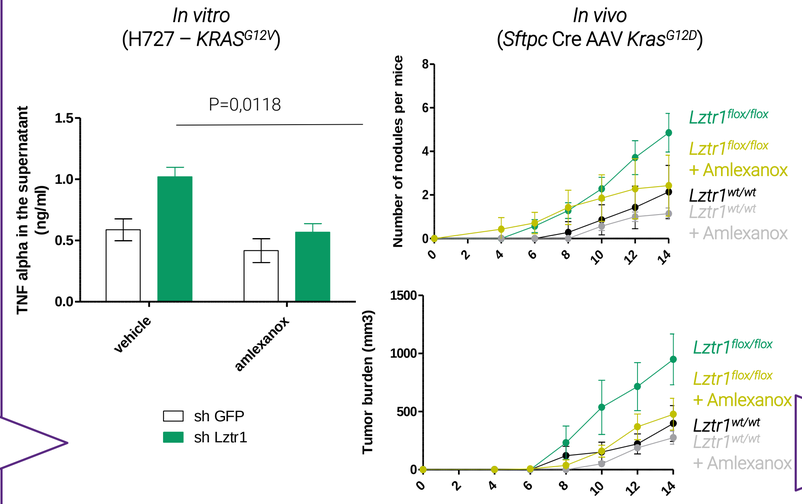


LZTR1 loss causes a pro-inflammatory phenotype

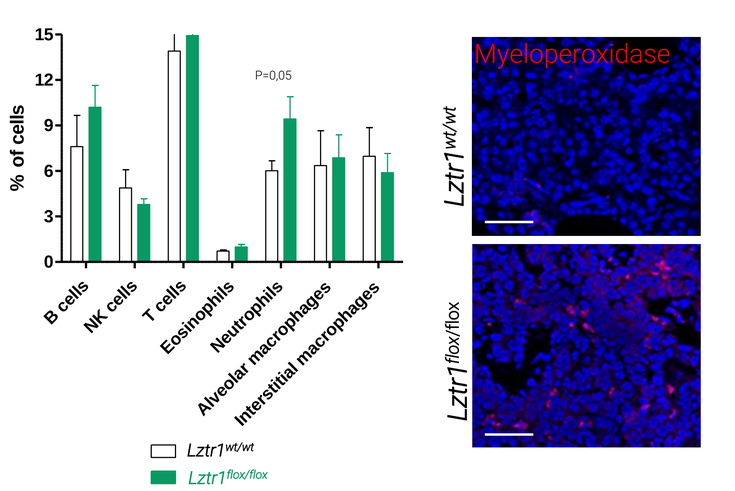
Proteomic analysis of *Sftpc* Cre; *Lztr1*$^{flox/flox}$ mouse lungs



Anti-inflammatory treatment using Amlexanox

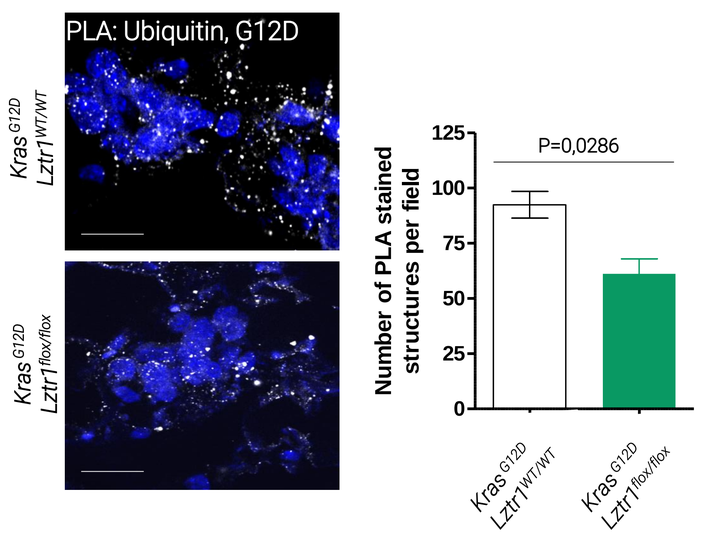


Lung immunophenotyping of *Sftpc* Cre; *Lztr1*$^{flox/flox}$ mouse lungs

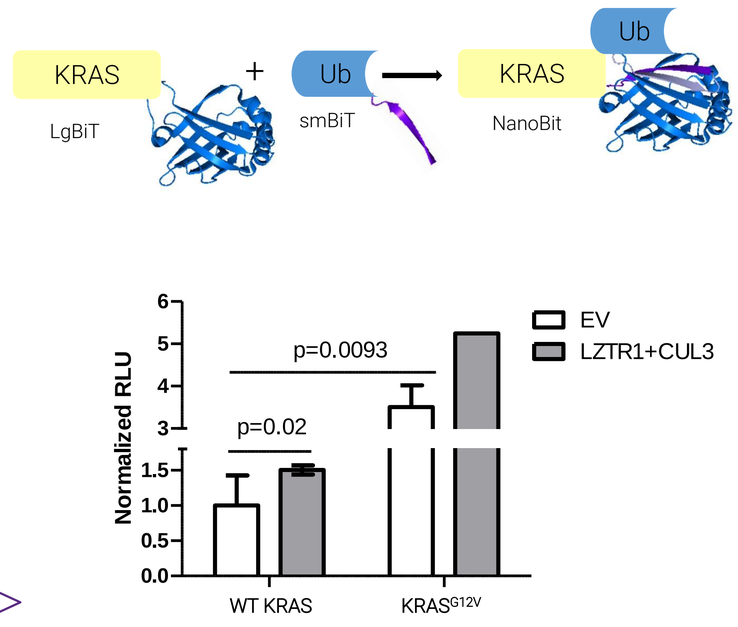


LZTR1 loss affects *KRAS* mutant ubiquitination

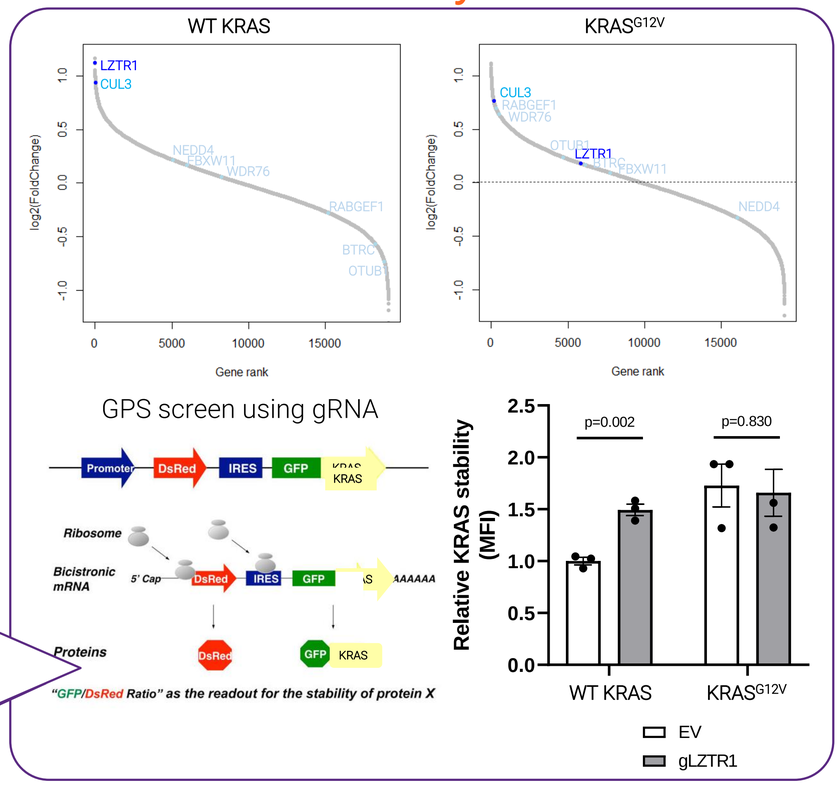
Proximity ligation assay done on mouse lung tumour sections



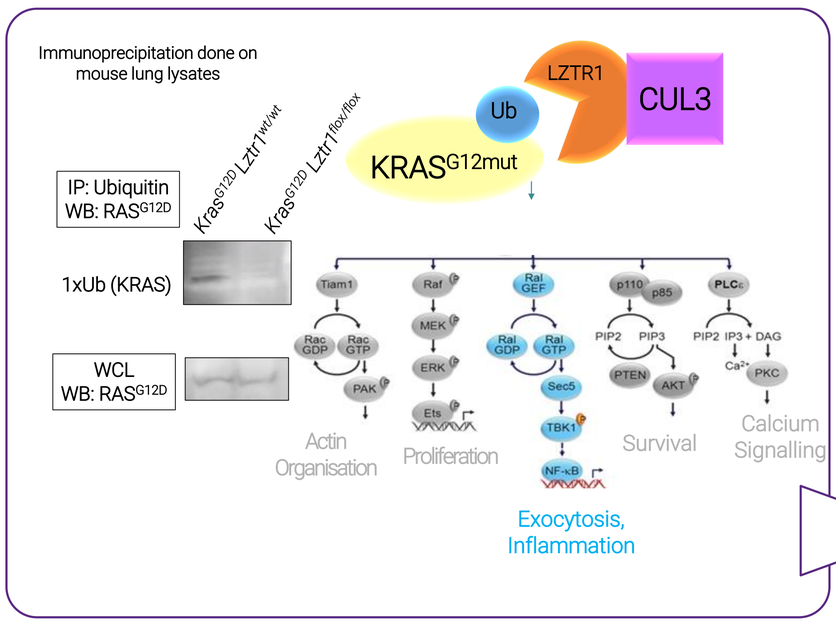
LZTR1 increases KRAS mutant and WT ubiquitination

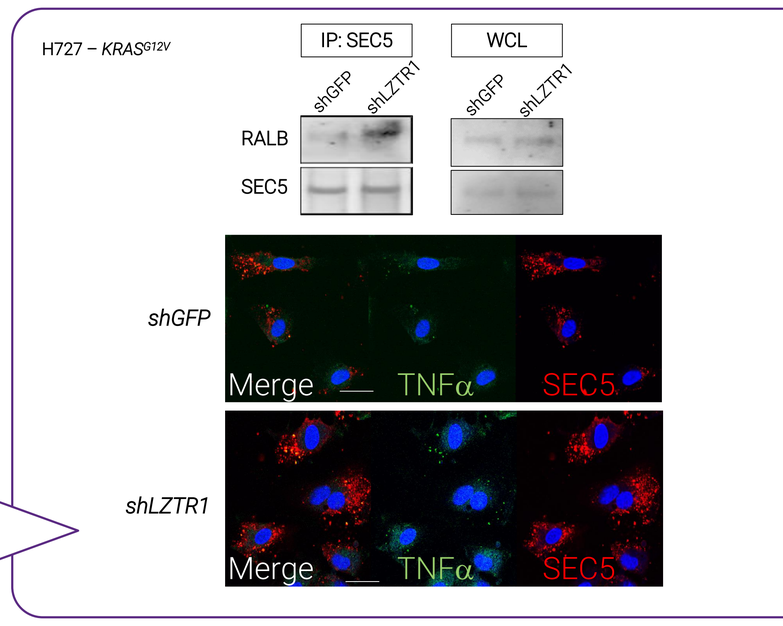


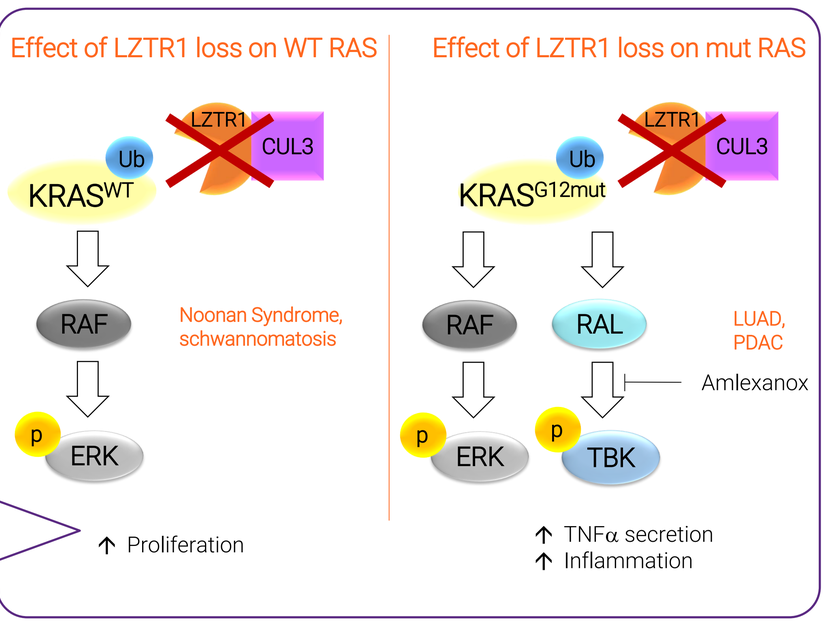
Mutant KRAS stability is not mediated by LZTR1



LZTR1 regulates RAS signalling heterogeneity







These results shed a light on the crosstalk between dysregulation of KRAS ubiquitination, paracrine communication exerted by the cancer cells, and the immune response in lung cancer, which has thwarted the effectiveness of therapy to date.

Stichting tegen Kanker
European Research Council
Supporting top researchers from anywhere in the world
2021-031
H2020 (ub-RASDisease)