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| Exploring the interactome of IKKα and its role in alternative RNA splicing in lung cancer**Besta S** 1,2, **Roupakia E** 1,2\*, **Kanellis D.C.** 3, **Samiotaki M** 4, **Foutadakis S** 5, **Vatsellas G** 5, **Giamas G** 6, **Jiri Bartek** 3,7and **Kolettas E** 1,2\*1 Laboratory of Biology, School of Medicine, Faculty of Health Sciences, University of Ioannina, Greece2 Molecular Cancer Biology & Senescence Group, Biomedical Research Institute, Foundation for Research and Technology, Ioannina, Greece3 Science for Life Laboratory, Division of Genome Biology, Department of Medical Biochemistry and Biophysics, Karolinska Institutet, S-171 21 Stockholm, Sweden4 Institute of Bioinnovation, Biomedical Sciences Research Centre ‘A. Fleming’, Vari, Attiki, Greece5 Center of Basic Research, Biomedical Research Foundation, Academy of Athens, Athens, Greece6 Department of Biochemistry and Biomedicine, School of Life Sciences, University of Sussex, Brighton, Sussex, UK7 Genome Integrity, Danish Cancer Institute, Danish Cancer Society, Copenhagen, Denmark# Presenting author: E. Roupakia, email: [ev.roupakia@bri.forth.gr](ev.roupakia%40bri.forth.gr)\* Corresponding author: E. Kolettas, email: ekoletas@uoi.gr  |

abstract

This Lung cancer is the leading cause of cancer deaths worldwide. Despite this, curative therapies are unavailable, and survival is poor, highlighting the need for the development of novel treatment approaches. IKKα is a nucleocytoplasmic Ser/Thr kinase which activates the non-canonical NF-κB signalling pathway, but it also has NF-κB-independent functions impacting on normal physiology but also on tumour development including lung cancer [1]. We previously showed that IKKα acts as a lung tumour suppressor (TS) by suppressing HIF and hypoxia-mediated processes, including carbohydrate metabolism, required for lung tumour growth *in vivo* [2]. To identify additional mechanisms accounting for IKKα’s TS activity in human lung cancer, we investigated the interactome of IKKα in human lung cancer cells. Here, through co-immunoprecipitation, combined with mass spectrometry, we identify novel interacting partners of IKKα, including eIF4A3 and RBM8A. Furthermore, we show that IKKα co-localises with these proteins in the nucleus, where they interact. eIF4A3 and RBM8A are core components of the Exon Junction Complex (EJC) which regulates RNA splicing, mRNA export to the nucleus, ribosome biogenesis, initiation of translation and nonsense-mediated mRNA decay (NMD) that regulates mRNA degradation [3]. We showed that IKKα depletion from human lung cancer cells results in global deregulation of alternative splicing, the transcription of ribosomal subunit isoforms and NMD. This study also shows that IKKα knockout (IKKαKO) results in transcriptomics and proteomics changes in human lung cancer cells, downregulating pathways involved in ribosome biogenesis. Phenotypically, this translates to IKKαKO human lung cancer cells being more resistant to chemotherapies, including doxorubicin and cisplatin. Overall, we demonstrate novel roles of IKKα tumour suppressor in lung cancer.

**REFERENCES**

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