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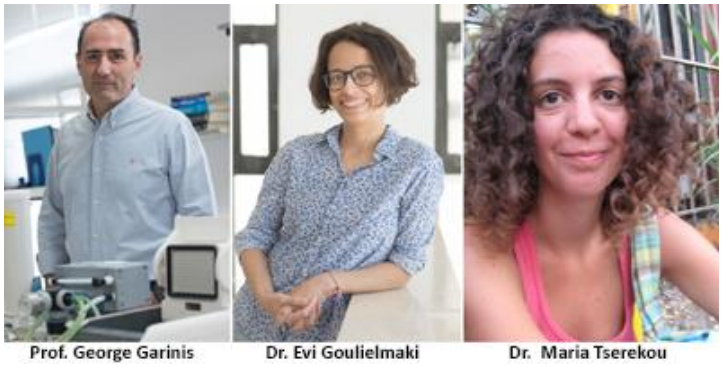
PRESS RELEASE

IMBB researchers reveal that XAB2 functionally links the spliceosomal response to DNA damage with R-loop processing with important ramifications for transcription-coupled DNA repair disorders

Research carried out at the Institute of Molecular Biology and Biotechnology-FORTH and published today in Nature Communications (https://www.nature.com/articles/s41467-021-23505-1) provides evidence that the XAB2 protein functionally links persistent DNA damage with the core spliceosome and the processing of R-loops highlighting the functional links between genome maintenance and the splicing machinery in development or disease.


Prof. George Garinis Dr. Evi Goulielmaki Dr. Maria Tserekou

Although the DNA is continually challenged by intrinsic and extrinsic genotoxic factors, cell have to maintain their genome and faithfully transmit it into the progeny. To meet this challenge, cells have evolved a number of overlapping DNA repair mechanisms that detect and repair DNA damage. Nucleotide excision repair (NER) is a major DNA repair mechanism that cells employ to remove a wide class of bulky, DNA-distorting lesions from the genome. The importance of NER defects in man is illustrated by rare syndromes that either show increased cancer predisposition or dramatic features of accelerated aging, including depletion of fat depots. However, with the exception of cancer and aging, the links between defects in NER and the rapid onset of developmental defects in humans are not well understood.

Recent findings reveal that DNA repair and RNA processing are functionally interconnected and that inborn defects in RNA processing or DNA repair associate with progeria, the metabolic syndrome, neurodegeneration and cancer. To gain insight into the links between RNA processing and genome maintenance, we established an in vivo biotinylation tagging approach in mice and primary cells to dissect the functional contribution of XAB2 in mRNA synthesis and DNA repair. Our findings provide evidence that XAB2 is essential for NER, the pre-mRNA splicing and for R-loop processing. Specifically, we show that XAB2 is part of a core spliceosome complex that associates with the UsnRNAs and that transcription-blocking DNA damage triggers the release of XAB2 from all RNA targets tested. RNAi-mediated knockdown of XAB2 leads to decreased RNA synthesis, aberrant intron retention, R-loop accumulation and DNA damage. A series of immunoprecipitation strategies revealed that XAB2 interacts with ERCC1-XPF and XPG endonucleases and that the XAB2 complex is recruited to RNA:DNA hybrids under conditions that favor the accumulation of R-loops.

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We propose that XAB2 functionally links persistent DNA damage with the core spliceosome and the processing of R-loops highlighting the causal contribution of transcription-blocking DNA lesions to the progeroid and developmental defects associated with TC-NER disorders.

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