

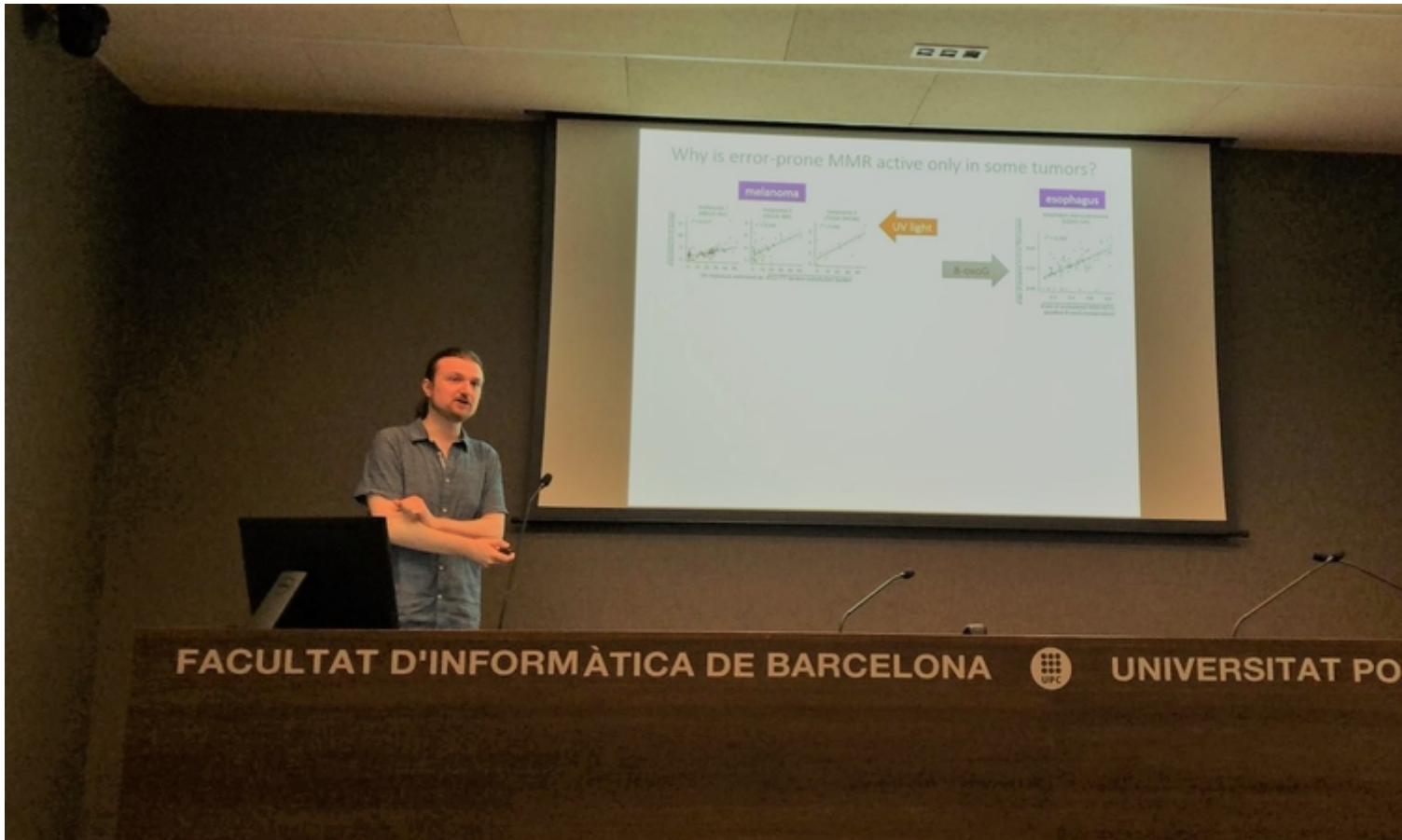
SORS: Error-free and error-prone DNA repair shape mutation landscapes in human tumors

Objectives

Abstract: Many processes can cause the same nucleotide change in a genome, making the identification of the mechanisms causing mutations a difficult challenge. Here, we show that clustered mutations provide a more precise fingerprint of mutagenic processes. Of nine clustered mutation signatures identified from >1,000 tumor genomes, three relate to variable APOBEC activity and three are associated with tobacco smoking. An additional signature matches the spectrum of translesion DNA polymerase eta (POLH). In lymphoid cells, these mutations target promoters, consistent with AID-initiated somatic hypermutation. In solid tumors, however, they are associated with UV exposure and alcohol consumption and target the H3K36me3 chromatin of active genes in a mismatch repair (MMR)-dependent manner. These regions normally have a low mutation rate because error-free MMR also targets H3K36me3 chromatin. Carcinogens and error-prone repair therefore redistribute mutations to the more important regions of the genome, contributing a substantial mutation load in many tumors, including driver mutations.



Fran Supek is an ICREA professor based at the Institute for Research in Biomedicine (IRB Barcelona), a part of the Barcelona Institute of Science and Technology. Fran leads the Genome Data Science laboratory, which specializes in large-scale statistical analyses of genomic, transcriptomic and epigenomic data. Fran obtained his PhD in Molecular biology in 2010 from the University of Zagreb, while working as an early-stage researcher at the RBI (Croatia). This was followed by a postdoctoral stay at the Centre for Genomic Regulation (as a Marie Curie fellow) and in 2017 he started his group at the IRB as a Ramon y Cajal fellow. Fran is the PI of the ERC Starting Grant HYPER-INSIGHT and an author on 34 research papers and 2 book chapters, cited 3614 times.



Speakers

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