OPENING SESSION

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

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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

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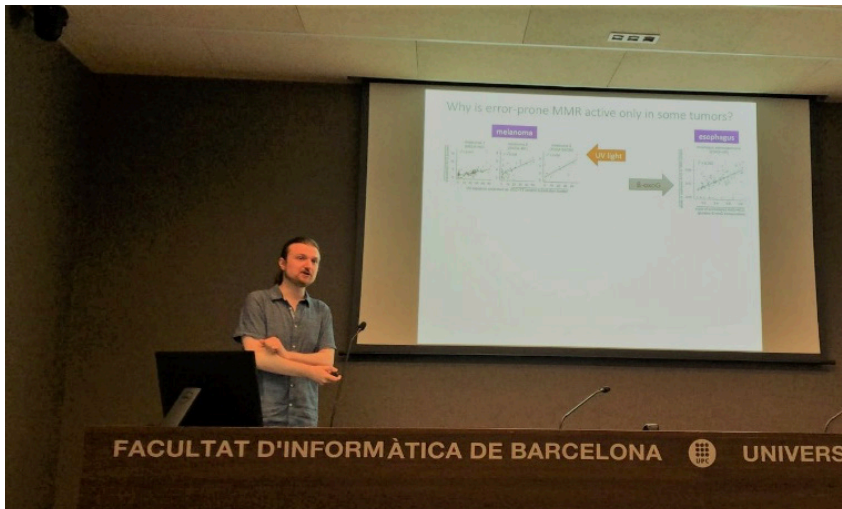
lymphoid cells, these mutations target promoters, consistent with AID-initiated somatic hypermutation. In solid tumors, however, they are associated with UV exposure and alcohol consumption and target the H3K36me3 chromatin of active genes in a mismatch repair (MMR)-dependent manner. These regions normally 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.

Short bio

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.