Mutational signatures of DNA repair deficiencies and cytotoxin exposures in C. elegans

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Abstract

Cancer is caused by alterations in the genome. These alterations can be an effect of combination of environmental factors damaging DNA and deficiencies in DNA repair and replication leading to characteristic mutational spectra.

Mutational signatures [1] became a very useful tool of cancer investigation in the last years. However, the signatures identified so far mostly represent complex conglomerates of the action of different mutational processes. For many signatures, the link with the underlying mutational processes is still unclear.

In this study we used C. elegans as a model organism to present a systematic screen with 9 types of genotoxins under 58 different genetic conditions including single and double knock-outs of DNA repair associated genes. Upon exposure over several generations we used whole-genome sequencing to study patterns of DNA damage.

We studied the mutational spectra by analysing different types of genetic lesions including point mutations, indels and structural variants using rigorous quality control procedure. This approach allows us to dissect the precise individual contributions of each factor using additive Poisson models, and also identify significant genetic and gene-mutagen interactions such as 3-fold increase in mutational burden for *pole-4; pms-2* double knock-out and mutational spectra expansion for DMS exposure in *polk-1* mutants.

We also compare the patterns extracted from *C. elegans* study and show that they can successfully be translated into human cancer investigation. In the case of mismatch repair deficient mutants we have shown that the pattern derived from *C. elegans* matches very well to a mismatch repair associated signature found in colorectal adenocarcinoma cohort [2], but both of them can only be represented as a combination of the mismatch associated COSMIC cancer signatures 6, 15, 20 and 26 [3] which indicates the presence of oversegmentation in the current signature set.

In summary, this analysis presents the first systematic catalogue of mutational signatures caused by genotoxins and DNA repair deficiencies.

References:

[1] Alexandrov et al. 2013. Signatures of mutational processes in human cancer. *Nature,* 500 (7463), 415-421.
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[3] Signatures of Mutational Processes in Human Cancer, http://cancer.sanger.ac.uk/cosmic/signatures