Changes in mutational processes and mutations patterns during cancer development

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Processes that influence cancer development can change during cancer evolution. Specific mutational signatures that they introduce have characterized many mutational processes in cancers (http://cancer.sanger.ac.uk/cosmic/signatures). Few studies using multiregional sequencing provide first evidences of differences in mutational spectra between trunk and branch mutations. Usually, we have only bulk sequences representing cancer metagenome. Clonal (present in nearly all cancer cells) and subclonal (present in a fraction of cancer cells) mutations which appear early and late in cancer development could be identified from bulk sequencing[1]. We applied this approach for whole genomes cancer data. In many cases, we were able to observe continuous changes in contribution of mutational signatures to overall mutational processes as a function of mutation occurrence time (Figure 1). We observed that some mutational signatures have similar trends in all cancer types they are present in. For example proportion of smoking or UV-light signatures are often prevalent in clonal mutations compared to subclonal (Figure 1A, B). Other signatures have different trends depend on cancer type, for example APOBEC signature arises late in cancer development in lung and breast cancer but early in bladder and head and neck cancers (Figure 1C).

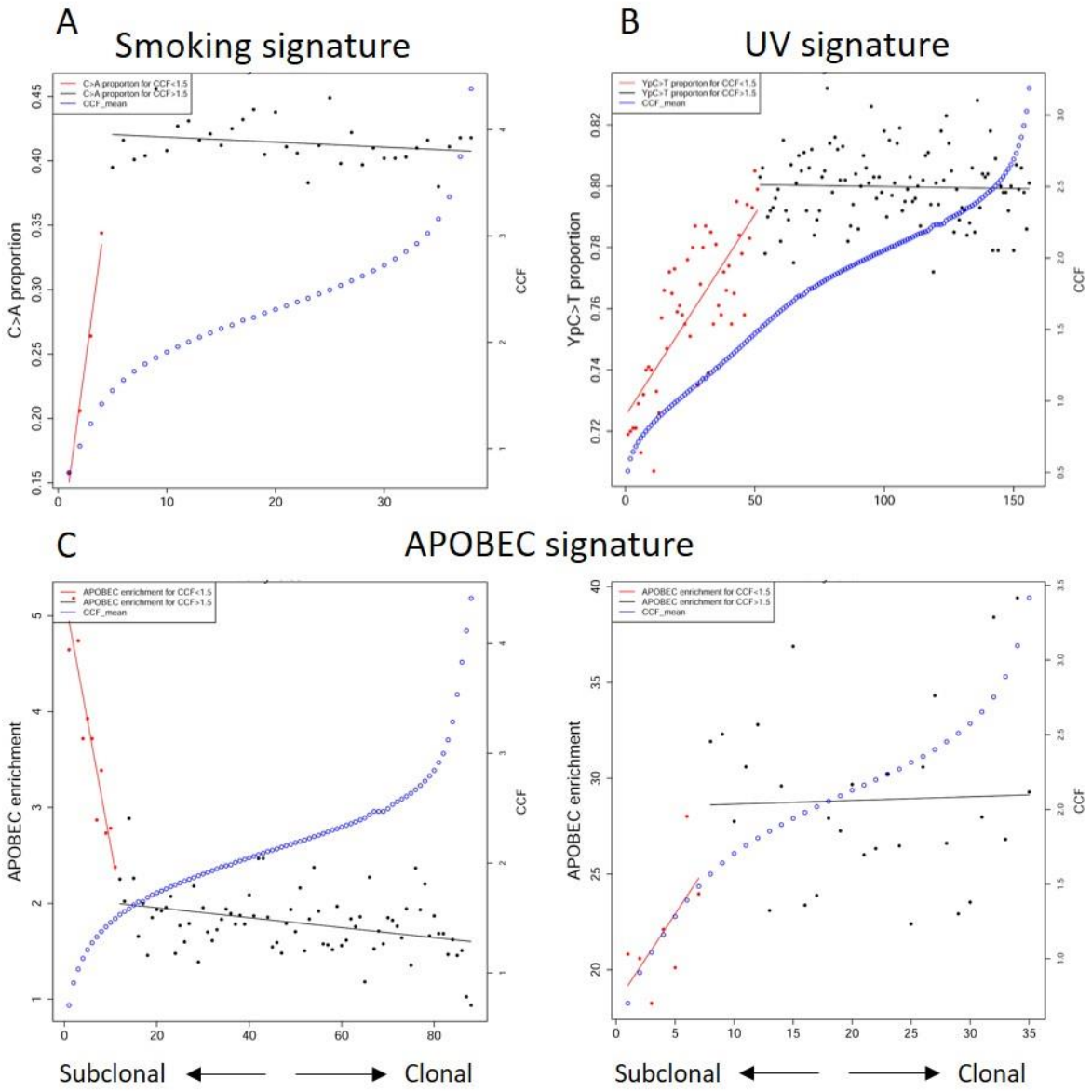

Figure 1. Changes in signature intensities between clonal and subclonal mutations. A) smoking signature, representative example for lung cancer sample; B) ultra-violet signature, representative example for melanoma sample; C) APOBEC signature, examples for lung cancer and bladder cancer samples.

For some signatures, specific dependencies on epigenetic properties of the cell or molecular processes are known, and we asked whether epigenetics of normal or tumor cell is a better predictor for distribution of early and late mutations. We have found that in melanoma the

clonal mutation rate is better predicted by the expression level in melanocyte, while the tumor-specific expression is a better determinant for the subclonal mutation rate (Figure 2A). This implies that most UV-induced mutations occur before tumor-specific changes in expression level, however some occur after it (Figure 2B). In contrast, in lung cancer we observed that most tobacco-induced mutations accumulate in cell after changes in expression profile to tumor state (Figure 2C, D). In the case of smoke-induced mutations, we can use the knowledge about time of lung exposure to mutagen as a proxy for time of accumulation of tobacco-induced mutations. We found that in people that quit smoking for example 10 years ago, distribution of mutations is better explained by tumor expression, than by expression of normal tissue. This suggests that expression changes occurred more than 10 years before cancer diagnosis. This observation is in line with smoke-induced mutation accumulation after big genetic rearrangements in former smokers[2], and in a good agreement with strongly increased probability to develop cancer for people with smoking history.

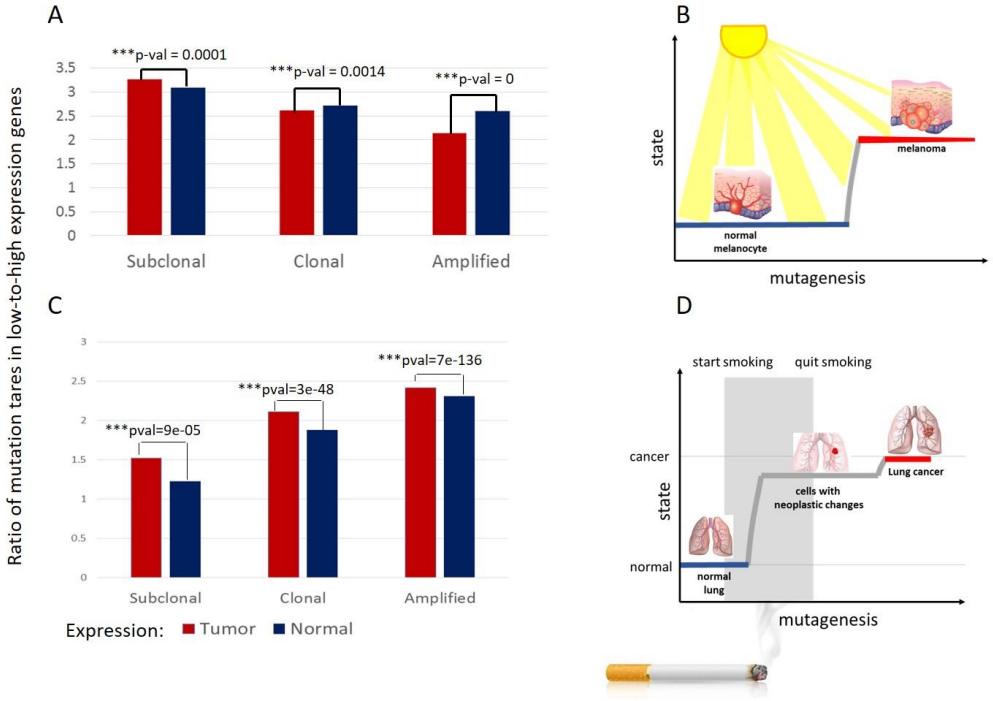

Figure 2. Ratios of mutation rate in low to high expressed genes for clonal and subclonal mutations using expression from tumor and corresponding normal tissue in melanoma (A) and lung cancer (C). Models of mutational process and changes in expression state in these cancer types (B, D).

Our study provides comprehensive description of plasticity of mutational processes in cancer development and shows utility of mutation based dating for cells malformation.

References

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2. Elza C. de Bruin et al. (2014) Spatial and temporal diversity in genomic instability processes defines lung cancer evolution, *Science,* **346**(6206): 251–256.