NUCLEOTIDE EXCISION REPAIR IS IMPAIRED BY BINDING OF TRANSCRIPTION FACTORS TO DNA

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Somatic mutations are one of the major genetic alterations that contribute to the transformation of normal cell into cancer cell. The rate of somatic mutations appear in great variability across the genome due to chromatin organization, DNA accessibility and replication timing. However, the impact of DNA-binding regulatory proteins, like transcription factors, on mutation rate variability in the local regions of the genome has not been studied in detail. Here, by analysing the whole genome somatic mutations of three different tumor types (melanoma, lung adenocarcinomas and lung squamous cell carcinomas) sequenced by TCGA, we demonstrate that the rate of somatic mutations is highly increased at active Transcription Factor binding sites (TFBS) compared to their flanking regions. Using the recently available excision-repair sequencing (XR-seq) data (Hu et al., 2015), we show that the higher mutation rate at these sites is caused by a decrease of the levels of nucleotide excision repair (NER) activity. Therefore, our work demonstrates that DNA-bound proteins interfere with the NER machinery, which results in an increased rate of mutations at their binding sites. This finding has important implications in our understanding of mutational and DNA repair processes and in the identification of cancer driver mutations.