Androgen receptor binding causes increased mutations in prostate cancer

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Background: Somatic mutations do not occur evenly across the genome. Variables including GC content, replication time, distance to telomeres and chromatin compaction can all alter the rate of mutations. Recent work has shown that in melanoma and colorectal cancer, transcription factor (TF) binding correlates with an increase in mutations. In melanoma this was demonstrated to occur due to the TF physically preventing access of nucleotide excision repair machinery to correct UV-mediated damage.

Methods+Results: To investigate the impact of TF binding in prostate cancer (PCa) we analyzed whole genome sequencing data of 197 primary prostate cancer patients from the Pan Cancer Analysis of Whole Genome project. We found that androgen receptor binding sites (ARBS) had, by far the highest rate of mutations of 20 TFs tested. In support of these results, the rate of ARBS mutations correlated with the relative AR peak height. The increase in mutations was not due to the location of TF binding, as both those sites which had an androgen response element but no androgen receptor binding and ARBS in non-AR driven cancer, had no change in the rate of mutations. ARBS mutations did not correlate with any histone mark or TF, suggesting that it solely due to AR binding. Interestingly, the mutations observed at the ARBS had a very high frequency of TpG->ApG mutations. These uncommon purine transversions typically occur due to failed DNA repair of abasic sites. We propose that the increase in mutations at ARBS may occur due to limited access of base excision repair machinery to the damaged DNA.

Conclusions: Overall this study demonstrates that ARBS have a higher rate of mutation in PCa. Further, we suggest that TF blockage of DNA repair machinery may affect several repair mechanisms including base excision repair. Work is currently ongoing to determine if these mutations alter the regulatory landscape of the cancer and provide an evolutionary advantage to the cancer.

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