Whole-exome sequencing evaluation of BCG responsiveness in high-risk non-muscle invasive bladder cancer (NMIBC)

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Abstract

Non-Muscle Invasive Bladder Cancer (NMIBC) accounts for 70-80% of the cases of bladder cancer. The gold-standard therapy for NMIBC are a transurethral resection of the lesion and an intravesical injection of Bacillus Calmette-Guerin (BCG). Immunotherapy using BCG are associated with the reduction of tumor recurrence and progression, but only approximately 50% of the patients benefit from this therapy and approximately 20% of the BCG treated patients interrupt the therapy due to side effects. The underlying mechanisms associated with the response of BCG immunotherapy are not yet well understood and there is not an available biomarker for response. Here, we sequenced the whole exome (WXS) from tumor of 35 (17 responsive, BCG-R; and 18 unresponsive, BCG-UR) high-risk NMIBC patients from Instituto do Câncer do Estado de São Paulo (ICESP) and performed a variant calling pipeline in order to find genomic variables associated with patient outcome. For the variant calling, we used the GATK best practices for variants calling and thereafter we filtered out germline variants by the presence in populational variants database (ExAC and 1000 Genomes) and the recurrence in our cohort. Our results show differences of tumor mutational burden (TMB) between BCG-R and BCG-UR (p-value = 0.045), in which the low-TMB group showed a higher relapse-free survival than the high-TMB group (p-value = 0.0092). We also evaluated tumor heterogeneity by Mutant-Allele Tumor Heterogeneity (MATH) score, however no statistical significance was found between BCG-R and BCG-UR. In the end, we found an import result to non-muscle invasive bladder cancer patients: TMB as a potential predictive biomarker for BCG immunotherapy response.

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