151 GENETIC HETEROGENEITY BETWEEN PAIRED PRIMARY AND METASTATIC SOLID TUMORS AND IMPLICATIONS FOR NEOANTIGEN-BASED PERSONALIZED CANCER VACCINES

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Background Neoantigen-based personalized cancer vaccines carry significant promise in treating solid malignancies. However, there are still uncertainties regarding the choice between the primary and metastatic tumor for neoantigen prediction in individual patients. Here, we conducted a thorough examination of somatic variations in 45 patients who had both primary and metastatic solid tumors

Methods Patients were enrolled in the Total Cancer Care protocol (NCT03977402) to which patients provided an IRB-approved written informed consent across the Oncology Research Information Exchange Network® (ORIEN). Whole-exome sequencing (WES) of primary and metastatic tumor pairs was performed for 45 patients. These included head and neck (n=8), renal cell carcinoma (n=7), non-small cell lung cancer (n=6), melanoma (n=5), bladder (n=3), sarcoma (n=3), ovary (n=3), esophageal (n=2), colorectal (n=2) and other singletons (n=5). The data was analyzed through the ORIEN AVATAR Molecular Analysis Pipeline for somatic mutation variant detection and variant annotation. In this analysis, we focused on somatic events that result in an in-frame alteration (such as missense, in-frame deletion, and in-frame insertion) and out-of-frame protein-altering mutations (such as frameshifts, de novo start, out-of-frame, and nonstop gain). Clonal population structure was determined based on pyclone-vi, and our TACIER(beta) pipeline was used to predict neoantigens presented by MHC-I and II.

Results For in-frame events, we noticed that bladder cancer, melanoma, and head-and-neck cancer shared close to 75% of the mutations between paired primary and metastatic cases. In contrast, esophageal, brain, and endometrial cancers had a low overlap (< 25%) of variants. For out-of-frame events, we found that these events tend to have a lower proportion of shared somatic variants between primary and metastasis than in-frame variants. Interestingly, antigens presented by MHC class II were more conserved between primary and metastasis cases when compared to antigens presented by MHC class I (paired T-test 0.02). Melanoma had a high overlap of antigens presented by MHC class I (~80.4%), and head-and-neck cancers had a high overlap of antigens presented by MHC class II (~79.5%). Finally, oncogenic drivers (such as BRAF V600E, NRAS G13R, KRAS G12A, and TP53 loss-of-function) were more likely to be presented in both paired primary and metastatic tumors.

Conclusions Our analysis demonstrates genetic variations that exist when comparing paired primary and metastatic tumors that appear to vary by histology. Variants are potentially undergoing negative selection supported by the preferential loss of out-of-frame events in metastatic tumors. Understanding the clonal structure will be key to neoantigen prediction for effective neoantigen-based vaccines.

Ethics Approval Patients were enrolled in the Total Cancer Care protocol (NCT03977402) to which patients provided an IRB-approved written informed consent across the Oncology Research Information Exchange Network® (ORIEN).

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