

Exploiting Functional Epigenomics and Proteomics to Unravel Neoantigens in Pediatric Leukemia

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Abstract: Pediatric tumors tend to have quiet genomes with few mutations and structural genomic aberrations and are thus thought to have low burden of neoantigens. Investigating the potential of immunotherapies geared towards increasing the patient's anti-tumor immune response, such as checkpoint blockade, has been limited in pediatric tumors, as these tumors are predicted to be non-responsive due to their low rate of genetic aberrations. Intriguingly, recent evidence suggests that neoantigens can also occur with splicing defects, many of which are present in pediatric malignancies. However, the exact mechanisms that lead to neoantigen expression outside of genetic aberrations remain poorly understood. We have discovered that aberrant splicing and non-canonical transcripts in acute leukemias result in neomorphic peptides that are computationally predicted to represent high affinity neoantigens. The presence of these neomorphic peptides coincides with dysfunctional CD8⁺ T-cells in the microenvironment suggesting an unexpected role for immune evasion in acute pediatric leukemias. In this project, we will determine neomorphic proteins generated by non-canonical transcripts in pediatric leukemias by combining full-length RNAsequencing and highly sensitive mass spectrometry (aim 1); define the epigenetic context and regulation of non-canonical transcripts by investigating DNA-methylation and chromatin accessibility of noncanonical transcripts (aim 2); and develop novel strategies to target non-genetic neoantigen expression in pediatric leukemias by perturbing the epigenetic and splicing machinery (aim 3). Studying the underlying mechanisms that govern non-genetic neoantigen expression in pediatric tumors has enormous therapeutic implications for developing novel immunotherapy strategies for pediatric tumors.