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5-Hydroxymethylcytosine Profiles in Circulating Cell-Free DNA Associate with Disease Burden in Children with Neuroblastoma

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Abstract

Purpose: 5-Hydroxymethylcytosine (5-hmC) is an epigenetic marker of open chromatin and active gene expression. We profiled 5-hmC with Nano-hmC-Seal technology using 10 ng of plasma-derived cell-free DNA (cfDNA) in blood samples from patients with neuroblastoma to determine its utility as a biomarker.

Experimental design: For the Discovery cohort, 100 5-hmC profiles were generated from 34 well children and 32 patients (27 high-risk, 2 intermediate-risk, and 3 low-risk) at various time points during the course of their disease. An independent Validation cohort encompassed 5-hmC cfDNA profiles (n = 29) generated from 21 patients (20 high-risk and 1 intermediate-risk). Metastatic burden was classified as high, moderate, low, or none per Curie metaiodobenzylguanidine scores and percentage of tumor cells in bone marrow. Genes with differential 5-hmC levels between samples according to metastatic burden were identified using DESeq2.

Results: Hierarchical clustering using 5-hmC levels of 347 genes identified from the Discovery cohort defined four clusters of samples that were confirmed in the Validation cohort and corresponded to high, high-moderate, moderate, and low/no metastatic burden. Samples from patients with increased metastatic burden had increased 5-hmC deposition on genes in neuronal stem cell maintenance and epigenetic regulatory pathways. Further, 5-hmC cfDNA profiles generated with 1,242 neuronal pathway genes were associated with subsequent relapse in the cluster of patients with predominantly low or no metastatic burden (sensitivity 65%, specificity 75.6%).

Conclusions: cfDNA 5-hmC profiles in children with neuroblastoma correlate with metastatic burden and warrants development as a biomarker of treatment response and outcome.

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