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Tobacco Exposure is Associated with Unique Cell-Type Specific Epigenetic Modifications Across Immune Cell Types

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Tobacco use impacts immune cell function and composition, potentially influencing cell-type-specific disease progression or early disease detection. This study hypothesizes that smoking-associated CpG DNA methylation varies across cell types and is enriched in genes related to smoking pathogenesis and comorbid conditions. Using computational deconvolution, we obtained cell-type-specific methylation profiles from whole blood and peripheral blood mononuclear cells (PBMCs) without cell sorting. We deconvoluted methylation data from whole blood and PBMC into CD4+ T-cells, CD8+ T-cells, B cells, Natural Killer (NK) cells, monocytes, and granulocytes in three independent cohorts (Ntotal=2,917). Cell-type EWAS of tobacco use was performed in each cohort separately, followed by a meta-EWAS and gene set enrichment analysis for each cell type. In the meta-EWAS analysis, we observed 3,641 differentially methylated positions (DMPs) in PBMC, 335 in CD4+ T-cells, 190 in CD8+ T-cells, 246 in B cells, 115 in NK cells, 222 in monocytes, and 2,015 in granulocytes, all significant at FDR <0.05. Among these, 31 DMPs were specific to CD4+ T-cells, 3 to CD8+ T-cells, 15 to B cells, 2 to monocytes, and 416 to granulocytes. Smoking-associated cell-type-specific CpG sites were enriched among genes involved in pathways linked to immune cell aging, disruptions in hormonal balance, oxidative stress responses, inflammation, metabolic alterations, and immune differentiation. These findings indicate that cell-specific epigenetic responses to tobacco exposure are common and may be missed using bulk cell EWAS but that deconvolution to cell types can provide insights into how tobacco influences specific immune cell function through epigenomic modifications.