TIME-RESOLVED MULTIOMICS REVEAL DISTINCT B CELL FATES AND GENE REGULATORY SIGNATURES IN THE EARLY STAGES OF EPSTEIN-BARR VIRUS INFECTION

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Epstein-Barr Virus (EBV) infection elicits diverse responses in host B cells via complex, well-adapted transcriptional control dynamics. Consequently, this host-pathogen interaction provides a powerful system to explore fundamental cellular processes that contribute to consensus fate decisions including cell cycle arrest, apoptosis, proliferation, and differentiation. Here we capture these responses and fates with matched single-cell transcriptomics and chromatin accessibility, from which we construct a genome-wide multistate model of early infection dynamics. Notably, our model captures a previously uncharacterized EBV^+ analog of a multipotent activated precursor state from which early memory B cells originate. We also observe a marked global reduction in host chromatin accessibility during the first stages of infection in subpopulations of EBV^+ cells exhibiting senescent and pre-apoptotic hallmarks induced by innate antiviral sensing and proliferation-linked DNA damage. However, cells in proliferative infection trajectories exhibit greater accessibility at select host sites linked to B cell activation and survival genes as well as key regions within the viral genome. To further investigate such loci, we develop and implement a bioinformatic workflow (crisp-ATAC) to identify phenotype-resolved regulatory dynamics. This customizable method applies user-specified logical criteria to produce genome-wide single-cell ATAC- and ChIP-seq range intersections, which are used as inputs for *cis*-linkage prediction and ontology tools. The resulting tri-modal data yield detailed hierarchical perspectives of the transforming regulatory landscape during critical stages of an oncogenic viral infection that simulates antigen-induced B cell activation and differentiation. We anticipate these resources will guide investigations of gene regulatory modules controlling EBV-host dynamics, B cell effector fates, and lymphomagenesis.