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Delta-9-Tetrahydrocannabinol Dynamically Alters Transcriptome at Single-Nucleus Resolution *in* Humans

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We aim to understand the transcriptomic impacts of Delta-9-Tetrahydrocannabinol (THC) in peripheral blood mononuclear cells among healthy human participants (N=9). Each participant received THC intravenously (0.03 mg/kg). Blood samples were collected at -30 minutes, +70-, and +300-minutes post-THC administration for 10x single-nucleus multi-omic profiling. A total of 66,538 nuclei were clustered into 7 major cell types, including CD4+ T cells, CD8+ T cells, B cell, natural killer cells, classical monocytes, non-classic monocytes, and dendritic cells. Using a linear mixed model, we found that the trajectories of 603 genes significantly changed by THC uniquely within each cell type (FDR<0.05, logFC> 0.1), showing 4 patterns, (Growth: increased with time; Recession: decreased with time; Peak: increased then decreased; and Trough: decreased then increased). For example, THC induced 32 growth genes, 68 recession genes, 263 peak genes, and 33 trough genes in classical monocytes. Notably, THC persistently decreased expression of S100A9 (a gene regulation of proinflammatory process) in monocytes (5.83×10^{-300}, logFC= 0.28), demonstrating THC's anti-inflammatory effects. Conversely, the expression of BTG1 (anti-proliferation factor 1**)** by THC showed a peak pattern (3.92×10^{-6}, logFC= 0.14), suggesting temporary induction of apoptosis. These 603 significant genes were enriched on pathways involving in inflammatory function, cell proliferation and differentiation, and regulation of apoptotic process. Our findings demonstrate that THC modulates immune function by altering cell-type-specific transcriptomes. Next step will integrate epigenetic and chromatin analysis to identify THC-induced epigenetically regulated gene dysfunction.