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T Cell Dysregulation in Long-COVID: Immune Profiling and the Potential Role of Short-chain Fatty Acids in Modulating T-cell Functionality

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Abstract

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Long-COVID (LC) affects over 400 million individuals globally and is characterised by persistent fatigue, cognitive dysfunction, and gastrointestinal disturbances[1,2]. The possible underlying immunological mechanisms associated with LC remain poorly understood. A possible mechanism would link gut dysbiosis and altered gut metabolic output- in particular with respect to the production of short-chain fatty acids (SCFAs)- to immune dysregulation in LC[3]. SCFAs, primarily acetate, propionate, and butyrate, are key modulators of T-cell function[4]. A deficiency in SCFAs due to prolonged dysbiosis and poor diet due to reduced mobility and fatigue may drive immune exhaustion and chronic low-grade inflammation commonly observed in LC patients. This study aims to characterise CD4+T cells in LC patients and explore the regulatory role of SCFAs on T-cell functionality under the context of LC.

Multiple flow cytometry panels were employed on PBMC from Long-COVID patients (LC, n=15) and matched No-Fatigue controls (CT, n=10), to quantify T-cell subsets (as % of CD4+T-Cells), assessing exhaustion (PD-1, CD44, LAG3, CD38, CD57), differentiation (CD45RO/RA, CD27, CD62L), activation markers (HLA-DR, CD25) and frequency of Treg (CD25high FOXP3highCD127low). Serum cytokine levels were quantified using a multiplex chemiluminescence-based assay platform. Stimulation assays were performed using CD3+ T-cells using CD3/CD28 activation-bead in the presence/absence of SCFAs (acetate, butyrate, propionate) at 0.125-2 mM/ml concentrations toward optimising inducible Treg assays in the future.

$CD4^+$ T cells in LC showed elevated exhaustion markers: PD-1 (34%, $p = 0.0001$), CD44 (24%, $p = 0.03$), CD38 (43%, $p = 0.07$), and LAG3 (19%, $p = 0.0063$). $CD8^+$ T cells had increased PD-1 expression in 15% of LC patients. $CD57^+$ memory $CD4^+$ T cells were reduced ($p = 0.006$), and $CD62L^+$ naïve $CD4^+$ T cells were higher in LC ($p = 0.008$). Naïve/memory balance in $CD8^+$ T cells shifted (−21% memory, +32% naïve). Treg frequencies showed a lower median in LC, though not statistically significant. CRP levels were elevated in 73% of LC patients vs. 12% of controls ($p < 0.0001$). IL-4 and IL-6 were elevated in 44% and 41% of LC patients, respectively ($p < 0.0001$). Hierarchical clustering revealed six immune clusters, four dominated by LC with distinct inflammatory or Th2/Th17 profiles.

Preliminary SCFA assays showed butyrate (≥0.5 mM) suppressed CD3/CD28-induced proliferation in $CD4^+$ and $CD8^+$ T cells. Propionate was effective at ≥1 mg/mL; acetate had no effect up to 2 mM.

LC patients show marked immune changes on CD4+T-cells for exhaustion but on CD8+T- cells for differentiation and high cytokine levels in the circulation. The observed heterogeneity may relate to symptoms, which will be explored later. Preliminary SCFA functional assay data suggest SCFAs, especially butyrate, can regulate T-cell proliferation, supporting the idea of a link between the gut (dysbiosis) and the immune system in LC pathophysiology.

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