Sepsis diagnosis through cellular morphology with biological insights and interpretations

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Sepsis, which is associated with high incidence and mortality, is a dysregulated immune response to infection that leads to organ dysfunction. The lack of reliable biomarkers for the rapid diagnosis of sepsis presents a significant obstacle in the sepsis management. In our study, we aimed to explore the potential of label-free 3D CD8+ T-cell morphology as a sepsis diagnostic biomarker. This study utilized 3D CD8 T cell images acquired from a septic shock cohort (n=8) and healthy controls (n=20) to further explore morphological features of patients and controls. We developed a deep learning model that predicts sepsis diagnosis using internal cell morphological features. Furthermore, we analyzed scRNA-seq data with sequenced data from PBMCs from the same patients used for image acquisition (n=6) and open healthy controls for biological interpretation. Significant variations between septic shock patients and healthy controls were observed in the cell morphological characteristics. The model showed an area under the receiver operating characteristic curve of almost 100% with minimal cell sampling. In addition, scRNA-seq analysis of differential gene expression (DEG) between septic shock and controls identified 191 genes, with 90 and 101 genes being up-regulated and down-regulated in septic shock, respectively. Among the genes up-regulated during shock, we identified genes such as *ACTR3*, *ARPC1B*, and *ARPC5*. Notably, these genes were known to be associated with the cellular actin cytoskeleton. Our study not only demonstrate the potential of using 3D CD8 T cell morphology as a biomarker for sepsis diagnosis, but also provide a biological interpretation. This approach opens new avenues for sepsis diagnosis and provides a basis for the development of improved diagnostic tools.