Study discovers T cells in human blood secrete a substance that affects blood pressure and inflammation

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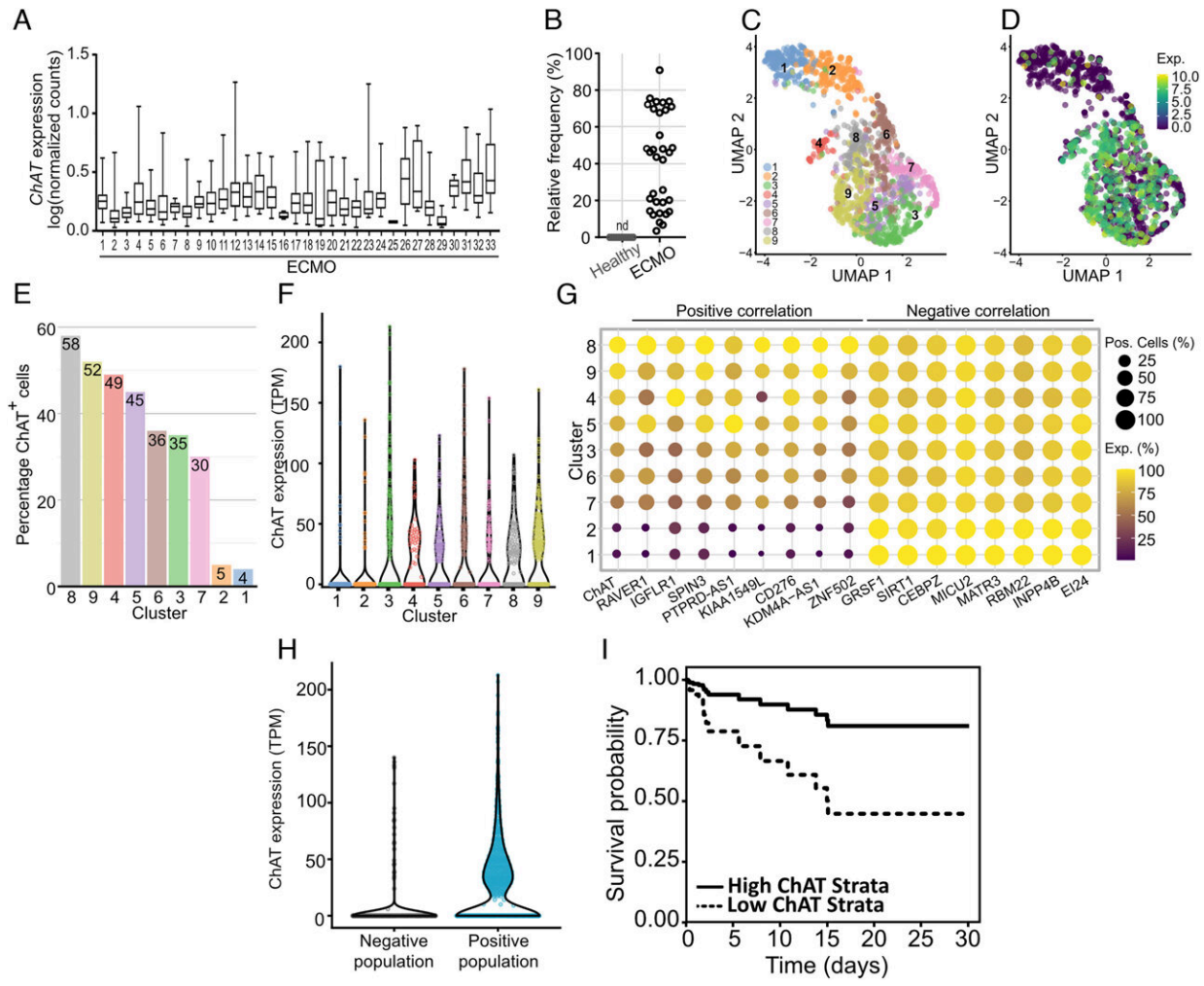

The relative frequency of $CD4^+$ $ChAT^+$ T cells in blood correlated with survival. (A) Box plots indicating ChAT expression in single-cell transcriptomic analysis of peripheral blood $CD4^+$ cells from patients in circulatory failure requiring veno-

arterial extra corporeal life support (extracorporal membrane oxygenation, ECMO) (n = 33). Transcript levels are shown as log normalized counts. The boxes indicate the interquartile range, the central bar indicates the median, and the whiskers show the 5th to 95th percentile range. (B) Scatter dot plot indicating the relative frequency of $ChAT^+$ cells within $CD4^+$ T cells in healthy control individuals (n = 11) and patients in circulatory failure ECMO (n = 33). Each circle indicates an individual patient. nd–not detected. (C) Uniform manifold approximation and projection (UMAP) of transcriptomic analysis of single $CD4^+$ cell from patients in circulatory failure ECMO (n = 33). Colors denote cell populations defined using Louvain clustering. (D) UMAP projection of ChAT expression. Expression (Exp.) is presented as log counts of ChAT. (E) Percentage of $ChAT^+$ cells in each of the cell populations defined using Louvain clustering identified in C. (F) Violin plot of transcripts per million (TPM) of ChAT expression in each of the cell populations defined using Louvain clustering identified in C. Clusters (x axis) are ordered by percentage of $ChAT^+$ cells. (G) Dot plot showing ChAT and the 16 transcripts most positively or negatively correlated with ChAT ($r > 0.3$, P^+ cells. The size of the dot corresponds to the percentage of positive cells in each cluster. The color Expression (Exp.) represents the average transcripts per million reads (TPMs) normalized by mean TPMs in all clusters and adjusted to 100%. (H) Violin plot of TPM of ChAT in single cells positive for at least one or negative for all eight significantly positively correlated genes identified in the correlation analysis in G. (I) The survival probability for patients (n = 32) with low $ChAT^+CD4^+$ T cell frequency (Low Strata, 25th percentile) and high $ChAT^+CD4^+$ T cell frequency (High Strata, 75th percentile) and all other significant variables (inotrope score and lactate) at their median. Credit: *Proceedings of the National Academy of Sciences* (2023). DOI: 10.1073/pnas.2212476120

Acetylcholine regulates blood flow, but the source of blood acetylcholine has been unclear. Now, researchers at Karolinska Institutet have discovered that certain T cells in human blood can produce acetylcholine, which may help regulate blood pressure and inflammation. The study, which is published in *PNAS*, also demonstrates a possible association between these immune cells in seriously ill patients and the

risk of death.

Blood flow regulation by acetylcholine is long established and highlighted by the 1998 Nobel Prize in Physiology or Medicine. Yet the sources of acetylcholine in human blood have been unclear. Previous research, such as studies by Peder Olofsson's group at Karolinska Institutet in Sweden, has shown that a certain type of immune cell known asChAT$^+$ T cells can produce acetylcholine and affect endothelial cells in the blood vessels of mice. However, it has not been known if these types of T cells exist in humans.

"We now show that human T cells can also release acetylcholine," says the study's joint first author Laura Tarnawski, assistant professor at the Department of Medicine (Solna), Karolinska Institutet. "This corroborates previous findings in different model systems and may contribute to the development of treatments for cardiovascular disease and inflammatory diseases."

Acetylcholine also plays a vital role as a neurotransmitter in the brain and nervous system, but the researchers are particularly interested in its role in inflammation.

"We're interested in how the brain communicates with the immune system, which is something we still know relatively little about," says the other first author Vladimir Shavva, assistant professor at the same department. "Our new study shows that acetylcholine in the blood can be secreted by immune cells, which can regulate inflammation in the blood vessels."

The findings are based on analyses of blood from healthy blood donors. The researchers also studied 33 patients with severe circulatory failure who had been admitted for intensive care, and found that higher relative blood levels of ChAT$^+$ T cells were associated with reduced risk of

death.

"Our findings are of clinical interest and could contribute to new diagnostic and therapeutic opportunities for seriously ill patients with excessive inflammation," says principal investigator Peder Olofsson, senior researcher at the Department of Medicine (Solna).

The group now plans to map the presence of $ChAT^+$ T cells in different patient groups and different organs, and how they affect metabolic and inflammatory processes.

More information: Laura Tarnawski et al, Cholinergic regulation of vascular endothelial function by human ChAT + T cells, *Proceedings of the National Academy of Sciences* (2023). DOI: 10.1073/pnas.2212476120

Provided by Karolinska Institutet