Science Immunology: Busy Tissues Need Bigger Cleanup Crews to Work at Their Best

04/09/2026

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Now scientists Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC) , Universidad Pompeu Fabra, UC San Francisco and Yale University, have uncovered how tissues adapt their clearance capacity to meet their waste-management needs. In a study published *Science Immunology* the researchers found that energy-demanding tissues harbor large clean-up crews of immune cells called macrophages, which means “big eater,” and the size of the clearance crews scales with the metabolic activity of each tissue and the amount of trash they produce.

Much of the trash is made of damaged mitochondria — the ‘power plant’ organelles that transform nutrients into energy cells can use. As mitochondria wear out from powering cells, they are discarded as waste. The greater a tissue’s energy demands, the more mitochondria get sent to the trash.

The scientists tracked mitochondria in heart muscle, skeletal muscle, and brown fat in mice and saw that spent mitochondria ended up inside of macrophages. When the team prevented macrophages from cleaning up the waste, the system broke down: heart muscle reduced pumping, skeletal muscle weakened, and brown fat grew cold. In other words, tissues need to stay clean to work at their best.

They traced the onset of the cleanup process to structural cells called fibroblasts, whose numbers increased in parallel with the tissue’s mitochondrial activity. The fibroblasts then made a signal that prompted the macrophages to multiply as well, thus providing a way for tissues to match the size of their cleanup crews to the amount of waste they produce.

Looking in publicly available datasets of human muscle cells, the researchers found that the number of macrophages tracked muscle mitochondrial activity, a proxy for exertion. The finding suggests that the same waste-management system discovered in mice may also scale with the metabolic demands of human muscles.

“This balance between high energy demands and number of macrophages seems to be critical for our health,” said José Angel. Nicolás-Ávila, PhD, an assistant professor of Microbiology and Immunology in the UCSF Cardiovascular Research Institute and senior author of the study. Laura Pena-Couso, PhD, first author of the study, added: "Tissue metabolism, waste accumulation, and macrophage numbers all change with aging. Our findings reveal the signals that couple these processes, opening the possibility that targeting this system could help preserve tissue function as we age.”

This work was supported in part by the National Institutes of Health, Fundación “la Caixa”, Transatlantic Network of Excellence de la Leducq Foundation; FET-OPEN of the European Commission , European Research Council (ERC); the María de Maeztu Programme for Units of Excellence at UPF , Cardiovascular Research Institute (CVRI) University of California San Francisco (UCSF), Dean’s Office UCSF, Pilot Feasibility Award de UCSF-NORC, and Sandler Program for Breakthrough Biomedical Research (PBBR).

- *Pena-Couso L, Sicilia J, Vieto S, Silva-Rojas R, Sánchez-Díaz M, Calvo E, et al. Tissue mitochondrial activity dictates the macrophage pool size. Sci Immunol. 2026. doi:10.1126/sciimmunol.aeb9244.*

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