Molecular 'brake' prevents excessive inflammation

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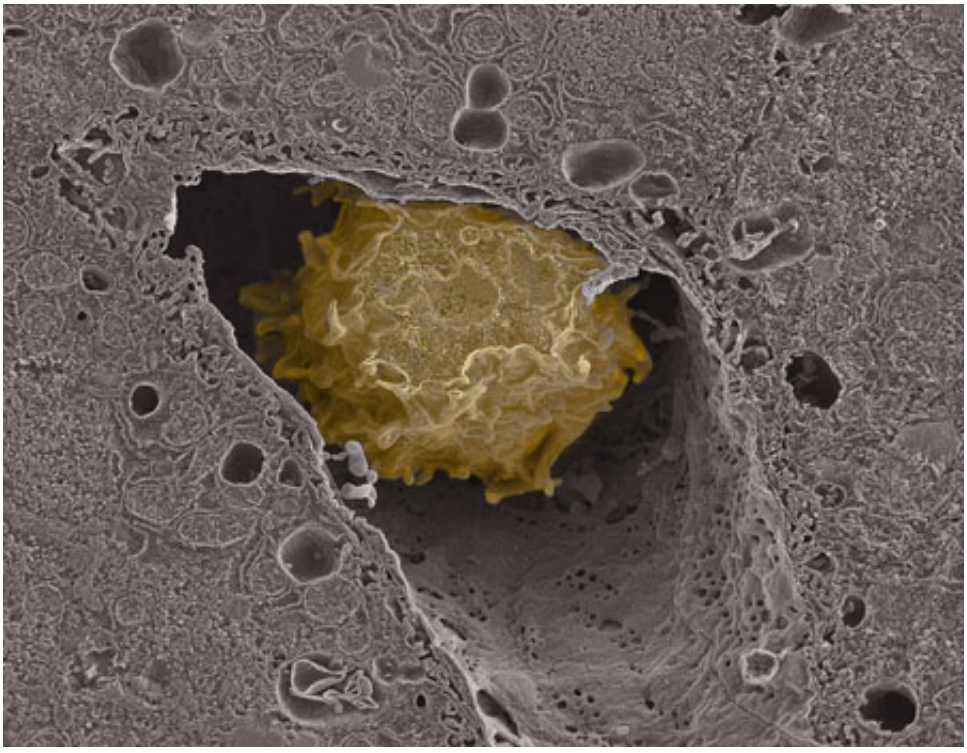

Macrophage (yellow, center) in the liver. Credit: UC San Diego Health

Inflammation is a Catch-22: the body needs it to eliminate invasive organisms and foreign irritants, but excessive inflammation can harm healthy cells, contributing to aging and sometimes leading to organ failure and death. Researchers at University of California, San Diego School of Medicine have discovered that a protein known as p62 acts as a molecular brake to keep inflammation in check and avoid collateral

damage. The mouse study is published February 25 in *Cell*.

"In addition to explaining how our bodies can turn off inflammation when it's no longer needed, these findings could have important implications for many age-related diseases," said Michael Karin, PhD, Distinguished Professor of Pharmacology and Pathology at UC San Diego School of Medicine. Karin led the study with Zhenyu Zhong, PhD, a postdoctoral researcher in his lab, and collaborators at Sanford Burnham Prebys Medical Discovery Institute.

Macrophages are cells that play a major role in inflammation—they detect and swallow invading microbes and foreign particles, such as asbestos microfibers. At the same time, activated macrophages release cytokines, small proteins that serve as signals to recruit and activate other immune cells for assistance. To produce and secrete one major inflammatory cytokine, interleukin-1beta (IL-1beta), macrophages employ molecular machines called inflammasomes. One of the most functionally diverse inflammasomes is the NLRP3-inflammasome, which releases IL-1beta when stimulated by toxins and microparticles such as silica, asbestos or cholesterol microcrystals.

However, foreign particles don't act directly on the NLRP3-inflammasome. Instead, Karin's team found, foreign particles damage the macrophage's mitochondria—the cell's energy-producing "power plant." In turn, damaged mitochondria release signals that activate the NLRP3-inflammasome and keep it cranking out IL-1beta.

That's a good thing if your body needs to clear out invading particles or microbes, but continuous production of IL-1beta is very dangerous—it can easily lead to an inflammatory chain reaction that results in multi-organ failure, septic shock and death. The body needs a way to turn off IL-1beta production by NLRP3-inflammasomes.

To do this, Karin's team discovered, macrophages responding to foreign microbes and irritants also bump up production of p62. This protein coats damaged mitochondria that release inflammasome-activating signals and ensures they are eliminated. Once these damaged mitochondria are removed, the NLRP3-inflammasome de-activates and IL-1beta production is turned off.

"We've suspected for quite some time that damage to mitochondria caused by either genetic or environmental factors is the root cause of many age-related diseases, all of which are associated with chronic, low-grade inflammation," said Zhong. "Therefore, p62—and its part in eliminating damaged mitochondria—could provide a new target for preventing such diseases. Indeed, we already know that another protein that collaborates with p62 to eliminate damaged mitochondria is Parkin, which plays a role in a rare form of Parkinson's disease."

More information: *Cell*, dx.doi.org/10.1016/j.cell.2015.12.057

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