IMMUNITY: Scientists identify a new therapeutic target in macrophages for the treatment of obesity-related diseases

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The discovery, published in the journal Immunity*, identifies a new therapeutic route for conditions associated with obesity and metabolic syndrome, including cardiovascular disease*

Macrophages are cells of the immune system that, in addition to playing an essential role in the early response to microbial infection, also regulate tissue function and inflammation. Inflammation is a physiological response that helps to repair damaged tissue, but if not correctly resolved it can become chronic inflammation, which lies at the origin of many conditions, including the metabolic syndrome associated with obesity, type 2 diabetes, and cardiovascular disease.

Now, a team at the Centro Nacional de Investigaciones Cardiovasculares (CNIC) has discovered that the metabolic requirements of macrophages differ depending on the organ in which they reside. In other words, these cells adapt to the needs of the organ in which they are located. The discovery "gives us a better understanding of how macrophages regulate their metabolism according to the organ in which they reside. In addition, our results reveal a vulnerability of macrophages that contributes to chronic inflammatory diseases and that could be exploited therapeutically for the treatment of conditions associated with obesity and metabolic syndrome, such as cardiovascular disease," said study leader Dr. David Sancho, who heads the CNIC Immunobiology group. The study is published today in an article in the journal *Immunity*.

Macrophages are immune cells that are normally distributed throughout the body and help to cleanse organs of all types of biological material that needs to be removed, from harmful particles such as mineral crystals or viruses to proteins or larger complexes that arise during development. Macrophages are also important for removing dead cells, thus contributing to tissue renewal.

The new study reveals that macrophages adapt their metabolism and function to the organ in which they reside. "In tissues with abundant extracellular fat and cholesterol, such as the lungs and spleen, macrophages adapt their metabolism to degrade these fats through mitochondrial respiration," explained first author Dr. Stefanie Wculek. "Using genetic or pharmacological methods to disrupt mitochondrial respiration, mitochondria can be eliminated from lung and spleen, whereas the macrophages in other organs, which don't depend on mitochondrial respiration, survive."

Another example is provided by the macrophages located in body fat, or adipose tissue. "**Macrophages residing in the body fat of a person of normal weight are unaffected by mitochondria-disrupting treatments because their metabolism is less dependent on mitochondrial respiration. This is because the fat cells, called adipocytes, are fully functional, leaving the macrophages in a resting state**," said Dr. Sancho. "However, in obese individuals, the excess fat surpasses the capacity of the adipocytes, and the resident macrophages become activated, converting into inflammatory cells that promote the development of insulin resistance, type 2 diabetes, and fatty liver."

But this change in adipose tissue macrophages also makes them vulnerable. "The activated macrophages depend on mitochondrial respiration to process the excess fat, and this makes them vulnerable to therapeutic interventions, including pharmacoligical inhibitors of mitochondrial respiration," explained Dr. Sancho.

The Immunity study shows that inihition of mitochondrial respiration killed these proinflammatory macrophages, preventing the progression of obesity, type 2 diabetes, and fatty liver (the key components of metabolic syndrome) in an experimental mouse model. The investigators conclude that this finding opens the way to new treatments for conditions linked to obesity and metabolic syndrome, like cardiovascular disease.

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- *Wculek SK, Heras-Murillo I, Mastrangelo A, Mañanes D, Galán M, Miguel V, Curtabbi A, Barbas C, Chandel NS, Enríquez JA, Lamas S, Sancho D. Oxidative phosphorylation selectively orchestrates tissue macrophage homeostasis. Immunity. 2023 Jan 31:S1074-7613(23)00021-3. doi: 10.1016/j.immuni.2023.01.011*