Study finds that salt cuts off the energy supply to immune regulators

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Salt disrupts the function of immune regulators (Tregs): Their mitochondria temporarily produce less energy, thus altering cellular metabolism. Credit: Felix Petermann, Max Delbrück Center

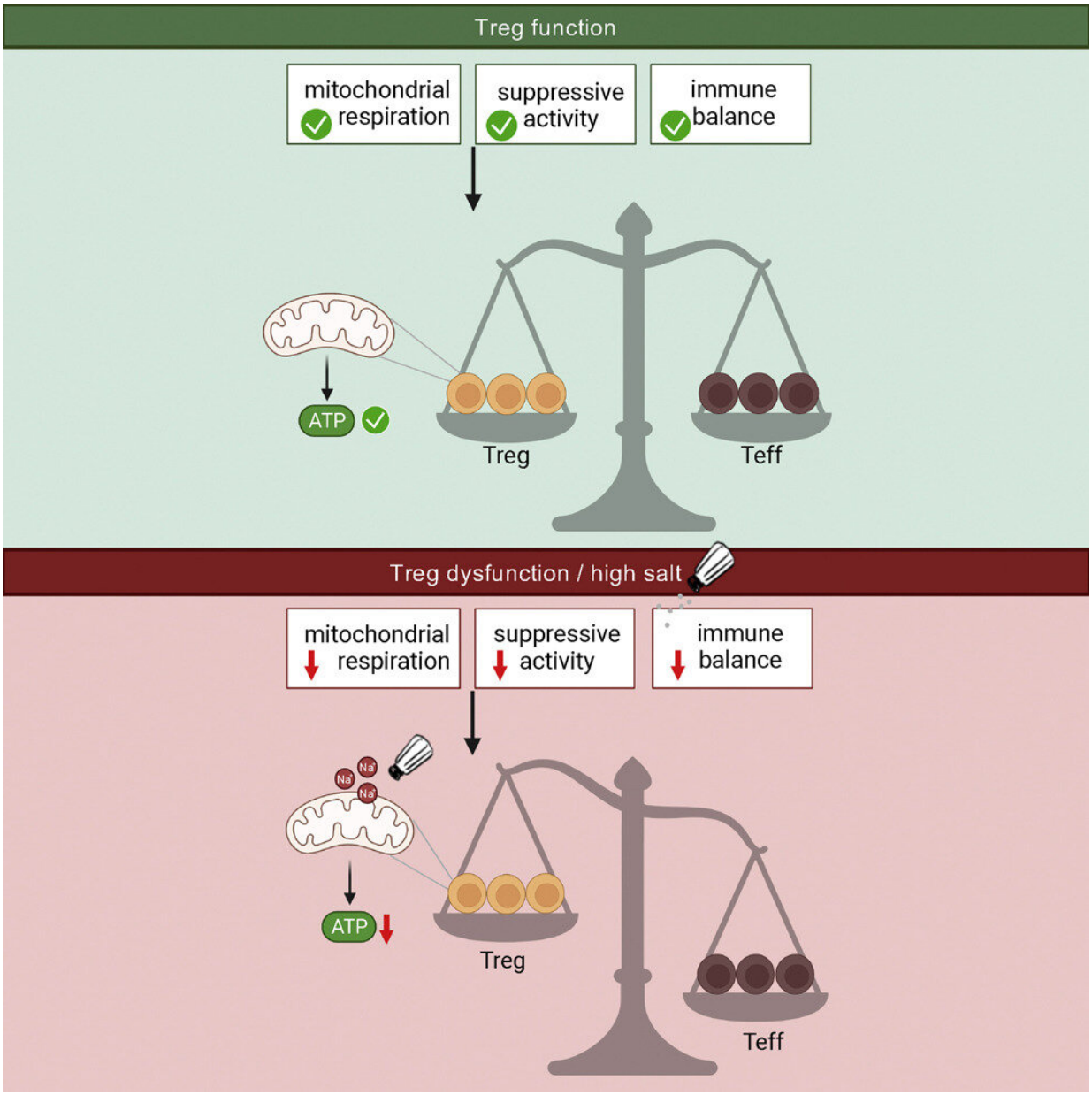
Eating too much salt, which is common in many Western societies, is not only bad for our blood pressure and cardiovascular system—it could also

adversely impact the immune system.

An international research team, coordinated by scientists at the VIB Center for Inflammation Research and Hasselt University in Belgium as well as the Max Delbrück Center in Germany, is now reporting in *Cell Metabolism* that salt can disrupt key immune regulators called regulatory T cells by impairing their energy metabolism. The findings may provide new avenues for exploring the development of autoimmune and cardiovascular diseases.

A few years ago, research by teams led by Professor Dominik Müller at the Max Delbrück Center for Molecular Medicine and the Experimental and Clinical Research Center, a joint institution of Charité—Universitätsmedizin Berlin and Max Delbrück Center (ECRC) in Berlin, Germany and Professor Markus Kleinewietfeld at the VIB Center for Inflammation Research and Hasselt University in Belgium, together with colleagues, revealed that too much salt in our diet can negatively affect the metabolism and energy balance in certain types of innate immune cells called monocytes and macrophages and stop them from working properly.

The researchers further showed that salt triggers malfunctions in the mitochondria, the power plants of our cells. Inspired by these findings, the research groups wondered whether excessive salt intake might also create a similar problem in adaptive immune cells like regulatory T cells.



Credit: *Cell Metabolism* (2023). DOI: 10.1016/j.cmet.2023.01.009

Important immune regulators

Regulatory T cells, also known as Tregs, are an essential part of the adaptive immune system. They are responsible for maintaining the

balance between normal function and unwanted excessive inflammation. Tregs are sometimes referred to as the "immune police" because they keep bad guys like autoreactive immune cells at bay and ensure that immune responses happen in a controlled way without harming the host organism.

Scientists believe that the deregulation of Tregs is linked to the development of autoimmune diseases like multiple sclerosis. Recent research has identified problems in mitochondrial function of Tregs from patients with autoimmunity, yet the contributing factors remain elusive.

"Considering our previous findings of salt affecting mitochondrial function of monocytes and macrophages as well as the new observations on mitochondria in Tregs from autoimmune patients, we were wondering if sodium might elicit similar issues in Tregs of healthy volunteers," says Müller, who co-heads the Hypertension-Mediated End-Organ Damage Lab at the Max Delbrück Center and the ECRC.

Previous research has also shown that excess salt could impact Treg function by inducing an autoimmune-like phenotype. In other words, too much salt makes the Treg cells look like those involved in autoimmune conditions. However, exactly how sodium impairs Treg function had not yet been uncovered.

Salt interferes with mitochondrial function of Tregs

The new international study led by Kleinewietfeld and Müller and first-authored by Dr. Beatriz Côrte-Real and Dr. Ibrahim Hamad—both of whom work at the VIB Center for Inflammation Research and Hasselt University in Belgium—has now discovered that sodium disrupts Treg function by altering cellular metabolism through interference with mitochondrial energy generation. This mitochondrial problem seems to

be the initial step in how salt modifies Treg function, leading to changes in gene expression that showed similarities to those of dysfunctional Tregs in autoimmune conditions.

Even a short-term disruption of mitochondrial function had long-lasting consequences for the fitness and immune-regulating capacity of Tregs in various experimental models. The new findings suggest that sodium may be a factor that could contribute to Treg dysfunction, potentially playing a role in different diseases, although this must be confirmed in further studies.

"The better understanding of factors and underlying molecular mechanisms contributing to Treg dysfunction in autoimmunity is an important question in the field. Since Tregs also play a role in diseases such as cancer or cardiovascular disease, the further exploration of such sodium-elicited effects may offer novel strategies for altering Treg function in different types of diseases," says Kleinewietfeld, who heads the VIB Laboratory for Translational Immunomodulation. "However, future studies are needed to understand the molecular mechanisms in more detail and to clarify their potential relationship to disease."

More information: Beatriz F. Côrte-Real et al, Sodium perturbs mitochondrial respiration and induces dysfunctional Tregs, *Cell Metabolism* (2023). DOI: 10.1016/j.cmet.2023.01.009

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