HHS Public Access

Author manuscript

Nature. Author manuscript; available in PMC 2024 September 20.

Published in final edited form as:

Nature. 2024 January ; 625(7993): 35–36. doi:10.1038/d41586-023-03972-w.

Muscle immune cells protect mitochondrial organelles during exercise

Gerald Coulis[1,2,3], **S. Armando Villalta**[1,2,3,*]

[1]Department of Physiology and Biophysics, University of California, Irvine, CA, USA

[2]Muscle Biology and Disease Researcher Center, University of California, Irvine, CA, USA

[3]Institute for Immunology, University of California, Irvine, CA, USA

Standfirst:

A suppressive type of immune cell called a regulatory T cell has a key role in helping muscles to adapt to exercise — guarding muscle mitochondrial organelles against damage mediated by proinflammatory factors generated during physical activity.

Although the health benefits of exercise are associated with immune-system activation, dysregulation of immunity with overtraining is often linked to detrimental effects on human health and exercise performance[1]. However, the immunological factors that regulate beneficial and damaging inflammation during exercise are not fully understood. Writing in Science Immunology, Langston et al.[2] report a previously unknown role for immune cells called regulatory T (Treg) cells in exercise adaptation and demonstrate that Treg cells dampen inflammation to protect mitochondrial organelles from destructive proinflammatory molecules called cytokines.

Treg cells are a specialized subset of immune cells, called T cells, that suppress other immune cells to dampen inflammation and autoimmune targeting of the body's own proteins (self-antigens). If Treg cells are absent or have functional defects, this can cause the catastrophic failure of immune regulation and death owing to the immunological attack of the host's own organs. Treg cells are already known[3] to orchestrate muscle repair through a protein called amphiregulin that stimulates the function of muscle stem cells. Adding to the list of complex physiological functions carried out by these cells, Langston and colleagues now show that exercise increases the number of Treg cells in skeletal muscle to curb inflammation and promote metabolic and functional adaptation.

The authors provide compelling evidence that Treg cells inhibit immune cells that produce a proinflammatory cytokine called interferon-γ (IFN-γ). Langston et al. studied resting (sedentary) and exercising mice that were genetically modified to enable the specific deletion of Treg cells. Using this system, the authors demonstrate that various immune cell types in exercised muscle that produce IFN-γ increased in number in the absence of Treg cells (Fig. 1). The rise in the expression of IFN-γ in these Treg-depleted mice, compared

*Corresponding author: villalts@uci.edu.

with that in animals with Treg cells, stimulated IFN-γ-mediated signaling pathways over metabolic and blood-vessel-forming pathways that are normally induced by exercise. This heightened IFN-γ signaling led to mitochondrial defects, including swelling, impaired structural integrity and the loss of components required for energy production (electron-transport-chain complexes).

The central role of IFN-γ in these effects was demonstrated through antibody-mediated neutralization of IFN-γ, which improved exercise performance (such as being able to spend a longer time running) and boosted mitochondrial function in Treg-depleted mice. Furthermore, the direct effect of IFN-γ signalling on muscle was demonstrated using mice specifically lacking the IFN-γ receptor (IFNγR1) in muscle. IFNγR1-deficient mice had improved exercise performance and increased expression of electron-transport-chain complexes compared with mice with the receptor.

In addition to using engineered mice, the authors also used antibodies that target the protein CD25 to deplete Treg cells. Although this approach efficiently depleted Treg cells that express CD25, an increase in Treg cells that lack CD25 — likely to be compensatory — resulted in no difference in the overall number of Treg cells compared with that of the control mice. This observation raises questions about the function and fate of Treg cells that lack CD25. The authors' findings suggest that such Treg cells do not have the functional capacity to promote adaptation to exercise in muscle. An alternative interpretation is that Treg cells lacking CD25 are functional, but deficits in muscle adaptation to exercise as a result of CD25-specific antibody treatment might be attributed to the depletion of a different cell population that expresses CD25. A type of immune cell called a group 2 innate lymphoid cell (ILC2) is a potential candidate.

ILC2s are immune cells that lack receptors that recognize protein fragments called antigens, which are needed for the recognition of specific proteins by the immune system. These immune cells are activated by proteins called alarmins, which are released from stressed tissues or dying cells and provide an 'alarm' for the immune system to initiate tissue repair4. Hallmarks of ILC2s are high expression of CD25 and type 2 cytokines, which include the protein IL-13. ILC2s are the main source of IL-13 in healthy and diseased skeletal muscle5. During endurance training, IL-13 promotes metabolic reprogramming to drive adaptation to exercise in mice — a conditioning response that is lost in IL-13-deficient mice[6]. Collectively, Langston and colleagues' work and previous research6 support the model of a coordinated response by Treg cells and ILC2s that induces metabolic changes in exercised muscle, which in turn drives muscle adaptation to meet the increased energy demands required during long-term exercise training.

Several intriguing questions arise from Langston and colleagues' study. Treg cells were depleted throughout the body (systemically), raising the question of whether Treg-mediated adaptations to exercise take place locally in the muscle or through suppression of systemic inflammation. This could be tested in mice by using a drug treatment to confine all T cells, including Treg cells, to a tissue called the lymph node and then transferring genetically modified Treg cells that can reach the muscle in these animals.

The speed of recruitment of Treg cells to muscle after exercise has ended was unexpectedly faster than that reported for toxin-induced, acute injury of muscle, suggesting that the proteins responsible for recruiting Treg cells are regulated differently for exercise and acute injury. Studies that define the muscle Treg-derived factors that are responsible for regulating the complex physiological responses to exercise will lead to the engineering of Treg cells that lack these factors as a way to address some of these questions.

Langston and colleagues' findings have provided an exciting opportunity for scientists to advance their understanding of the complexity of Treg cells in human health, especially in the context of active lifestyles. Not only do the researchers' results have important implications for immunoregulation in exercise, they also suggest that a combination of exercise with standard therapies (such as immunomodulatory steroids) could be used to treat autoimmune and chronic inflammatory conditions[7,8].

References:

1. da Rocha AL et al. Cytokine 119, 57–61 (2019). [PubMed: 30884427]
2. Langston PK et al. Sci. Immunol 8, eadi5377 (2023). [PubMed: 37922340]
3. Burzyn D et al. Cell 155, 1282–1295 (2013). [PubMed: 24315098]
4. Messing M, Jan-Abu SC & McNagny K Int. J. Mol. Sci.21, 1350 (2020). [PubMed: 32079296]
5. Kastenschmidt JM et al. Cell Rep. 35, 108997 (2021). [PubMed: 33852849]
6. Knudsen NH et al. Science 368, eaat3987 (2020). [PubMed: 32355002]
7. Dos Santos AM, Misse RG, Borges IBP, Perandini LAB & Shinjo SK Curr. Opin. Rheumatol. 33, 563–569 (2021). [PubMed: 34456254]
8. Martin SJ & Schneider R Front. Neurol. 14, 1190208 (2023). [PubMed: 37885474]

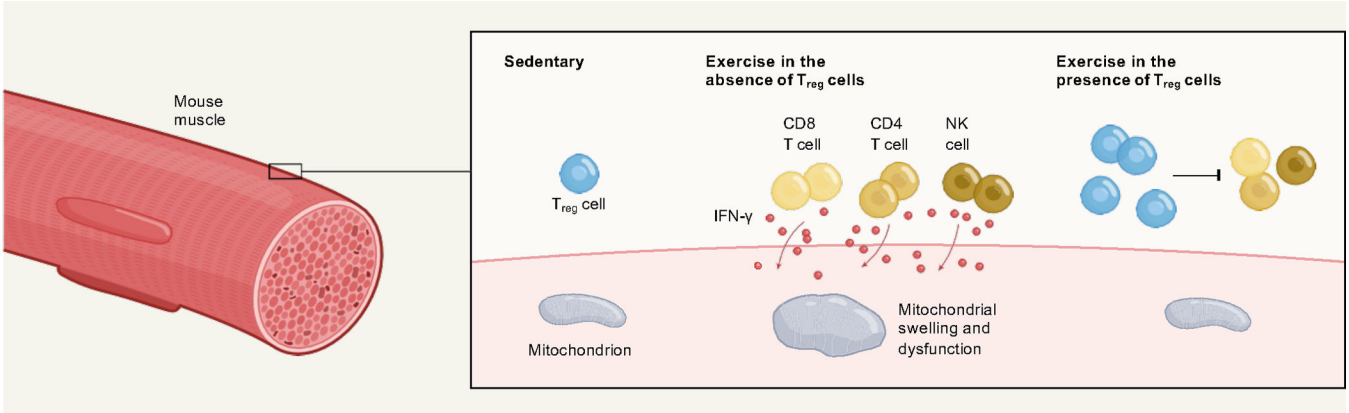

Figure 1 |. A protective immune-cell response during exercise.

Langston *et al.*[2] report data from mice which reveal that immune cells called regulatory T (T_{reg}) cells can protect mitochondrial organelles from damage during exercise. Treg cells are present in samples of sedentary (resting) muscle. In mice engineered to lack these cells, the authors report, during exercise there is a rise in the number of various immune cells (CD4 T cells, CD8 T cells and natural killer (NK) cells) that release the proinflammatory protein IFN-γ. This IFN-γ damages mitochondria, causing swelling and other alterations that impair organelle function. If Treg cells are present, they suppress the immune cells that release IFN-γ and lower the numbers of these cells, thereby protecting mitochondria from damage.