maintain the silicon–carbon stoichiometry and limit growth to the buffer layer only, suppressing the formation of subsequent graphene layers (Fig. 1a). The controlled environment enabled the generation of large flat terraces on the SiC surface, which gave rise to long-range order in the buffer layer.

The bandgap of this layer is about 0.6 electronvolts, around half that of silicon (1.1 eV), close to that of germanium (0.65 eV), and much narrower than that of SiC, which can be more than 3 eV. At room temperature, Zhao and colleagues' buffer layer has a hole mobility (a measure of the performance of a semiconductor) nearly three times that of germanium, and about ten times that of silicon (see go.nature.com/4anxwnk). Layered semiconducting materials, such as those comprising stacked sheets of molybdenum disulfide, have mobilities much lower than that of silicon[15].

Although several challenges remain, both fundamental and technical in nature, work on combining layered materials in 'beyond-silicon' technologies should be intensified. This is particularly true for devices based on semiconductors with wide and ultrawide bandgaps (ranging from around 2 eV to more than 6 eV), for which techniques must be developed to integrate layered materials into hybrid systems on chips. Such research could be key to developing photonics and quantum technologies, and for applications that aid the transition to renewable energy, such as solar cells and power electronics for electric vehicles.

However, when Zhao *et al*. incorporated their buffer layer into a transistor structure, they found that its mobility was 200 times less than it was when isolated. The authors attribute this drop to the fact that the dielectric material used for the transistor gate was not optimized. Determining whether a better dielectric could improve mobility is the first of many challenges ahead. Others include obtaining consistent control over the type and amount of charge induced in the buffer layer, as well as regulating how this layer interacts with other nearby materials in an integrated structure, such as a transistor.

Zhao and colleagues' material is not intended to replace silicon-based electronics, but it could be promising for fabricating logic gates on SiC. Substrates made from SiC are not directly compatible with silicon technologies, but they are increasingly being used in power electronics and are attracting interest for spacecraft electronics and micro-electromechanical systems[16], as well as biomedical devices. This is thanks to the material's wide bandgap and its ability to withstand harsh conditions, such as high temperatures and pressures, radiation and corrosive environments, all of which compromise silicon's performance[17].

A key advantage of Zhao and co-workers' approach is that it naturally pairs SiC with a material that has a narrow bandgap (the graphene buffer layer). The resulting hybrid structure could be used, for example, to integrate devices with different functions into the same SiC chip[18] (Fig. 1b). This would enable improved efficiency for systems that combine sensing with computing logic components. These could benefit renewable-energy generation, which can experience irregular input owing to changing weather conditions.

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Physiology

Muscle immune cells alleviate exercise woes

Gerald Coulis & S. Armando Villalta

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 (T_{reg}) cells in exercise adaptation and demonstrate that T_{reg} cells dampen inflammation to protect mitochondrial organelles from destructive proinflammatory molecules called cytokines.

T_{reg} 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 T_{reg} 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. T_{reg} 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 T_{reg} cells in skeletal muscle to curb inflammation and promote metabolic and functional adaptation.

The authors provide compelling evidence that T_{reg} 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 T_{reg} 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 T_{reg} cells (Fig. 1). The rise in the expression of IFN-γ in these T_{reg}-depleted mice, compared with that in animals with T_{reg} cells, stimulated IFN-γ-mediated signalling pathways over metabolic and blood-vessel-forming

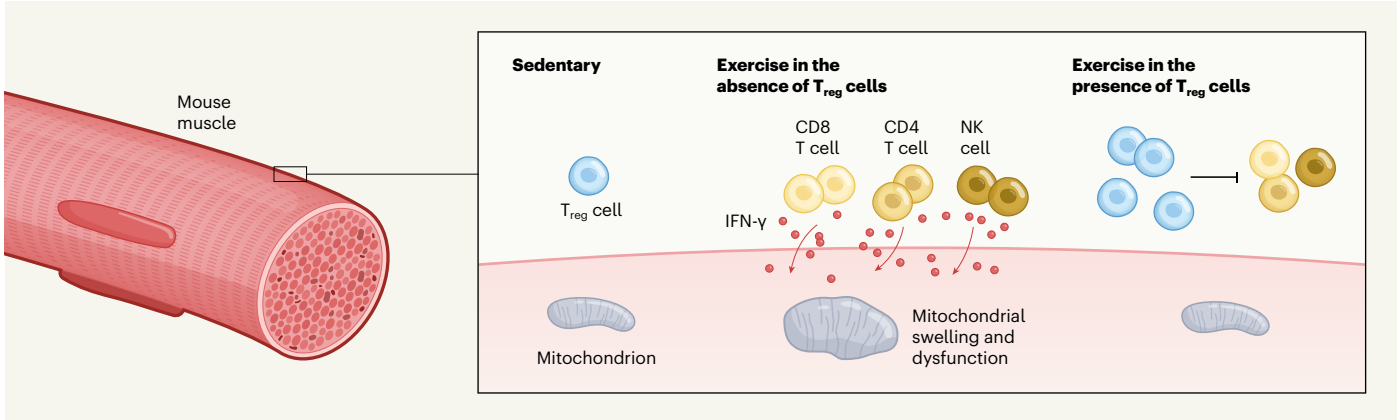

Figure 1 | A protective immune-cell response during exercise. Langston *et al.*[2] report data from mice which reveal that immune cells called regulatory T (T_{reg}) cells can protect mitochondrial organelles from damage during exercise. Treg cells are present in samples of sedentary (resting) muscle. 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.

pathways that are normally induced by exercise. This heightened IFN-γ signalling 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 T_{reg}-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 T_{reg} cells. Although this approach efficiently depleted T_{reg} cells that express CD25, an increase in T_{reg} cells that lack CD25 — likely to be compensatory — resulted in no difference in the overall number of T_{reg} cells compared with that of the control mice. This observation raises questions about the function and fate of T_{reg} cells that lack CD25. The authors' findings suggest that such T_{reg} cells do not have the functional capacity to promote adaptation to exercise in muscle. An alternative interpretation is that T_{reg} 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 repair[4]. 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 muscle[5]. 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 research[6] support the model of a coordinated response by T_{reg} 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.

> **"The researchers' results have important implications for immunoregulation in exercise."**

Several intriguing questions arise from Langston and colleagues' study. T_{reg} cells were depleted throughout the body (systemically), raising the question of whether T_{reg}-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 T_{reg} cells, to a tissue called the lymph node and then transferring genetically modified T_{reg} cells that can reach the muscle in these animals.

The speed of recruitment of T_{reg} 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 T_{reg} cells are regulated differently for exercise and acute injury. Studies that define the muscle T_{reg}-derived factors that are responsible for regulating the complex physiological responses to exercise will lead to the engineering of T_{reg} 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 T_{reg} 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].

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