Defend or reproduce? Muscle-derived glutamate determines an immune/reproductive energetic tradeoff

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There are dramatic disparities in infection susceptibility within populations. In this issue of *Cell Metabolism*, Zhao and Karpac uncover a muscle-adipose-gut axis in *Drosophila* that explains variability in pathogen susceptibility. The degree of intramuscular NF-kB activation accounts for differences in circulating glutamate, which enhances resistance at the expense of reproduction.

Nutrient handling and protection from environmental challenges are ancestral needs shared by most life forms. To ensure survival, organisms including humans rely on deeply conserved signaling pathways that not only sense nutritional and immune challenges, but also ensure coordination of immune and metabolic responses. Such pathways are not hardwired: self-preservation, immunity and reproduction are all energetically costly processes so, when faced with external choices, animals have to make tough choices (Hotamisligil, 2017). They may choose to extend their lifespan at the expense of reproductive capacity, or they may opt to put their offspring at risk in favor of boosting their immunity. Where and how are these decisions made? This is the question Zhao and Karpac set out to address (Zhao and Karpac, 2021).

Zhao and Karpac investigated inter-individual differences in susceptibility to bacterial infection in *Drosophila* flies, which allow high-throughput interrogation of the relevant pathways – both descriptively (in large numbers of flies) and functionally (by genetically interfering with candidate genes/pathways with spatiotemporal resolution). Using an NfκB-dependent fluorescent reporter in live flies, they observed that flies infected with the entomopathogen *Pseudomonas entomophila* systemically – but diferentially – activated the NfκB innate immune response; intriguingly, flies with a milder NF-kB activation response displayed better infection survival, due to a striking mobilisation of lipids from the fly's adipose tissue-like fat body. These lipids may sustain the energetically costly immune defense. In particular, they increase defecation and, consequently, excretion of *Pseudomonas enterophila* from the gut.

The authors then delved deeper into the nature and significance of the inter-individual variation in innate immune responses, revealing a somewhat unexpected tissue source: the indirect flight muscles (the highest oxygen-consuming tissue in insects). Through a series of cell type-specific genetic experiments, the authors demonstrated that, whilst an attenuated NF-kB activation response specifically in these muscles drives adipose lipid mobilisation and infection survival, it also reduces the fecundity of female flies post-infection. By contrast, flies with high intramuscular innate immune signaling (which fail to mobilise their lipids and, consequently, suffer the consequences of pathogen infection) are more fertile. Hence, in female flies, infection resistance comes at the cost of reduced fecundity, underscoring an energetic tradeoff between immunity and reproduction (Schwenke et al., 2016).

How do muscles sense infection and trigger this systemic response? Through extensive detective work involving sequential iterations of transcriptomics, tissue-specific genetic targeting and protein and metabolite profiling, Zhao and Karpac uncovered the nature of this muscle-adipose-gut axis.

They first observed that attenuated intramuscular NfκB signaling is associated with enhanced mitochondrial function. Genetic experiments and life-history events that shift muscle mitochondrial dynamics both revealed a causal role for enhanced intramuscular mitochondrial function in mediating infection-induced energy substrate reallocation and, ultimately, survival. The authors suggest that life history events that alter mitochondrial dynamics may account for the phenotypic variation in host-pathogen response within a population. This antagonism between innate immune signaling and mitochondrial function also resonates with the increasing recognized links between inflammation, mitochondrial dysfunction and obesity (Hotamisligil, 2017).

Amongst the mitochondrial metabolism genes upregulated by intra-muscular attenuation of NfκB signaling, Zhao and Karpac revealed a key role for Glutamate dehydrogenase (Gdh): a deeply conserved enzyme found in all living organisms. Infection-induced intramuscular expression of Gdh elevated levels of circulating glutamate, imported into adipose tissue via the dietary and metabolic glutamate transporter (dmGlut). Glutamate import into adipose tissue adjusts vitamin metabolism (mediated by the sodium-dependent multivitamin transporter *svmt*), ultimately leading to enhanced lipid mobilisation and intestinal defecation response.

This work provides a striking example of how immunomodulation of organelle plasticity within a specific organ (namely, muscle mitochondria) can have an acute effect on infection survival through mobilisation of energy stores in another organ (adipose tissue). Muscles are a major source of circulating metabolites released mainly during contraction but also in resting state. Changes in the availability of these muscle-derived metabolites can have indirect effects on inter-organ signaling. For instance, muscle exercise decreases circulating levels of kynurenine (a tryptophan metabolite produced under stress and in inflammatory conditions), enhancing resilience to stress-induced depression (Agudelo et al., 2014). Additionally, muscle-derived metabolites such as amino acids can be “instructive” and promote secretion of hormones or activate amino acid-sensitive pathways such as mTOR (Rai and Demontis, 2016). The work of Zhao and Karpac extends the roles of muscle-derived metabolites to immune-metabolic surveillance.

The finding of a systemic role for glutamate in mediating this metabolic communication across organs is somewhat unexpected given its major roles as a neurotransmitter. It will be interesting to explore how immune and neuronal roles are segregated spatially, temporally and/or chemically: do cells such as gut muscles distinguish between “immune glutamate” and “neuronal glutamate”? The systemic roles of glutamate in immunity are also reminiscent of those of GABA: another neurotransmitter taken up by blood progenitor cells, where it plays both signaling and metabolic roles to maintain blood progenitors and elevate immune potential (Madhwal et al., 2020; Shim et al., 2013). Together with another recent example (Hudry et al., 2019), these studies illustrate how sophisticated genetic tools in *Drosophila* can be leveraged to discover novel instructive roles of metabolites in inter-organ communication.

As with most novel discoveries, many other questions remain: how are immune, nutritional and metabolic signals sensed and integrated by muscle? What are the mechanisms mediating the memory of life history events? Given the deep conservation of key immune-metabolic signaling pathways, their investigation in *Drosophila* should continue to provide valuable insights into the links between metabolic dysregulation, inflammation and disease in humans.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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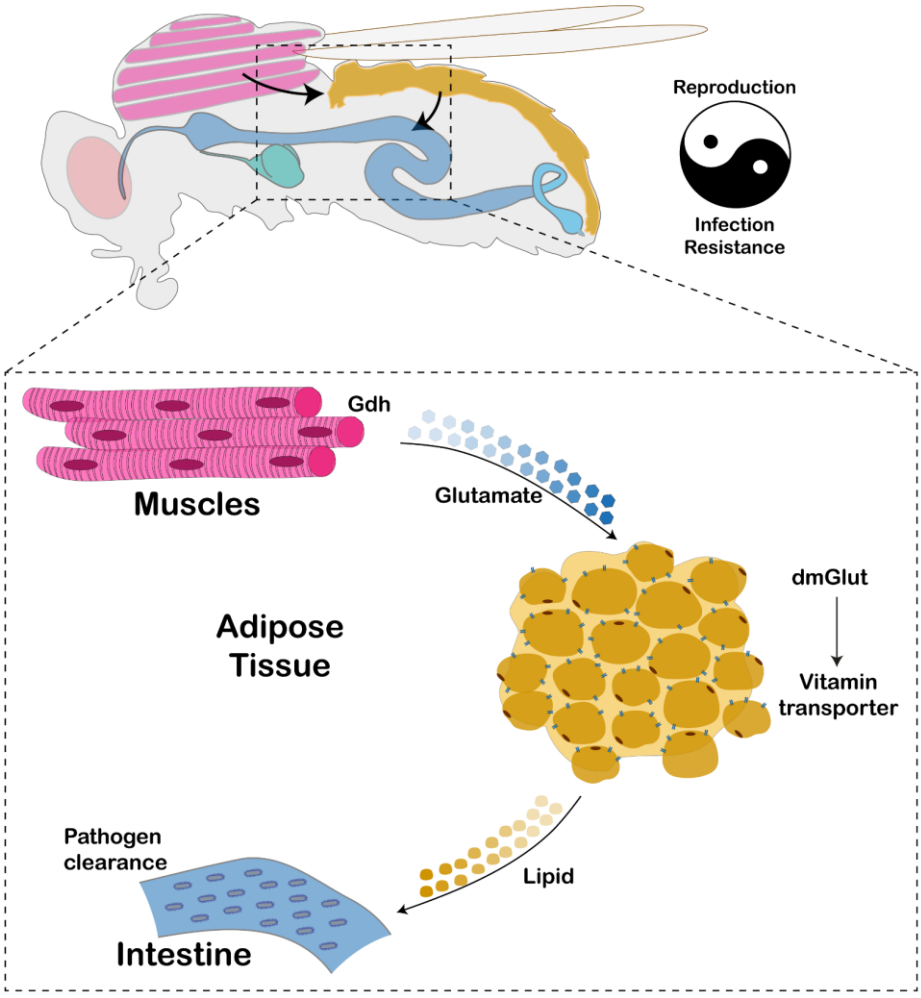

Figure 1. Muscle-derived glutamate initiates tripartite communication between muscle, adipose tissue and the intestine
Glutamate secreted by thoracic muscles acts on the adipose tissue to promote vitamin-dependent lipid mobilization. This, in turn, increases defecation and bacterial clearance in the intestine. Enhanced lipid mobilisation is associated with reduced reproductive capacity, pointing to an energetic trade-off between reproduction and infection resistance.