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Previews

A FAsT contribution: Adipocytes rewire their metabolism to acquire immune functions

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Adipose tissue has been linked to inflammation and various physiological processes. In this issue of *Cell Metabolism*, Caputa et al. describe that perinodal adipocytes adapt their metabolism to actively participate in an immune response against intracellular *Listeria monocytogenes*.

Adipose tissues (ATs) control physiological processes, including metabolic, endocrine, and immunological responses. Two types of ATs with distinct functions have been characterized: white and brown adipose tissues (WAT and BAT), which function as an energy depot or regulate adaptive thermogenesis, respectively. WAT maintains the body's energy balance by storing excessive nutrients as triglycerides and by releasing them as fatty acids (FAs) to supply energy under starvation. It also mitigates mechanical impact to protect internal organs and serves as a niche for the immune cells (Zwick et al., 2018). Immune cell-mediated inflammation in adipose tissues has been implicated as a major pathological event in infections, cancer, and metabolic syndromes, and has a significant impact on clinical outcomes (Baazim et al., 2021; Trim and Lynch, 2021).

Immune cells are found in stromal vascular fraction (SVF) of adipose tissues, influencing the inflammatory environment in the local tissue. Healthy AT homeostasis is maintained by anti-inflammatory immune cells, such as regulatory T cells (Tregs), anti-inflammatory macrophages, type 2 innate lymphoid cells (ILC2s), invariant natural killer T (iNKT) cells, natural killer (NK) cells, and eosinophils. By contrast, the state of metabolic imbalance, exemplified by obesity, exhibits predominant infiltration by pro-inflammatory immune cell populations, including inflammatory macrophages; $CD8^+$ T cells; type 1 helper $CD4^+$ T cells, associated with decreased abundance of Tregs; iNKT cells; and ILC2 eosinophils (Trim and Lynch, 2021). The immunological profile of the local adipose environment is therefore a critical determinant of metabolic function and the physiological states of ATs.

In this issue of *Cell Metabolism*, Caputa et al. (2022) uncovered the role of perinodal ATs (PATs) in actively exerting an immune response against intracellular bacteria, *Listeria monocytogenes* (*Lm*). PATs are specialized architectures that surround lymph nodes and have a distinct lipid content enriched with polyunsaturated FAs, and are highly responsive to inflammatory cytokines IL-6 and TNF (Knight, 2008).

The authors found that acute *Lm* infections in footpad led to a rapid increase in PAT weight, which is associated with enhanced immune cell infiltrates. This was followed by bacterial clearance in the PAT prior to infected footpad and popliteal lymph nodes, indicating PAT is the first site to clear these infections. Unexpectedly, the bacterial clearance in PAT was independent of $CD8^+$ T cells that play an important role in protection against *Lm*. Instead, the bactericidal function of adipocytes was crucial.

Upon *Lm* infection, adipocytes in PAT underwent transcriptional reprograming leading to downregulation of lipid metabolism. In parallel, genes linked to an active immune response, including *Ifngr1* and *Nod1*, were upregulated. Single-cell RNA sequencing and immune profiling revealed NK and iNKT cells as a major source of IFN-γ in infected PAT. The intracellular immune sensor Nod1, which is triggered by bacterial ligands, was upregulated in adipocytes by IFN-γ (Figure 1).

Both signals, NK/NKT cell-derived IFN-γ and Nod1 triggered by live *Lm*, synergized to activate iNOS expression and NO production in adipocytes. NO production was critical to rewire adipocyte metabolism. Co-administration of *Lm* and IFN-γ to PATs led to a metabolic shift from oxidative phosphorylation (OXPHOS) to glycolysis in an NO-dependent manner (Figure 1). Furthermore, the metabolism of adipocytes was rewired to support NO synthesis through the increased activity of the urea cycle and the aspartate-argininosuccinate shunt, which was fueled by increased arginine uptake. NO produced by PATs was then identified as critical for bacterial clearance in this tissue (Figure 1).

This study provides comprehensive evidence that adipocytes actively participate in the immune response against pathogens, and that the integration of bacterial, immunological, and metabolic signals is critical for adipocyte bactericidal function.

The immunological ability of PATs to actively combat infections implies that specific AT-targeted therapies may be able to modulate the topical infection and inflammation. Treatment of PAT may be beneficial for early pathogen clearance and targeting it might improve therapies. Evaluation of treatment strategies aimed at such therapeutic benefits will require further investigations. The findings reported in this study stimulate a number of research

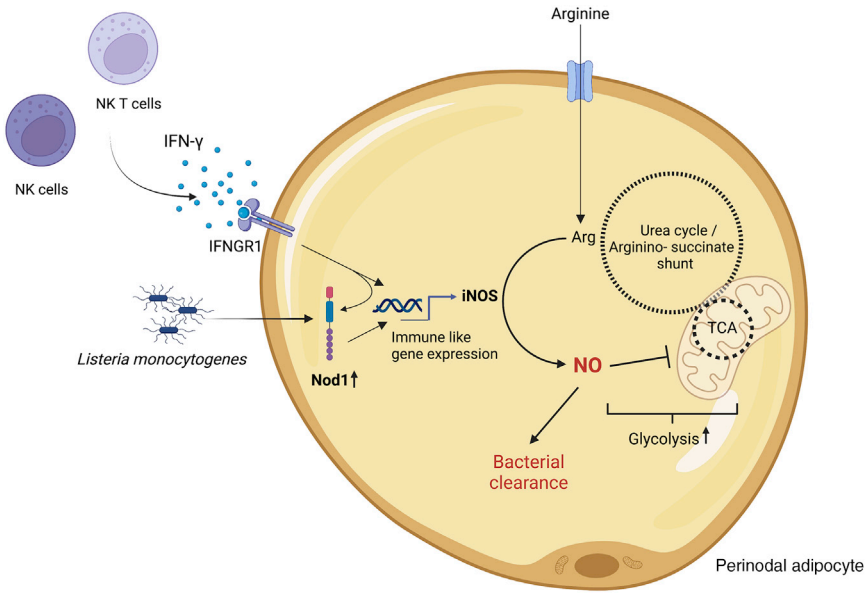

Figure 1. Perinodal adipocytes exert a bactericidal immune response
Perinodal adipose tissue (PAT) surrounding the draining lymph nodes of an infected tissue rapidly clears *Listeria monocytogenes* (*Lm*). Upon *Lm* infections, IFN-γ produced by natural killer (NK) and invariant NKT (iNKT) cells enhances NOD1 expression in PATs. This leads to enhanced bacterial sensing by PATs and triggers upregulation of inducible nitric oxide synthase (iNOS). iNOS produces NO, a potent bactericidal molecule. The NO in PAT induced a metabolic reprogramming to decrease OXPHOS while promoting the aspartate-argininosuccinate shunt and urea cycle, which is supported by an increased uptake of extracellular arginine. This further accelerates the NO synthesis and bactericidal response in PAT. Created with BioRender.com.

questions. For example, this study specifically examined immunometabolic response by PAT in acute *Lm* infection. Dissecting the immunometabolic features of PAT in different settings like acute and chronic infections by other pathogens would widen the scope and clarify whether PAT can elicit broader immunological host-protecting responses.

In particular, the long lifespan (Spalding et al., 2008) and the ample energy storage of adipocytes may provide favorable environments for some pathogens. Indeed, ATs are infected by various bacterial, viral, and parasitic species including *Trypanosoma cruzi* (González et al., 2019), *Mycobacterium canettii* (Bouzid et al., 2017), *Coxiella burnetii* (Bechah et al., 2014), HIV (Couturier and Lewis, 2018), and SARS-COV-2 (Reiterer et al., 2021). *T. cruzi* has been reported to be found in adipocytes for more than 300 days after infection (Combs et al., 2005), indicating that some pathogens might escape antibacterial immune responses mediated by adipocytes.

From the immunological perspective, this study describes an essential role of NK and NKT cells to initiate an adipocyte immune response against intracellular bacteria. Adipocyte features to engage interactions with NKT cells through CD1d-dependent cognate lipid presentation might be essential for PAT immune responses, which is consistent with the authors' finding that hexosylceramide is increased in PAT. However, whether NK/NKT-adipocyte crosstalk is universally required for initiation of PAT activation or whether other populations, such as $CD8^+$ T cells, can substitute this role as a source of IFN-γ in chronic infections, remains to be determined. Finally, examining immunometabolic features of human PATs is essential to translate the key findings into clinical applications in this study.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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