ΓΔ17 T CELLS

Got my γδ17 T cells to keep me warm

γδ T cells accumulate with age in adipose tissue and produce the cytokine IL-17, which controls the homeostasis of regulatory T cells and adaptive thermogenesis. Thus, maintenance of core body temperature unexpectedly relies on these adipose tissue–resident γδ17 T cells.

Pedro H. Papotto and Bruno Silva-Santos

While they share many functional properties with their αβ T cell counterparts, γδ T cells typically mount very rapid responses that align with innate (rather than adaptive) immunity. These kinetics are particularly clear for antigen-nonspecific production of the cytokine IL-17 by γδ T cells in response to inflammatory cytokines (IL-23 and IL-1β),

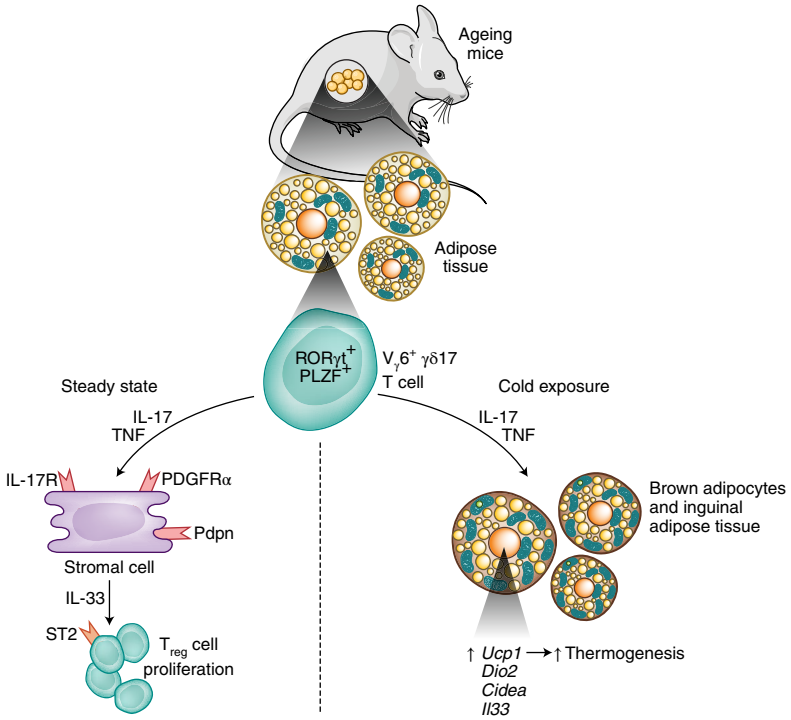

Fig. 1 | Adipose tissue–resident γδ T cells secrete IL-17 and TNF, which control thermogenesis. The cellular and molecular mechanisms that operate in adipose tissue at thermoneutrality (left) or after exposure to cold (right). Adipose tissue–resident γδ17 T cells express $V_\gamma6^+$ T cell antigen receptors and the transcription factors RORγt and PLZF. During aging, adipose tissue γδ17 T cells increase in number and, through the production of IL-17A and TNF, stimulate IL-17R$^+$ stromal cells to secrete IL-33, which underlies the accumulation of ST2$^+$ T_{reg} cells and the maintenance of tissue homeostasis. In contrast, after exposure to cold, IL-17A and TNF act directly on adipocytes to induce a UCP1-dependent thermogenic program. IL-17R, IL-17 receptor; PDGFRα, growth-factor receptor; Pdpn, podoplanin; *Ucl1*, *Dio2*, *Cidea*, *Il33*, genes upregulated after exposure to cold.Credit: Katie Vicari/Springer Nature

which precedes the contribution of the T_H17 subset of helper T cells to multiple disease models[1]. A distinctive characteristic of IL-17-producing γδ T cells (γδ17 T cells) that underlies this phenomenon is their 'developmental pre-programming' in the fetal thymus[1–3]. Interestingly, as they egress from the thymus, γδ17 T cells populate a discrete set of non-lymphoid tissues, such as the peritoneal cavity, lungs, dermis, tongue and uterus, where they are sustained as self-renewing, long-lived cells. In this issue of *Nature Immunology*, Kohlgruber et al. characterize a population of γδ17 T cells that accumulate in the adipose tissue, which unexpectedly controls adaptive thermogenesis and thus the maintenance of core body temperature[4].

The adipose tissue harbors myriad immune cell populations with different functions. Among these, regulatory T cells (T_{reg} cells) have been critically linked to obesity and insulin resistance[5,6]. Adipose tissue T_{reg} cells have been shown to be maintained in young adult mice by a resident population of natural killer T cells[7]. However, whereas the number of natural killer T cells in adipose tissue decreases with age[4], the number of T_{reg} cells continuously increases[5–7], which suggests that another cellular mechanism might underlie T_{reg} cell homeostasis in aged mice. Kohlgruber et al. now find that the number of γδ T cells increases concurrently with that of T_{reg} cells in aging mice, with the adipose tissue of mice older than 20 weeks of age showing considerable enrichment for these cells[4]. Of note, γδ T cells also make up a substantial fraction of lymphocytes in human adipose tissue[4]. Further characterization of adipose tissue–resident γδ T cells in mice has shown that they express the transcription factor PLZF, the key developmental regulator of innate-like lymphocytes, and bear $V_\gamma6^+$ T cell antigen receptors (TCRs), characteristic of fetal thymus–derived γδ T cells[1]. Notably, mice that lack all γδ T cells, or, more specifically, $V_\gamma6^+$PLZF$^+$ γδ T cells, are impaired in their age-dependent accumulation of T_{reg} cells[4]. Adipose tissue γδ T cells also express the type 17 master transcription factor RORγt while lacking expression of CD27, a member of the tumor-necrosis factor (TNF) receptor superfamily, both characteristics of γδ17 T cells[2]. Consistent with that, when stimulated in vitro with IL-1β and IL-23, they produce abundant IL-17A, as well as TNF. Notably, these cytokines stimulate stromal cells expressing the IL-17 receptor to produce IL-33 in vivo and thus provide a molecular link to T_{reg} cells expressing the IL-33 receptor ST2 in the adipose tissue[4]. Of note, IL-17A deficiency results in profound depletion of adipose tissue T_{reg} cells. Moreover, primary culture of human preadipocytes in the presence of IL-17A and TNF also induces substantial production of IL-33.

Since IL-33 is a potent stimulus of thermogenesis[8], Kohlgruber et al. investigate the effect of IL-17A and TNF on this process and find that the two cytokines synergistically induce a thermogenic program that is dependent on the uncoupling protein UCP1 and is required for lipolysis induction[4]. Unexpectedly, IL-17A and TNF act directly on stromal cells and differentiated adipocytes independently of IL-33. Consequently, mice that lack either γδ T cells or IL-17A show substantial defects in the maintenance of body temperature (i.e., they display lower body temperatures and higher breathing activity than that of their wild-type counterparts) both at thermoneutrality and especially after cold challenge (Fig. 1).

Until now, γδ17 T cells have been associated mostly with inflammatory responses, both in protective immunity to fungal and bacterial infections and in pathogenic autoinflammation[1]. On the other hand, γδ17 T cells, together with type 3 innate lymphoid cells, constitute major sources of IL-17A in various peripheral tissues at steady state and might thus contribute decisively to their normal physiology. In fact, IL-17A, provided mainly by γδ17 T cells, has been shown to inhibit adipogenesis and regulate glucose metabolism and thus control diet-induced obesity[9]. Together with the current study[4], these results establish the importance of γδ17 T cells in adipose tissue. Elsewhere, γδ17 T cells have been linked to bone regeneration through IL-17A-mediated stimulation of the proliferation and osteoblastic differentiation of mesenchymal progenitor cells[10]. However, the physiological roles of γδ17 T cells in other tissues in which they reside, such as the uterus or the lungs, remain to be clarified.

We postulate that γδ17 T cells might shape tissue architecture starting at early life and actively participate in key physiological processes throughout life. When investigating this possibility, it will be important to consider some

unresolved fundamental issues in γδ17 T cell biology, such as the extent to which γδ17 T cell responses rely on thymically pre-programmed effector cells ('thymic γδ17 T cells') or inflammation-induced 'peripheral γδ17 T cells'. Thus, in addition to long-standing thymic γδ17 T cells[1–3], peripheral γδ17 T cells can be generated from uncommitted precursor cells in secondary lymphoid organs exposed to inflammatory IL-23 and IL-1β signals[11,12]. That finding has been observed in mouse models of the critical autoinflammatory diseases multiple sclerosis[11] and psoriasis[12]. Interestingly, both reports demonstrated the potential of $V_\gamma4^+$ γδ T cells to differentiate into IL-17A-producing cells in the periphery, whereas $V_\gamma6^+$ γδ17 T cells are expected to develop exclusively in the fetal thymus[1]. Taking into account that the current study by Kohlgruber et al. demonstrates that adipose tissue γδ17 T cells are mostly $V_\gamma6^+$ cells[4], we are tempted to speculate a dichotomy between tissue-resident 'thymic' $V_\gamma6^+$ γδ17 T cells that support physiological functions and tissue regeneration and recruited 'peripheral' $V_\gamma4^+$ γδ17 T cells that participate in autoinflammatory processes, although some exceptions to this working model have been reported[1]. Notably, when it comes to immunity to infectious microorganisms, protective γδ17 T cell responses seemingly rely on both tissue-resident $V_\gamma6^+$ cells and lymphoid $V_\gamma4^+$ cells[1].

In the case of tissue-resident $V_\gamma6^+$ γδ17 T cells, it will be relevant to clarify which signals are responsible for their local activation. As inflammatory cytokines (IL-23 and IL-1β) probably do not have a substantial role at steady state, other molecular cues must account for the 'basal' production of IL-17A. TCR signals remain logical but highly controversial candidates[1]. In any case, it is interesting to question the evolutionary meaning of having $V_\gamma6^+$ γδ 17 T cells, the product of intricate T cell antigen receptor rearrangement coupled with thymic effector 'pre-programming', as key providers of IL-17A in situ, when other innate lymphoid population (type 3 innate lymphoid cells) can also reside in peripheral non-lymphoid tissues and secrete IL-17A. In conclusion, the findings of Kohlgruber et al.[4] heat up long-standing discussions while opening new paths for better understanding of the primordial roles of γδ T cells in their vertebrate hosts. ❐

Pedro H. Papotto and Bruno Silva-Santos*
Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal.
**e-mail: bssantos@medicina.ulisboa.pt*

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Competing interests

The authors declare no competing interests.