Killer ILCs in the Fat

Emilie Narni-Mancinelli1,* and Eric Vivier1,2
1Centre d’Immunologie de Marseille-Luminy, Aix Marseille Université, INSERM, CNRS, 13009 Marseille, France
2Hôpital de la Timone, Assistance Publique-Hôpitaux de Marseille, 13009 Marseille, France
*Correspondence: narni@ciml.univ-mrs.fr
http://dx.doi.org/10.1016/j.immuni.2017.02.004

Innate lymphoid cells (ILCs) residing in adipose tissue participate in the pathogenesis of obesity, but their contribution toward adipose tissue homeostasis in the lean state is unclear. Boulenouar et al. (2017) now report that heterogenous type 1 ILCs in adipose tissues regulate macrophage homeostasis through cytotoxicity.

Adipose tissue (AT) is central to energy storage and for the regulation of nutrition, systemic metabolism, and immunity. Immune cells are numerous in AT, their numbers being surpassed only by adipocytes. In the lean state, AT immune cells include T regulatory (Treg) cells, NKT cells, group 2 innate lymphoid cells (ILC2s), and M2 macrophages; these cell types have distinct roles in the maintenance of AT homeostasis (Yang et al., 2016). Obesity is associated with changes in the numbers, phenotype, and functions of AT immune cells. Numbers of resident Treg cells decrease, while the increased presence of pro-inflammatory cells fosters chronic inflammation and ultimately leads to insulin resistance (Yang et al., 2016). Recently, interferon (IFN)-γ produced by group 1 ILCs has been shown to participate in the pathogenesis of obesity by promoting macrophage differentiation to the inflammatory M1 phenotype (Lee et al., 2016; O’Sullivan et al., 2016; Wensveen et al., 2015). In this issue, Boulenouar et al. (2017) characterize the heterogeneity of type 1 ILCs in adipose tissues of humans and mice in lean and obese conditions. They find that the cytotoxic potential of these ILCs toward adipose tissue macrophages (ATMs) regulates adipose tissue homeostasis and impacts systemic metabolism.

AT-ILC characterization in obesity has been previously reported but no study has addressed their composition in the lean state. Boulenouar et al. (2017) first show that human visceral omental fat and murine epididymal white adipose tissue (WAT) are enriched in group 1 ILCs as compared to other tissues, with group 1 ILCs constituting the most abundant lymphocyte population in AT. Parabiosis experiments revealed that AT group 1 ILCs are tissue-resident cells, with only a minor contribution from the periphery, similarly to the well-defined liver-resident ILC1s. These cells do not constitute a homogeneous population. In the mouse, Ly49− AT1-ILCs could be subdivided into three subsets according to surface expression of CD49a and CD49b: double-negative immature NK cells (CD49a−CD49b−; iNK), a mixed ILC1-like (CD49a+CD49b− and CD49a+CD49b+) population, and mature NK cells (CD49a−CD49b+; mNK) (Figure 1). The proportion of each of these subsets is unique to AT.

Previous studies defined mouse AT type 1 ILCs as c-kit−CD127−Tbet+, showing also that these cells had no history of RORγt expression (Lee et al., 2016; O’Sullivan et al., 2016). While mNK cells and CD49a−CD49b+ mixed ILC1s are uniformly Eomesodermin+ (Eomes) similar to splenic conventional NK cells, 15% and 60% of iNK cells and CD49a+CD49b− ILC1s, respectively, are Eomes−, highlighting a heterogeneous transcriptional programing. Further analysis showed the Tbet dependence of mNK cells and the Tbet independence of iNK cell and mixed ILC1 subsets. Finally, unlike liver ILC1s, AT1-ILCs do not express TRAIL and exhibit low levels of granzyme B. AT1-ILCs, however, are genetically labeled in IFN-γ reporter mice as other group 1 ILCs present in
spleen or liver. Thus, mouse AT1-ILCs present unique features as compared to type 1 ILCs present in other tissues.

Human AT1-ILCs also exhibit a unique phenotype. Whereas blood NK cells are mostly composed of CD56<sup>bright</sup>CD16<sup>−</sup> cells (5%) over CD56<sup>dimm</sup>CD16<sup>+</sup> (95%) cells, there are no CD56<sup>bright</sup> type 1 ILCs in human visceral omental. In addition, 50% of the CD56<sup>dimm</sup> cells are CD16<sup>+</sup>. Human AT is therefore enriched in an unconventional CD56<sup>dimm</sup>CD16<sup>+</sup> ILC1-like population with poor expression of cytotoxic molecules and also contains peripheral-like CD56<sup>dimm</sup>CD16<sup>−</sup> cells (Figure 1).

The number of peripheral NK cells is reduced in obese patients (Lynch et al., 2009). In concordance with these earlier findings, Boulenouar et al. (2017) find that omental AT in obese individuals contains a lower frequency of AT1-ILCs than that of lean counterparts. Interestingly, the numbers of AT1-ILCs increased in individuals who underwent bariatric surgery. Thus, reduced number and/or the impaired cytotoxic function of AT1-ILCs contributes to glucose intolerance in obese mice.

Figure 1. AT1-ILC Subsets in Mice and Humans

The characterization of distinct AT1-ILCs subsets in human and murine AT and the revelation that the cytotoxic function of these cells has a role in AT homeostasis (Boulenouar et al., 2017) raises a number of interesting questions for future investigations. The signals responsible for AT1-ILC activation and regulation in the lean state remain to be defined; it is interesting to speculate that these may be AT-derived metabolites or cytokines. In chronic obesity, AT1-ILCs are decreased in numbers and intrinsically impaired in their killing ability against ATMs. This defect may be partly responsible for the increase in macrophages associated with obesity. Mouse AT1-ILCs are more effective at killing M2 rather than M1 macrophages. This result is puzzling since M2 macrophages are known to display beneficial effects on tissue homeostasis and anti-inflammatory properties. The authors hypothesize that M2 macrophages are indeed very active in lean adipose tissue engulfing and remodeling the AT. M2 macrophage elimination could thus prevent their harmful conversion into pathogenic pro-inflammatory M1-like macrophages. Furthermore, no metabolic disorders have been reported thus far in mice deficient for group 1 ILCs (NKp46<sup>Cre</sup>xROSA26<sup>KO/DTat1</sup> mice) (Deauvieau et al., 2016) or in
RSV Takes Control of Neonatal Breg Cells:
Two Hands on the Wheel

Peter J.M. Openshaw1,*

1Respiratory Sciences, National Heart and Lung Institute, Imperial College London, St Mary’s Campus, Norfolk Place, London W2 1PG, UK
*Correspondence: p.openshaw@imperial.ac.uk
http://dx.doi.org/10.1016/j.immuni.2017.01.011

The viral attachment protein of RSV has many surprising features, especially its mimicry of fractalkine (CX3CL1). Zhivaki et al. (2017) now show that, in addition to using this homology to attach to ciliated cells, it activates human neonatal regulatory B cells, thereby inhibiting immunological responses.

Respiratory syncytial virus (RSV) is a common pathogen that infects the ciliated respiratory epithelium, causing variable disease that ranges from severe infantile bronchiolitis to a mild (or unapparent) common cold. It infects virtually all children by the age of 3 and repeatedly re-infected them throughout life. It has two major surface proteins, one mediating fusion (F) and the other attachment (G). The latter has a structure similar to the chemokine fractalkine (CX3CL1), binding CX3CR1 on the apical surface of ciliated cells in the lung. In a new twist, Zhivaki et al. (2017) now show that RSV G also binds to a novel subset of neonatal regulatory B (nBreg) cells that make the immunosuppressive cytokine interleukin 10 (IL-10), thus inhibiting protective immune responses.

Rather than depending on rapid evolution to escape immune pressure, the success of RSV seems to depend on a partial but specific immunological amnesia (Openshaw et al., 2017). RSV’s attachment protein G has few parallels in the viral kingdom. It is known to inhibit Toll-like receptor (TLR)-induced type I interferon host responses. One of the several interesting properties of RSV G is that vaccinating mice with it can induce enhanced and eosinophilic lung disease during subsequent RSV infection, a phenomenon that requires an intact central conserved domain (Sparer et al., 1998).

When the structure of CX3CL1 was first described in 1997, RSV aficionados immediately appreciated its close resemblance to RSV G. Both G and CX3CL1 have heparin binding domains, and both have membrane bound and soluble forms and both have “mucinoid” proximal regions on extended serine-threonine rich stalk that ends in a cysteine-rich chemokine domain (Melero et al., 2017). News of this remarkable similarity spread quickly in the RSV community and by 2001, Tripp et al. (2001) showed that the attachment protein G does indeed bind to the receptor CX3CR1. RSV exploits this property to infect the respiratory epithelium by binding of G to CX3CR1 on ciliated cells (Jeong et al., 2015; Johnson et al., 2015), although it remains a mystery why CX3CL1 should be present at this site.

CX3CL1 is chemotactic for both lymphocytes and monocytes and is normally made by activated endothelial cells. Its receptor is naturally present on cells with high cytotoxic potential (such as natural killer [NK] cells, cytotoxic T cells, and γδ T cells). Presumably, the soluble form of RSV’s attachment protein recruits