IMMUNOMETABOLISM IN 2018

Organismal immunometabolism: advances in both directions

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Immunometabolism is a relatively new field, first cited on PubMed in 2011. It is also a field that is increasingly 'en vogue', with over 200 PubMed citations so far in 2018. Since its beginning, the field of immunometabolism has been operating on two different planes: one set of investigators works at the organismal level, studying interactions between the immune and metabolic systems; a second set operates at the cellular level, examining metabolic aspects of immunocytes. The focus here is on organismal immunometabolism. One topic related to the control of metabolism by the immune system and, conversely, one concerning metabolic control of the immune system will be highlighted.

It is now well accepted that parallel increases in obesity and cardiometabolic disorders, in particular type 2 diabetes, over the past several decades reflect obesity-induced, chronic, low-grade inflammation of adipose tissue (notably, visceral adipose tissue (VAT)) and eventually systemic inflammation[1]. Macrophages were the first culprits to be identified in this process and were thus the subject of most studies in this area for a decade. But there has been a growing appreciation of the roles of additional members of the innate and adaptive immune systems: mast cells, neutrophils, eosinophils, type 2 innate lymphoid cells (ILC2s), natural killer (NK) cells, $CD4^+$ and $CD8^+$ effector T cells, $FOXP3^+$ regulatory T (T_{reg}) cells, NKT cells and B cells. This long line-up is not really surprising for an inflammatory reaction: some elements function early in the response, others later; some promote the response, others inhibit it.

2018 brought us a more profound understanding of the immunocyte populations that are found in VAT and that regulate local and systemic metabolism. Important new players were identified and their function characterized and integrated with those of interacting cells. Cellular and molecular mechanisms of immune cell specialization within adipose tissue began to be elucidated.

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Kohlgruber et al.[2] noticed that certain fat pads of lean mice, especially epididymal VAT (eVAT), had an enriched population of γδ T cells. These long-dwelling cells were generated perinatally, primarily expressed a $V\gamma6^+$ T cell receptor (TCR) and produced IL-17, characteristics of a γδ T cell population implicated in promoting several autoimmune, inflammatory or antimicrobial responses. In lean mice, VAT-localized γδ T cells accumulated with advancing age, in parallel with T_{reg} cells and in contrast to ILC2s and NKT cells, whose numbers decline with age. The T_{reg} cell increase was muted in mice genetically deficient in γδ T cells, $V\gamma4^+$ and $V\gamma6^+$ T cells or IL-17A. As an underlying mechanism, the investigators proposed that the $V\gamma6^+$ T cell population in VAT produces IL-17, which collaborates with TNF to induce local stromal cells to secrete IL-33, which in turn promotes the accumulation of T_{reg} cells. This scenario is consistent with several previous studies identifying a crucial role for IL-33 produced by stromal cells in nurturing both VAT T_{reg} cells and ILC2s. Unfortunately, the investigators did not report the impact of γδ T cells on local or systemic inflammation or insulin sensitivity, but their proposed functional allies, T_{reg} cells, are known to regulate these processes.

eVAT T_{reg} cells have a transcriptome and TCR repertoire that is distinct from those of T_{reg} cells in lymphoid or other non-lymphoid organs. The unique eVAT T_{reg} cell signature includes transcripts encoding a variety of chemokine receptors, cytokine receptors, transcription factors (TFs) and proteins involved in lipid metabolism, and the signature is largely driven by the TF PPARγ, a member of the steroid receptor family that is considered to be a 'master regulator' of adipocyte differentiation. The crucial questions of where and how VAT T_{reg} cells diversify from other T_{reg} cell populations have been extremely difficult to address because of the rarity and fragility of these cells.

Li et al.[3] side-stepped these issues by generating a TCR-transgenic mouse line carrying the rearranged *Tcra* and *Tcrb* genes from an expanded VAT T_{reg} cell clone. Clonotype-positive cells localized highly preferentially to eVAT in these mice, resulting in an unusually large VAT T_{reg} cell compartment and an improvement in local inflammatory and systemic metabolic tenors. Display of the transgene-encoded TCR and expression of a novel PPARγ-reporter were used to follow the generation and fate of VAT T_{reg} cells. A combination of population-level RNA sequencing (RNA-seq), flow-cytometric, adoptive-transfer and single-cell RNA-seq (scRNA-seq) approaches uncovered the following sequence of events: VAT T_{reg} cells emerge from the thymus in the first week of life, seemingly undifferentiated from other T_{reg} cell populations; they seed lymphoid organs such as the spleen, where they undergo a weak activation event that includes a slight upregulation of PPARγ expression

Key advances

- Vascular adipose tissue (VAT) hosts a population of γδ T cells that promotes regulatory T (T_{reg}) cell accumulation therein.
- The unique phenotype of VAT T_{reg} cells is set in stages, the last stage being within VAT.
- Obesity can promote tumorigenesis by reprogramming the metabolism and dampening the effector functions of natural killer cells.
- Obesity can also promote tumorigenesis by inducing PD-1 expression on T cells, thereby rendering the tumour more susceptible to inhibition by checkpoint blockade.

and sub-maximal induction of about half of the VAT T_{reg} cell signature; consequently, they exit the lymphoid organs, survey parenchymal tissues and are retained in VAT, where the TCR recognizes cognate antigen; and finally, they express the definitive VAT T_{reg} cell transcriptional signature in response to local cues. Open questions remain with regard to the factors that elicit their weak activation in spleen and whether this splenic compartment harbours precursors of just VAT T_{reg} cells or non-lymphoid-tissue T_{reg} cells more generally.

These findings were later augmented in two ways. In one study, assay for transposase-accessible chromatin using sequencing (ATAC-seq), scRNA-seq and a powerful combination of the two technologies were used to dissect the molecular mechanisms behind the diversification of various non-lymphoid-tissue T_{reg} cell populations (including those in VAT) from lymphoid organ T_{reg} cells and from each other[4]. A tissue–T_{reg} cell TF network was constructed and bioinformatically and experimentally validated, permitting the interesting observation that all of the tissue–T_{reg} cell populations relied on the same limited set of TF families to distinguish themselves but that different individual family members dominated in different tissues. In another study, ILC2s, including the ILC2s found in eVAT, were reported to adopt tissue-specific gene expression profiles[5]. However, other than variable cytokine dependencies, the cellular and molecular underpinnings of ILC2 diversification remain largely unexplored.

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Concerning the impact of organismal metabolism on the immune system, it has become increasingly clear that obesity has broad-ranging and long-lasting detrimental effects on immune responsiveness[6]. Not only are there defects in antimicrobial responses both within adipose tissue and systemically, but antitumour responses at a variety of sites are also compromised. The current challenge is to unravel the mechanistic scenarios linking obesity and such immune system laxity.

2018 brought deeper mechanistic insights into how obesity can promote dysregulation of the immune system and thereby compromise antitumour responses in particular. Effects on NK cells were highlighted in one study[7], while influences on effector T cells dominated another[8]. The same changes in effector T cells also seemed to be behind a greater efficacy of checkpoint blockade in patients with obesity[9].

Michelet et al.[7] explored the influence of obesity on NK cells and their ability to rein in the growth of tumours. The investigators observed abundant transcriptional changes in circulating NK cells of both mice and humans. Major upregulated pathways included PPAR signalling and glycerolipid metabolism, while mTOR signalling and NK cell-mediated cytotoxicity were downregulated. Reflecting these alterations, NK cells were metabolically ‘paralysed’, with dampening of both glycolysis and oxidative phosphorylation; they also showed deficiencies in effector functions such as killing and IFNγ production. The metabolic abnormalities were due to PPAR-driven accumulation of lipid droplets, which inhibited mTOR-mediated glycolysis. A second effect of lipid accumulation was that it prevented the trafficking of the cytotoxic machinery to the NK cell–tumour synapse and thus the killing of tumour cells. Obese mice were less effective than their lean counterparts at controlling the growth of injected B16 melanoma cells, which was associated with fewer NK cells and less IFNγ production in the tumours. Hence, the investigators argued that obesity-induced NK cell defects were responsible for the compromised antitumour response in mice and potentially in humans. This may be true, but a broader perspective incorporating potential influences of obesity on other cells of the immune system, notably on $CD8^+$ T cells (which can also express the NK cell marker NK1.1 and produce IFNγ) or on the growth properties of the tumour, itself, would further support their case. Nonetheless, a strength of this study is its rare combination of insights into both organismal and cellular metabolism.

Wang et al.[8] have highlighted a different mechanism responsible for enhanced tumorigenesis promoted by obesity. They found obese mice to have an elevated frequency of T cells expressing the checkpoint molecule, PD-1, compared with non-obese controls, especially as they get older. These cells were dysfunctional, displaying a reduced proliferative capacity and cytokine production. Non-human primates and humans with obesity also exhibited these aberrant properties. A variety of tumours grew more rapidly in obese than in non-obese mice. This difference was associated with both a more metabolically active tumour and a higher fraction of $PD\text{-}1^+$ T cells, with a signature of ‘exhaustion’, within the tumour. The elevated levels of leptin with increasing adiposity, which can control STAT3 expression in activated T cells, was one reason for the poor antitumour response in obese mice, although almost certainly not the only one. Unexpectedly, the higher PD-1 expression (and likely other abnormalities) induced by obesity rendered tumours more susceptible to blockade of the PD-1–PD-L1 pathway. Importantly, a greater sensitivity to checkpoint blockade was reported for melanomas of humans with obesity[9], which was also confirmed in the report by Wang et al.[8] using The Cancer Genome Atlas (TCGA) database.

These findings presage next year’s advances. Hopefully, 2019 will see more integrative studies, exploiting the impressive menu of powerful ‘omics’ and single-cell approaches that are now available. How do various classes of immunocytes interact to regulate sterile inflammation, insulin sensitivity and the growth of diverse tumours? When, where and how are the key tissue-adapted immunocyte populations generated? To what extent are defects in organismal metabolism subtended by changes in immunocyte metabolism?

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Competing interests
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