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Innate lymphoid cell immunometabolism

Timothy E. O'Sullivan¹ and Joseph C. Sun^{2,3}

¹Department of Microbiology, Immunology, and Molecular Genetics, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095

²Immunology Program, Memorial Sloan Kettering Cancer Center, New York, NY, 10065

³Department of Immunology and Microbial Pathogenesis, Weill Cornell Medical College, New York, NY 10065

Abstract

Innate lymphoid cells (ILCs) are tissue-resident “first responders” of the immune system that function to protect epithelial barriers against pathogens and maintain tissue homeostasis. However, because ILCs are finely tuned to perturbations within tissue microenvironments, they can also contribute to host pathology when upstream activating signals are dysregulated. Recent work has demonstrated that the crosstalk between ILCs and their environment has a significant impact on host metabolism in health and disease. In this brief review, we summarize recent studies that demonstrate the ability of ILCs to influence tissue and systemic metabolism, as well as how ILC biology can be regulated by environmental changes in host metabolism. We also highlight studies showing how ILC-intrinsic metabolism influences their activation, proliferation, and homeostasis. Finally, this review discusses the challenges and open questions in the rapidly expanding field of immunometabolism.

Graphical abstract

Correspondence: Joseph C. Sun, PhD, Memorial Sloan Kettering Cancer Center, 408 East 69th Street, ZRC-1462, New York, NY 10065, Phone: 646-888-3228, Fax: 646-422-0452, sunj@mskcc.org.

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Introduction

Innate lymphoid cells (ILCs) consist of a heterogeneous family of lymphocytes that do not express rearranged antigen receptors, but instead express a wide variety of germline-encoded activating and inhibitory receptors[1, 2]. ILCs can be identified in lymphoid and non-lymphoid tissues, and are enriched at epithelial barrier surfaces such as the intestine, lung, and skin[1, 2]. Recent evidence has suggested that mature ILCs can be further classified into group 1, 2, and 3 ILCs based on different expression of transcription factors, cell surface markers, and effector cytokines[1, 2]. Group 1 ILCs, which include natural killer (NK) cells and ILC1, can be distinguished from other ILCs based on their constitutive expression of the transcription factor T-bet, co-expression of activating receptors NKp46 and NK1.1, and production of interferon (IFN)- γ following stimulation with proinflammatory cytokines interleukin (IL)-12 and IL-18[3]. NK cells, the original member of group 1 ILCs[4], are cytotoxic innate lymphocytes that constitutively express the transcription factor Eomes and the integrin CD49b (also known as DX5 or $\alpha_2\beta_1$ integrin), and survey peripheral tissues by continuous circulation through the vasculature to perform host immunosurveillance against viruses and tumors[5–8]. In contrast to NK cells, ILC1 lack Eomes and CD49b expression, but express CD49a ($\alpha_1\beta_1$ integrin). ILC1 are long-term tissue resident in peripheral organs, and may be required to protect the host from bacterial infections at barrier sites such as the intestine[5, 6, 9–13]. Group 2 ILCs (ILC2) express the transcription factor GATA3 and produce type 2 cytokines such as IL-4, IL-5, and IL-13, along with the tissue reparative factor amphiregulin, to promote host resistance to helminth infection[14–18]. Lastly, group 3 ILCs consist of lymphoid tissue inducer (LTi) cells, and NKp46[–] and NKp46⁺ ILC3s that express retinoid-related orphan receptor γ t (ROR γ t) and can produce IL-22, IL-17A, and lymphotoxin to maintain tissue homeostasis and antibacterial immunity in the intestine[19–24].

ILCs are rapid producers of both proinflammatory and regulatory cytokines in response to local injury, inflammation, pathogen infection, or commensal microbiota perturbation[1, 2]. Because most ILCs have been shown to be tissue-resident (with the exception of circulating NK cells) in almost all organs analyzed[5, 13], their ability to quickly respond to tissue stress and inflammation underpins their critical role in regulating tissue homeostasis and repair during infection or injury[1, 2]. However, persistent inflammatory signals can also lead to unrestrained activation of certain ILC populations at barrier surfaces, thereby exacerbating colitis, dermatitis, and contributing to tumorigenesis[25–29]. Collectively, these studies demonstrate the impact of ILCs in tissue microenvironments and highlight the delicate balance between ILC-mediated immune protection and pathology. Recent reports have identified certain ILC populations in non-barrier tissues with important host metabolic function (i.e. liver and adipose tissue) and collectively suggest a broader role for ILCs in the maintenance of both tissue homeostasis and systemic host metabolism[30, 31]. Given the contribution of ILCs to tissue inflammation in other diseases, it may not be surprising that recent studies have also implicated ILCs in the disruption of host tissue homeostasis and systemic metabolism during diet-induced obesity[13, 32–34]. This review summarizes recent findings in the field of ILC biology that address three central questions in the field of immunometabolism: What are the cell-intrinsic metabolic pathways that are utilized by ILCs during activation and homeostasis? How does host tissue and systemic metabolism impact the homeostasis or activation state of ILCs? And finally, how do ILCs maintain or disrupt host tissue and systemic metabolism in disease states?

Cell-intrinsic metabolism of ILCs

The study of cellular immunometabolism focuses on cell-intrinsic changes to metabolic pathways that influence discrete cellular states such as activation, proliferation, and homeostasis. Naïve lymphocytes are generally thought to be quiescent and largely use metabolic pathways that efficiently metabolize glucose through glycolysis-linked mitochondrial oxidative phosphorylation (OXPHOS) to generate energy in the form of adenosine triphosphate (ATP). During activation, adaptive and innate immune cells increase the rate of glycolysis to meet higher biosynthetic demand by metabolizing glucose into lactate in a process called aerobic glycolysis to provide the cell with essential precursors for amino acids, lipids, and nucleotides[35–37]. However, the differential metabolic pathways that ILCs utilize during homeostasis versus host defense have only recently begun to be unveiled. In this section, we summarize the relatively few studies that offer insight on the cell-intrinsic metabolic pathways used by ILCs during steady state and activation.

Group 1 ILC-intrinsic metabolism

Similar to naïve T cells, freshly-isolated naïve mouse and human NK cells rely on OXPHOS (Fig. 1A), but quickly shift to aerobic glycolysis following culture with high-dose IL-15, which induces the activation and proliferation of NK and T cells[38–42]. In terms of effector function, NK cells differ from T cells through their use of an aerobic glycolysis-independent mechanism for IFN- γ production following stimulation with IL-12 and IL-18 *ex vivo*[38], although another study found that IL-15-expanded NK cells require aerobic glycolysis for optimal IFN- γ production following IL-2 and IL-12 stimulation *in vitro*[39]. However,

because *in vitro* culture conditions may not accurately reflect physiologic levels of oxygen, nutrient concentrations (i.e. glucose, glutamine, and fatty acids), and cytokine concentrations, these conclusions may be limited by how the differences in these conditions impact cellular metabolism *in vitro* versus *in vivo*.

Nevertheless, the *in vivo* role for aerobic glycolysis in promoting NK cell cytokine production remains unclear. IL-15 stimulation *in vitro* and poly(I:C) stimulation *in vivo* increase mammalian target of rapamycin (mTOR) signaling, which is associated with an increase in aerobic glycolysis in activated NK cells[40]. Poly(I:C) injection and mouse cytomegalovirus (MCMV) infection, both of which induce IL-15, IL-12, and IL-18 *in vivo*[43], lead to decreased IFN- γ production by NK cells in the presence of either glycolysis pathway inhibitors or mTOR inhibitors[39, 44], suggesting that pro-inflammatory cytokine induction of mTOR signaling may lead to increased aerobic glycolysis in NK cells to potentiate IFN- γ production. However, it remains difficult to determine the role of mTOR signaling on NK cell IFN- γ production *in vivo* because systemic treatment with these inhibitors during inflammation could have cell-extrinsic effects that indirectly decrease NK cell IFN- γ production. This point is supported by the observation that NK cell-intrinsic loss of mTOR does not impact IFN- γ production during MCMV infection or following *ex vivo* stimulation with IL-12 and IL-18[40]. It should be noted, however, that mTOR-deficient NK cells do not progress past an immature stage, suggesting that mTOR signaling is necessary for the optimal proliferation of immature NK cells to populate the mature NK cell pool during development and homeostasis[40]. These observations make it difficult to dissociate the role of mTOR-induced IFN- γ production in mature rather than immature NK cells. To rule out these observed developmental defects, adoptive transfer studies using NK cells with inducibly-deleted mTOR suggest that while mTOR is dispensable for mature NK cell homeostasis, its signaling is necessary for optimal NK cell cytotoxicity and proliferation during poly(I:C)-induced inflammation[40]. Therefore, while increased mTOR signaling and aerobic glycolysis control NK cell proliferation and cytotoxicity in NK cells during inflammation-induced activation (Fig. 1B), the metabolic pathways NK cells utilize to produce IFN- γ *in vivo* remain unclear.

Although the growing consensus is that mTOR inhibition *in vivo* restrains NK proliferation and cytotoxicity early during inflammation, recent studies have also demonstrated that inhibition of mTOR following periods of inflammation or proliferation can lead to enhanced survival of group 1 ILCs. Specifically, inhibition of mTOR by rapamycin treatment or stimulation of AMPK (which can inhibit mTOR signaling)[45] through metformin treatment lead to enhanced induction of the cellular catabolic process of autophagy to limit apoptosis and promote survival of adoptively transferred ILC1 or NK cells in a cell-intrinsic manner during homeostatic proliferation or viral infection [46–48]. Whereas autophagy is critical for the development of all known lymphocytes[48, 49], autophagy was not found to be necessary for the basal turnover and homeostasis of mature ILCs and their precursors in a cell-intrinsic manner through inducible deletion of the core autophagosome machinery component *Atg5*[48]. Thus, while initial activation of mTOR signaling is required for optimal proliferation of NK cells *in vivo*, subsequent metabolic adaptation to suppress anabolic mTOR-induced glycolysis and induce catabolic autophagy is essential to inhibit

apoptosis in group 1 innate lymphocytes following periods of cell differentiation or stress, such as during lymphopenia or viral infection.

ILC2 and ILC3-intrinsic metabolism

Although aerobic glycolysis-fueled proliferation and effector function are key characteristics of NK cell and T cell responses to activating signals *in vitro* and *in vivo*, whether other ILC populations utilize similar metabolic pathways to fuel effector responses remains unclear. Recent studies have demonstrated that both ILC2 precursors and mature ILC2s express high levels of the metabolic enzyme arginase-1 [50, 51]. Arginase-1 metabolizes the amino acid L-arginine into urea and ornithine to generate downstream metabolites that fuel bioenergetic pathways critical for cellular proliferation [52]. In one study, conditional deletion of arginase-1 in all lymphocyte-lineage cells revealed defects in lung ILC2 proliferative capacity and cytokine secretion during papain-induced lung inflammation in the absence of apparent developmental defects [50]. Reduced proliferation and effector function in lung ILC2s was caused by cell-intrinsic defects in arginine catabolism and aerobic glycolysis (Fig. 1C) [50]. However, using a genetic method to selectively target this pathway in mature ILC2s, another study found that deletion of arginase-1 did not impact lung ILC2 proliferation or production of IL-5 and IL-13 during helminth infection [51]. These conflicting results suggest either that the requirement of arginase-1 activity to promote effector functions in mature ILC2s may be dictated by specific inflammatory contexts, or that arginase-1 activity may metabolically license ILC2 precursors to potentiate the optimal effector functions of mature ILC2s. While transcriptional profiling of intestinal ILC3s has revealed pathways enriched in glycolysis [53], in line with another study showing mTOR to be required for NCR⁺ ILC3 development [40], arginase-1 was found to be dispensable for ILC3 development and antibacterial immunity [50]. Together, these results suggest that ILC3s may not utilize arginase-1 activity to fuel glycolysis and cellular proliferation during development and inflammation. Thus, the metabolic pathways that ILC3s utilize during these processes remain unclear.

Other studies suggest that intestinal ILC2s express a genetic signature enriched in genes involved in fatty acid metabolism [54], and intestinal ILC2s as well as ILC3s have been shown to uptake extracellular fatty acids from their environment during homeostasis [55]. Inhibition of systemic fatty acid oxidation (FAO) by treatment of etomoxir *in vivo*, but not systemic inhibition of glycolysis, reduced intestinal ILC2 accumulation and production of IL-13 and IL-5 in response to helminth infection [55]. These results suggest that ILC2s may be metabolically distinct from other lymphocytes in that they could preferentially use lipid-fueled FAO to support their proliferation and effector functions during pathogen-induced inflammation (Fig. 1D). However, whether this mechanism is ILC2-intrinsic or specific to intestinal ILC2s is still unclear. Although ILC2s and ILC3s have increased rates of extracellular fatty acid uptake compared to regulatory T cells in the small intestine, blockade of FAO by etomoxir does not perturb ILC2 homeostasis *in vivo* [55]. Therefore, future work will be needed to uncover the specific metabolic pathways that are utilized by ILC2s and ILC3s during activation and homeostasis.

Tissue immunometabolism and ILCs

The study of tissue immunometabolism focuses on how immune cells influence tissue and systemic metabolism at steady state and in responses to environmental changes. These findings have been reviewed in detail previously[31]. Reciprocally, the immunometabolism field has also investigated how changes in local and systemic metabolism (often in metabolic disease settings) influence the immune system. Metabolic tissues, such as the liver and adipose tissue, consist of stromal, parenchymal, and immune cells that coordinate their cellular functions to maintain the metabolic functions carried out by parenchymal cells (i.e. hepatocytes and adipocytes). Immune and stromal populations are thought to maintain these functions through the production of various cytokines, growth factors, and hormones[31]. In addition, the immune system has evolved to be closely regulated by host nutritional status and environmental changes[31]. In this section, we will review studies demonstrating how ILCs influence tissue immunometabolism, and how environmental metabolic changes influence ILC biology.

ILCs maintain metabolic homeostasis

The main function of the white adipose tissue (WAT) is to store excess lipids from the circulation when nutrient availability exceeds energy expenditure. In addition, when nutrients are limited, adipocytes induce lipolysis to break down stored lipid droplets to provide lipid fuel to other tissues[56, 57]. Adipocytes also produce a plethora of secreted molecules called adipokines (i.e. leptin, resistin, and adiponectin) that maintain local and systemic tissue metabolic homeostasis[31]. A key characteristic of metabolic fitness of the adipose tissue is insulin sensitivity, which has been shown by several studies to be maintained by type 2 immune cells such as alternatively activated macrophages (M2), eosinophils, and Th2 cells[58–61]. Although the roles of these cells in adipose metabolic homeostasis have been reviewed previously[31, 61], ILC2-derived IL-5 and IL-13 has recently been shown to maintain insulin sensitivity in lean mice through the recruitment of eosinophils by IL-5, and by maintenance of M2 macrophage polarization by IL-13[58, 59]. ILC2s may also control certain aspects of weight gain in mice, as IL-33-deficient mice (which have reduced functional ILC2s) develop spontaneous weight gain and fat mass on a low fat diet[62]. However, whether the spontaneous weight gain observed during IL-33 deficiency is caused by defects in adipocyte-intrinsic mitochondrial respiratory capacity and metabolism[63], or ILC2-derived IL-5 production, remain unclear.

A recent study demonstrated through lineage tracing and parabiosis experiments that the adipose tissue contains a heterogeneous mixture of group 1 ILCs, consisting of circulating mature NK cells, and tissue-resident ILC1 and immature NK cells during steady state[13]. Although these cells do not display activated phenotypes in lean mice, a subsequent study proposed that group 1 ILCs function to maintain macrophage homeostasis in the visceral white adipose tissue (VAT) by preferentially killing adipose M2 macrophages *in vivo*[34]. This was suggested to be caused by enhanced expression of the NKG2D ligand RAE-1 on adipose macrophages during homeostasis[34]. However, these results are controversial because the consensus in the field is that M2 macrophages serve a protective rather than detrimental role in the homeostasis of the adipose tissue[31, 61], and our laboratory and

others, have not observed metabolic defects nor altered M2 macrophage homeostasis in group 1 ILC-deficient mice (T.E.O. & J.C.S. unpublished observations) or NKG2D-deficient lean mice[64]. Therefore, while group 1 ILCs are enriched in the adipose tissue, their role in maintaining adipose macrophage numbers and metabolic fitness during homeostasis requires more precise investigation.

Although gut commensal bacteria are not of host origin, current evidence strongly suggests that the microbiota can influence the host response to dietary intake by altering the metabolism, storage, and absorption of calories[65]. This notion of the microbiota as a metabolic “organ” is highlighted by studies demonstrating that germ-free rats have reduced weight and harvest less energy despite increased food intake compared to microbiota-sufficient controls[66, 67]. Emerging evidence suggests that ILC3s can regulate the homeostasis and composition of the intestinal microbiota. In mice, ILC3s are the main source of IL-22[22, 23, 68], which is important to stimulate intestinal epithelial cells to produce antimicrobial peptides and mucins for containment of commensal bacteria within the intestine[68, 69]. In addition, ILC3s function to promote fucose transfer to the surface of epithelial cells in the intestine, which is used by the commensal microbiota as a carbohydrate source[70], and have been found to be important for controlling cecal homeostasis in a non-redundant manner[71]. Given the intimate relationship between ILC3s and the microbiota, it will be of interest to investigate whether ILC3-mediated control of the microbiota can indirectly regulate whole-body metabolism.

Environmental changes in host metabolism influence ILC biology

Although ILCs have been shown to have important roles in the regulation of host metabolism, several studies have also shown that environmental changes to host metabolism can directly regulate key facets of ILC biology. Following exposure to cold temperatures, certain WAT tissues are able to perform thermogenesis to provide heat for the host by inducing enhanced expression of uncoupling protein 1 (UCP1) in beige adipocytes. This environmental change in temperature is sensed by adipose-resident ILC2s in response to local production of IL-33 to produce IL-13 and potentiate the lineage commitment and proliferation of PDGFR α ⁺ stromal cells to beige fat cells[72]. IL-33 can also induce the production of methionine-enkephalin peptides by adipose ILC2s, resulting in increased UCP1 expression in the WAT[62]. While this provides a direct example of environmental metabolic changes resulting in ILC responses, how IL-33 is produced in response to cold stress, and the host cells that produce IL-33 *in vivo* are unknown.

The intestinal microbiota can also influence ILC homeostasis by providing bacterial-derived metabolites to host cells based on dietary input from the environment. Vegetable-derived phytochemicals can influence ILC3 and ILC2 cytokine secretion and survival by modulation of the transcription factor AHR[73–75]. The microbiota can also indirectly influence levels of indole 3-aldehyde, a tryptophan-derivative that binds to AHR, to promote IL-22 production by ILC3s[76]. ILC3s may be unique in their dependence on microbiota-derived metabolites, because NK cell and ILC2 development is not perturbed whereas Nkp46⁺ ILC3s can be reduced in germfree mice[24, 77, 78]. However, other studies have reported that ILC3 development is normal in the absence of the microbiota[21, 22, 68], suggesting

that the development and homeostasis of ILCs may not depend on the microbiota. Using single cell RNA sequencing analysis of ILC population in the small intestine, a recent study found a high degree of transcript regulation in ILC1 and ILC2 in response to the presence of commensal microbiota, while transcript levels of IL-22 did not change in ILC3s[53]. These results collectively suggest that the microbiota may influence certain aspects of the steady-state transcriptional landscape rather than development of ILCs in the intestine, although future work is needed to clarify the role of the microbiota on ILC function and development.

Whether or not host microbiota directly influences ILC development and effector function, there is a clear consensus in the field that diet can influence ILC biology. Dietary nutrient deficiencies, such as Vitamin A deficiency, leads to a loss of ILC3s in the gut[79], while ILC2 number and effector function are enhanced by increased FAO and acquisition of long-chained fatty acids[55]. Dietary nutrient oversupply of fat, which leads to obesity, results in the hypertrophy of adipocytes, limiting their nutrient and oxygen availability and resulting in a sustained stress response in both adipocytes and stromal cells[80–82]. This stress response results in the recruitment, activation, and proliferation of IFN- γ -producing circulating CD8⁺ T cells, Th1 cells, and NK cells, as well as tissue-resident adipose ILC1, to drive the accumulation of proinflammatory macrophages in the adipose tissue[13, 32, 33, 83–85]. Together, these studies highlight the sensitive balance between environmental dietary inputs and ILC homeostasis and activation and warrant further investigation into the mechanisms underlying these processes.

ILC activation disrupts metabolic homeostasis during diet-induced obesity

During diet-induced obesity, unrestrained type 1 responses promote the production of the cytokines tumor necrosis factor (TNF)- α and IL-6 by proinflammatory macrophages, which can reduce insulin sensitivity over time[86–88]. Given that group 1 ILCs are activated during diet-induced obesity in mice, recent studies have shown that systemic depletion of NK1.1⁺ or Nkp46⁺ cells reduces diet-induced obesity-associated insulin resistance by decreasing the polarization of proinflammatory macrophages[32, 33, 89]. Although the genetic or antibody depletion methods utilized in these studies also reduced adipose NKT cells, which can suppress insulin resistance during diet-induced obesity[90, 91], adoptive transfer of splenic CD49b⁺ NK cells into the VAT of *Ifng*^{-/-} mice is sufficient to exacerbate insulin resistance following HFD administration[33]. Similarly, adoptive transfer of splenic CD49b⁺ NK cells into *Nfil3*^{-/-} mice is sufficient to enhance insulin resistance during diet-induced obesity[32], demonstrating that CD49b⁺ NK cells can contribute to insulin resistance in the presence of an intact adaptive immune system. However, because of the heterogeneity of group 1 ILCs present in the adipose tissue, the contribution of other tissue-resident group 1 ILCs in obesity-associated insulin resistance remained unknown from these studies.

Recent evidence suggests that adipose-resident ILC1 proliferated locally and produced the highest amounts of IFN- γ early during HFD feeding compared to other known IFN- γ producing lymphocytes in the adipose tissue, including NK cells[13]. Furthermore, adipose ILC1 polarized adipose proinflammatory macrophages and contributed to metabolic dysfunction to a greater extent on a per cell basis (relative to immature or mature NK cells), suggesting that adipose ILC1 responses to HFD-induced inflammation are the most potent

among group 1 ILCs in driving disease progression[13]. A caveat with this hypothesis is that the genetic ablation tools to definitively differentiate between the contribution of each subset of group 1 ILCs to obesity-associated insulin resistance do not currently exist. However, these results collectively suggest that each member of the group 1 ILCs is sufficient to polarize adipose proinflammatory macrophages through HFD-induced IFN- γ production, and therefore represent a functional spectrum of immune cells able to contribute towards insulin resistance during diet-induced obesity. Other recently proposed mechanisms of how group 1 ILCs increase adipose proinflammatory macrophages during HFD, such as increased TNF- α production[32] or decreased killing of adipose M2 macrophages[34] by group 1 ILCs, are likely secondary to enhanced IFN- γ production, because adoptively transferred *Ifng*^{-/-} group 1 ILCs from HFD fed mice do not increase the density of proinflammatory macrophages in lymphocyte-deficient mice during HFD[13]. Therefore, it is more likely that these alternative mechanisms can contribute to obesity-associated systemic insulin resistance by other mechanisms that will need further investigation.

The growing consensus in the field is that group 1 ILCs are sufficient and necessary to drive obesity-associated inflammation in the adipose tissue by polarizing local proinflammatory macrophages. However, the mechanisms by which adipose-resident and circulating group 1 ILCs are activated during HFD remain unclear. Adipose NK cells from obese patients displayed higher NKG2D levels compared to lean individuals[92], and increased expression of NKG2D ligands was observed in adipocytes from the VAT of obese mice compared to lean controls[64]. However, NKG2D-deficient mice did not display reduced insulin resistance, or increased numbers of proinflammatory macrophages, suggesting that NKG2D is not required for this process [64]. A recent study indicated that NK cell production of IFN- γ is stimulated by ligation of the activating receptor NKp46 by unknown ligands present on VAT adipocytes, and that this pathway is responsible for driving early proinflammatory macrophage polarization in the VAT, but not the SAT[33]. In contrast to these findings, we observed similar proliferation, accumulation, and IFN- γ production between WT and NKp46-deficient group 1 ILCs in the SAT and VAT after HFD administration (T.E.O & J.C.S unpublished observations). Instead, it is well established that IL-12 and STAT4 signaling are critical for NK cells to produce IFN- γ and proliferate following viral infection[93, 94] and elevated IL-12 transcripts are found in the adipose tissues of mice early following HFD feeding[13, 95, 96]. In support of these findings in mice, clinical studies have observed higher serum levels of IL-12 in obese individuals compared to lean individuals[97, 98]. A recent study also demonstrated that IL-12 is induced as early as 3 weeks after HFD administration in the VAT and SAT, and IL-12 signaling is an absolute requirement for driving the proliferation and accumulation of group 1 ILCs in the adipose tissue during diet-induced obesity[13]. Therefore, while the conflicting results regarding NKp46 ligand induced activation of group 1 ILCs during HFD may be dependent on differences in microbiota or the content of experimental HFD used, early mouse and clinical data suggests that IL-12 plays an important role in this process.

Concluding Remarks

Evidence is now becoming apparent that ILCs can influence and be influenced by host metabolism, and the cellular and molecular mechanisms are just now becoming elucidated.

However, many unresolved questions remain regarding ILC immunometabolism. What are the metabolic pathways that are utilized by ILCs to maintain their tissue-residency and turnover? Can ILC3s influence microbial composition to impact host metabolism? What is the role of adipose-resident group 1 ILCs during homeostasis? Future studies will also need to address whether the observed discrepancies observed in ILC2-intrinsic metabolism during inflammation are due to differences in tissue-specific biosynthetic precursors or model-specific activating signals. Despite these questions, studies of host metabolism collectively support that adipose ILC2s regulate insulin sensitivity of the adipose tissue by production of IL-5 and IL-13, whereas group 1 ILCs play a detrimental role in host metabolism during diet-induced obesity in mice through IFN- γ -dependent polarization of adipose proinflammatory macrophages. Given the prevalence and alarmingly increasing rate of global obesity, studies further elucidating the mechanisms by which ILCs influence host metabolism may prove to be beneficial for therapeutic use in obesity-associated diseases such as cancer and type II diabetes.

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Highlights

- ILCs utilize aerobic glycolysis and fatty acid oxidation to fuel effector functions
- ILCs contribute to host tissue homeostasis and systemic metabolic homeostasis
- ILCs may control dietary metabolism by influencing the composition of host microbiota
- Dietary deficiency or oversupply impacts ILC homeostasis and activation

Figure 1. Metabolic Pathways utilized by ILCs during homeostasis and activation

(A) Resting ILCs are generally thought to be quiescent and largely use metabolic pathways that efficiently metabolize glucose through glycolysis-linked mitochondrial oxidative phosphorylation (OxPhos) to generate energy in the form of adenosine triphosphate (ATP). However, during inflammation ILCs respond to increased levels of proinflammatory cytokines that cause their activation and concomitant changes in cellular metabolism. (B) NK cells respond to heightened levels of the cytokines IL-12, IL-18 and IL-15 through activation of mTOR signaling, which is associated with an increased rate of glycolysis to meet higher biosynthetic demand by metabolizing glucose into lactate in a process called aerobic glycolysis. Aerobic glycolysis is needed to provide the cell with essential precursors for amino acids, lipids, and nucleotides to fuel effector function and proliferation. (C) Following IL-33 stimulation, activated ILC2s can also increase aerobic glycolysis, which is dependent on arginase-1 (*Arg1*) activity to metabolize extracellular L-arginine into ornithine-derived polyamines to fuel increased glycolysis. (D) During helminth infection *in vivo*, ILC2s in the intestine do not require glucose uptake to fuel their effector functions. Rather, ILC2s take up extracellular long chain fatty acids through an undefined transporter and utilize mitochondrial fatty acid oxidation (FAO) to fuel proliferation and effector function.