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Regulation of Systemic Metabolism by Tissue-Resident Immune Cell Circuits

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Abstract

Recent studies have demonstrated that tissue homeostasis and metabolic function are dependent on distinct tissue-resident immune cells that form functional cell circuits with structural cells. Within these cell circuits, immune cells integrate cues from dietary contents and commensal microbes in addition to endocrine and neuronal signals present in the tissue microenvironment to regulate structural cell metabolism. These tissue-resident immune circuits can become dysregulated during inflammation and dietary overnutrition, contributing to metabolic diseases. Here, we review the evidence describing key cellular networks within and between the liver, gastrointestinal tract, and adipose tissue that control systemic metabolism and how these cell circuits become dysregulated during certain metabolic diseases. We also identify open questions in the field that have the potential to enhance our understanding of metabolic health and disease.

Abstract

Tissue-resident immune cell interactions with structural cells in metabolic organs influence systemic metabolism in health and disease. Li, Hepworth, and O'Sullivan review the key tissue-resident immune cell circuits that regulate metabolic homeostasis in the liver, gastrointestinal tract, and adipose tissue to provide insight into how these circuits communicate between metabolic organs to regulate systemic metabolism.

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Declaration of Interests

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Introduction

Single cell sequencing and spatial transcriptomics studies have changed our perception of mammalian organs from structural cell-dominated tissues into complex heterogeneous cellular networks incorporating a layered tissue-resident immune system. These studies have revealed the interactions between neighboring cells that constitute local tissue niches and provide important regulatory signals that dictate cell state, metabolic function, and orchestrate organ-wide cellular processes. These combined with functional studies in mice have revealed a key role for immune cells in the maintenance of tissue homeostasis[1–6]. Therefore, current evidence suggests that the immune system, in contrast to its classically defined role in pathogen defense, is critical for the homeostasis and function of metabolic tissues.

We propose that the complete understanding of systemic metabolic homeostasis requires deep characterization and validation of tissue-resident immune and structural cell interactions that regulate metabolic function locally and systemically. We focus on three organs that play important roles in the regulation of systemic metabolism (liver, adipose, and gastrointestinal tract), and review the evidence describing tissue-resident cellular circuits within and between these organs that act in concert to promote systemic metabolism, or that are dysregulated during metabolic diseases. We also identify open questions in the field focusing on the regulation of these cell circuits. A network-based approach to systemic tissue metabolism will provide the context necessary to interpret metabolic disruptions driven by cell type-specific perturbations, providing insight into both mechanisms of systemic metabolic homeostasis and the signaling networks that must be restored during metabolic diseases.

Liver

The liver plays a key role in regulating metabolic and hormonal balance, systemic immune activation, and detoxification of circulating blood. As a primary site of gluconeogenesis, glycogen storage, and lipolysis, liver function is critical for the maintenance of systemic metabolic homeostasis. Liver metabolism is largely orchestrated by hepatocytes, which regulate blood glucose levels in response to insulin by increasing circulating glucose through gluconeogenesis or storing it in the form of glycogen[7]. Hepatocytes also store or release triglycerides through a dynamic process of lipogenesis and lipid droplet synthesis, frequently in interplay with the uptake or release of triglycerides from the adipose tissue[8]. Disruption of these processes upon liver injury results in both local and systemic metabolic dysfunction in settings such as metabolic-associated fatty liver disease (MAFLD) or metabolic syndrome, as hepatic lipid accumulation results in the failure of insulin receptor signaling and subsequent systemic pathology[7,8].

Hepatocyte metabolism is spatially heterogeneous across the liver lobule. The liver parenchyma is classically divided into hexagonal lobules of hepatocytes bordered by portal triads (hepatic artery branch, portal vein branch, and bile ductule) and surrounding a central vein[9]. Lobules are functionally zonated into periportal, intermediate, and pericentral zones. Liver zones experience differential gradients of nutrients, morphogens,

and immunomodulatory molecules that integrate to influence zonal hepatocyte metabolism[9]. For example, periportal hepatocytes express higher levels of enzymes responsible for gluconeogenesis (glucose-6-phosphatase (G6Pase), phosphoenolpyruvate carboxykinase (PEPCK)) in addition to fatty acid oxidation compared to pericentral hepatocytes displaying enriched expression of glycogen and fatty acid synthesis enzymes[10]. These hepatocytes are additionally supported by stromal cells including hepatic stellate cells (HSCs) and liver sinusoidal epithelial cells (LSECs) which metabolize and store molecules such as vitamin A. Alongside a variety of structural cells and heterogeneous hepatocytes, unique liver-resident immune cells conserved between human and mouse livers have been identified by recent single-cell RNA sequencing and mouse parabiosis studies: Kupffer cells (KCs), plasmacytoid (pDC) and conventional type 1 (cDC1) and type 2 (cDC2) DCs, tissue resident αβ and γδ T cells, mucosal-associated invariant T cells (MAITs), and innate lymphoid cells (ILCs)[11–25]. In this section, we will discuss current evidence supporting how structural and liver-resident immune populations form distinct cellular circuits to regulate metabolic homeostasis (Figure 1).

Hepatocytes maintain systemic glucose homeostasis by acting as a major glycogen store and balancing glucose storage and breakdown, a critical role that can be controlled by tissue-resident immune cells. IL-6 and IL-1β regulate hepatic glycogen storage by inhibiting hepatocyte glycogen synthase and activating glycogen phosphorylase[26]. IL-6 can also inhibit expression of hepatocyte gluconeogenesis enzymes such as glucose-6-phosphatase (G6PC) via STAT3 signaling. However, both chronic IL-6 exposure or liver-specific loss of STAT3 result in insulin resistance due to increased glucose breakdown[27–31]. While elevated levels of IL-6 in circulation may originate from the adipose tissue during obesity[32], liver-resident sources of these cytokines (including KCs and cDC1s[33,34]) may also form an active circuit with hepatocytes to control insulin-stimulated glycogen deposition. Particularly in the periportal region, highly abundant KCs and hepatic DCs may control the local cytokine milieu to regulate gluconeogenesis and glycogen synthesis in periportal hepatocytes already enzymatically poised for glucose breakdown. Increased levels of proinflammatory IL-6 during obesity or type 2 diabetes may preferentially engage this periportal circuit to disrupt glucose homeostasis.

IL-13 has also been suggested to influence hepatocyte metabolism through STAT6 signaling, as IL-13-deficient mice become hyperglycemic and insulin resistant due to increased gluconeogenesis enzyme expression[35]. Hepatocyte stimulation with IL-13 was also found to decrease hepatocyte lipid droplet accumulation through STAT6 activation[36], suggesting that IL-13 may be broadly advantageous for maintaining hepatocyte metabolic homeostasis. IL-25 treatment was sufficient to protect against diet-induced hepatic steatosis by inducing ILC2 responses and activating IL-13/STAT6 signaling[36]. Subsequent studies confirmed that liver ILC2s are a major source of IL-13, capable of suppressing hepatocyte G6PC expression and subsequent gluconeogenesis[37]. Further characterization of a hepatocyte-ILC2 circuit, including other non-hepatocyte sources of IL-25 or IL-33, may reveal additional regulators of protective hepatocyte IL-13 signaling. For instance, IL-25 can be expressed by Th2 cells or circulating $CD4^+$ or $CD8^+$ T cells upon tissue insult[38,39].

Hepatic lipid processing can additionally be modulated by IL-17A signaling. Despite gaining more body weight and WAT mass upon high fat diet (HFD) administration, IL-17RA$^{-/-}$ mice were ultimately protected against obesity-induced insulin resistance, end-organ damage, and steatohepatitis[40]. A separate study found that IL-17A and free fatty acid exposure in culture disrupted AKT and IRS-1 activation downstream of insulin signaling and exacerbated steatosis, while also stimulating IL-6 production and activation of Th17 cells[41]. IL-17RA-deficient hepatocytes have also been found to decrease cholesterol synthesis after induction of steatosis[42]. In the absence of diet-induced inflammation, homeostatic levels of IL-17A may act to tune local hepatocyte lipid accumulation and insulin responsiveness. Liver-resident sources of IL-17A can include γδ T cells, MAIT cells, and ILC3s[43], though the source of activating signals for these cell types requires further study. In other settings, DCs secrete IL-23 to activate IL-17 responses including during hepatitis B infection[44–47], suggesting that a hepatic cDC-type 3 lymphocyte-hepatocyte circuit may regulate hepatocyte lipid homeostasis. MAIT cells have been found to exhibit less spatial preference for the periportal zone than other resident lymphoid cells and instead are distributed more evenly throughout the liver lobule, suggesting that they may interact with lipogenic hepatocytes in the pericentric zone[48]. Collectively, these findings suggest that hepatic metabolism can be directed by local immune networks in a spatially distinct manner, consistent with the observed functional zonation of the liver. Further functional experiments will be needed to validate these potential immune regulatory circuits controlling liver parenchyma metabolism.

Due to the liver's extensive exposure to circulating toxins and metabolites, maintenance of hepatocyte integrity is essential to liver homeostasis. Recent studies suggest that the liver's unique ability to regenerate after injury is also regulated in part by immune cells. Upon liver damage, crosstalk between neutrophils, KCs, NK cells and/or ILC1s maintains the balance of hepatocyte proliferation and survival. KCs, activated by circulating neutrophils recruited to the liver, produce IL-6 and TNF-α to promote hepatocyte proliferation and liver repair by activating hepatocyte gp130-STAT3 signaling and production of a protective IL-8 ortholog and serum amyloid proteins[49,50]. This regenerative signaling can be counterbalanced by NK cell-derived IFN-γ to limit hepatocyte proliferation, as mice treated with mouse cytomegalovirus or poly-I:C after partial hepatectomy displayed impaired liver regeneration due to NK cell activation in an IFN-γ dependent manner[51]. TNF-α from KCs in conjunction with IL-12 or IL-18 from other sources yet to be identified may differentially stimulate both hepatocytes and NK cells, suggesting a self-regulating immune circuit active during liver repair. Recently, studies using a model of carbon tetrachloride-induced liver injury revealed activation of a cDC1-ILC1-hepatocyte axis. In this setting, resident cDC1s stimulated to produce IL-12 through activation of the cGAS-STING pathway to increase IFN-γ production by liver-resident ILC1s and to a smaller extent, NK cells[52,53]. ILC1-derived IFN-γ upregulated hepatocyte expression of pro-survival Bcl-xL to limit acute liver injury[52]. These models suggest opposing roles for NK cell and ILC1-derived IFN-γ controlling hepatocyte integrity during viral versus toxin-mediated liver injury, and may point to additional differences in cytokine secretion, function, or spatial contributions between liver-resident ILC1s and liver-infiltrating NK cells.

Clearance of dead cells, a process termed efferocytosis, is important for both the liver's maintenance of systemic homeostasis as well as continued metabolic function of the liver itself[54,55]. Recent studies suggest that impaired efferocytosis of lipid-laden apoptotic hepatocytes can contribute to the development of chronic liver inflammation during non-alcoholic steatohepatitis (NASH). Overfeeding resulted in loss of the phagocytic receptor TREM2 on liver macrophages, impairing efferocytotic capacity and contributing to accumulation of steatotic hepatocytes[56]. While multiple "find-me" and "eat-me" signals such as ATP/UTP, lyso-phosphatidyl choline (LPC), CX3CL1, and membrane-exposed phosphatidylserine are known to be associated with efferocytosis, S1P-S1PR1 interactions were identified to be the major driver for the clearance of lipid-loaded hepatocytes[55,56]. Increased levels of inflammatory TNF-α and IL-1β inhibited TREM2 macrophage efferocytosis via shedding of TREM2 receptors by macrophage-expressed ADAM17 metalloproteinase; while the sources of TNF-α and IL-1β that regulate efferocytosis remain to be determined, other studies have suggested cDC1s to be a significant producer of IL-1β during NASH[33,56]. Interestingly, efferocytotic KCs activated by apoptotic cell signals like ATP can also release IL-6 and IL-1β upon activation, which could promote the differentiation of infiltrating monocyte-derived macrophages during liver injury toward an efferocytosis-competent state[57–59]. Together, these suggest communication between efferocytotic KC/liver macrophages, cDC1, and hepatocytes in homeostasis that is disrupted by proinflammatory cytokine imbalance during pathology.

During liver injury, damaged hepatocytes can secrete IL-33 or IL-25 to activate ILC2s, which may downregulate local hepatocyte gluconeogenesis and lipid storage via IL-13 secretion as previously described[60,61]. Indeed, patients with either acute or chronic liver injury from various etiologies are at heightened risk of hypoglycemia, pointing to the need for tight control of hepatocyte metabolism to regulate systemic glucose balance[62]. Systemic inflammation similarly can result in severe hypoglycemia due to dysregulated hepatic metabolism. For example, depletion of hepatic glycogen occurs clinically in adverse inflammatory responses to blood infection, referred to as sepsis[63]. High levels of inflammatory cytokines associated with sepsis such as TNF-α and IL-6 directly inhibited hepatocyte G6Pase and PEPCK activity, preventing normal hepatocyte-mediated regulation of blood glucose levels[29,64,65]. During sepsis, both systemic and local liver-resident sources of inflammatory cytokines such as KCs likely synergize to skew the liver cellular circuitry toward metabolic imbalance.

Uncontrolled liver damage results in fibrosis due to activation of HSCs and resultant secretion of extracellular matrix (ECM) proteins, a process normally mitigated by protective immune cell networks. These ECM-driven changes in local environmental cues drive a drastic transcriptional shift in hepatocytes, associated with loss of chromatin accessibility and expression in metabolic, bile processing pathway, and hormone synthesis genes[66]. Ligands that were predicted *in silico* to regulate hepatocyte transcriptional changes during fibrosis included TGF-β, HMGB2, and COL4A1 from HSCs and endothelial cells[66]. Consistent with this hypothesis, patients with cirrhosis (a clinically severe presentation of liver fibrosis) exhibit dysregulated glucose storage and depleted hepatic glycogen stores accompanied by decreased expression of the glucose sensor glucokinase[67]. HSCs can be activated by KC-derived inflammatory molecules such as TNF-α, IL-6, PDGF, and TGF-β

as well as IL-17A secreted by MAIT cells or ILC3s[34 43]. Once activated, HSCs differentiate into myofibroblasts with increased expression of NK cell activating ligands such as RAE-1/NKp46, becoming prime targets for NK cell-mediated clearance[68,69].

During NASH, which involves liver inflammation, damage, and eventual fibrosis due to fat accumulation, cDC1-derived IL-1β and IL-12 can activate pathogenic $CD8^+$ T cells[33]. Additional studies have identified the presence of autoreactive $CXCR6^+$ liver-resident $CD8^+$ T cells in NASH, induced by IL-15 and short-chain fatty acid stimulation to kill hepatocytes in an MHC-independent manner[70]. However, liver $CD8^+$ T cells may also be polarized toward a regulatory phenotype, where atypical $CD8^+$ Tregs can activate HSCs via production of IL-10 to promote liver fibrosis and subsequent metabolic dysfunction[71]. While the upstream cellular signaling partner inducing $CD8^+$ Treg differentiation remains to be identified, previous studies suggest that IL-4 and IL-12 can drive this shift[72]. Thus, both metabolite and toxin mediated liver damage can dysregulate homeostatic liver circuits while promoting injury-specific communication, resulting in disruption of total liver metabolism.

Gastrointestinal Tract

Metabolic health is also inherently linked with the gastrointestinal tract. In addition to being the primary site of nutrient absorption, the intestinal tract is also host to the commensal microbiota, which in turn acts in a mutualistic manner to metabolize complex dietary nutrients and regulate the metabolic state of the host. Multiple interconnecting immune networks act in concert to orchestrate homeostatic tissue function and metabolic activity in the gut, particularly through regulation of the intestinal epithelial barrier. Central to the regulation of intestinal metabolic circuits are resident myeloid cells and type 3 lymphocytes including group 3 ILC (ILC3), γδ T cells, MAITs and Th17 cells that act predominantly via the production of the cytokines IL-17A and IL-22. Another critical determinant of metabolic health in the gut is the commensal microbiota, which acts in a mutualistic manner to metabolize complex dietary substrates, regulate nutrient availability, and influence the metabolic state of the host directly. Moreover, changes in diet can dramatically perturb intestinal commensal microbial communities with consequences for metabolic health and disease. While the microbiota itself is a key factor in the role of the gastrointestinal tract as a metabolic organ, it has been reviewed extensively elsewhere[73,74]. Here, we discuss the key gut-resident immune circuits that regulate barrier integrity and nutrient uptake, circadian rhythm, and microbial tolerance (Figure 2).

The intestinal epithelium represents the initial barrier to the outside world and acts to determine nutrients absorption from the diet into the bloodstream for subsequent energy production. The balance of nutrients absorbed by the gut epithelium is tuned in response to features of mammalian feeding including macronutrient diversity, microbial abundance, and circadian feeding cues. Immune regulation of gut nutrient uptake heavily focuses around interactions between epithelial cells and local cytokine producing subset of myeloid and lymphoid cells. Type 3 cytokines, including IL-17A, IL-17F, and IL-22, have been attributed roles in regulating systemic metabolism, while emerging evidence suggests they may mediate their function via regulation of nutrient absorption in intestinal epithelial cells (IEC). While IL-17A and IL-17F have been described to have critical roles in modulating

metabolism in metabolically active tissues such as the liver and adipose (reviewed herein and previously[75]), the contribution of these cytokines to nutrient uptake and metabolism in the gut is not completely understood. In contrast, the contributions of IL-17A/F to epithelial barrier integrity and antimicrobial responses have been extensively defined[76,77]. Here we will focus largely on the role of the IL-22 pathway as an example of a type 3 cytokine-associated metabolic axis in the gut. Myeloid-derived cues, including IL-1β and IL-23, act locally to induce IL-22 production by innate and adaptive lymphocytes[2,4]. IL-22 is a critical determinant of systemic metabolic balance, as mice lacking IL-22 receptor gained more weight and became glucose intolerant and insulin resistance when fed a high fat diet, which could be rescued by administration of a IL-22 fusion protein[78]. ILC3-derived IL-22 exerts direct control of IEC metabolic function by modulating nutrient transporter programs in IECs. Mice fed a high carbohydrate diet exhibit a γδ T cell-mediated suppression of IL-22 from ILC3s, resulting in a switch towards a carbohydrate metabolism transcriptional program in IECs[79]. In similar findings, $CD4^+$ T cells were found to suppress IL-22 production and STAT3 signaling in both ILC3 and IEC in neonates as a response to microbial colonization following weaning to regulate intestinal metabolic tone, IEC lipid transporter expression and lipid absorption[80]. Loss of $CD4^+$ T cells resulted in persistent ILC3 activation and production of IL-22, which decreased gut lipid absorption and body fat mass[80]. ILC3s were also found to regulate the development of cDC2-like cells which conversely enhanced lipid uptake by sequestering IL-22 via secreted IL-22 binding protein, releasing IL-22-mediated suppression of IEC lipid transporters[81]. These circuits are disrupted during obesity, as HFD-fed mice display loss of IL-22-secreting ILC3s in the colon accompanied by increased epithelial permeability and systemic glucose intolerance[82]. Together, these findings suggest communication within a complex circuit of γδ T cells, $CD4^+$ T cells, ILC3s, cDC2s, and IECs determines levels of tonic IL-22 that control gut carbohydrate metabolism and lipid absorption in response to nutrient availability.

To align the metabolic tone of intestinal structural cells with regular feeding patterns, the metabolic and absorptive capacity of IECs is also regulated by intrinsic and extrinsic circadian clocks and via an ILC3 and IL-22-dependent circuit[83–88]. IEC-intrinsic *Nfil3* was found to imprint diurnal transcriptional activity within the gut, under the control of ILC3-derived IL-22, and in response to cues from the microbiota[87]. Mechanistically IL-22 was found to gate IEC circadian activity and *Nifl3* expression in a STAT3-dependent manner. Lack of IEC-intrinsic *Nfil3* led to resistance to high fat diet-induced obesity and metabolic disease that was associated with decreased expression of genes associated with lipid transport and metabolism, preventing lipid uptake from the intestinal lumen and into IECs[87]. Similarly, ILC3 production of IL-22 was found to be regulated by ILC-intrinsic expression of the circadian clock, and ILC3 lacking the clock gene *Bmal1* exhibited perturbations in expression of lipid transporters and metabolic genes and accumulated gonadal and subcutaneous fat[83]. These circadian ILC3 responses can be regulated by the central nervous system, specifically the suprachiasmatic nucleus in response to diurnal light cues[83], but also locally by enteric neuronal circuits in response to feeding events[84,89,90]. Moreover, several studies highlighted vasoactive intestinal peptide (VIP) release by enteric neurons in determining IL-22 release by resident ILC3 in response to feeding cues. Food consumption was demonstrated to rapidly induce VIP release to modulate IL-22 production[84,89,90], and

subsequently lipid absorption at the epithelial barrier[89]. Together these findings suggest that a neuronal component interacts with ILC3-IEC circuits to regulate circadian cycling of gut nutrient absorption.

While immune pathways can control the absorption of nutrients and response to diet in a direct manner, resident immune circuits of the healthy intestinal tract must also orchestrate immunologic tolerance to the commensal microbiota. The microbiota in turn provides important metabolic capacity to the mammalian host through the breakdown of complex dietary derived nutrients and acts to suppress inflammation and tissue damage by eliciting regulatory metabolites such as short chain fatty acids. Moreover, changes in microbial composition, or loss of barrier function and microbial translocation, have been extensively described to lead to worsen metabolic disease and obesity[73,91]. Disrupted homeostatic gut-resident circuitry can exacerbate perturbations to the microbiome, with studies implicating significant alterations in intestinal MAIT distribution and effector function in obesity and type 2 diabetes[92,93]. While clinical studies primarily suggest a loss of circulating MAITs, concurrent with enrichment of adipose-resident MAITs, contribute to metabolic dysfunction, studies of HFD-fed and ob/ob mice showed that obesity also results in increased inflammatory IL-17A-producing MAITs in the ileum[94]. Inflammatory MAITs contributed to loss of intestinal barrier integrity and changes in gut microbiome, while altered fecal microbial content due to increased MAITs in HFD-fed $V\alpha19^{+/-}$ was sufficient to confer increased gut leakiness and decreased ileal Tregs in obese wild-type mice receiving fecal matter transplant. Conversely, transfer of fecal matter from obese mice lacking MAITs resulted in decreased permeability and increased ileal ILC2 and ILC3. However, inflammatory MAIT-associated dysbiosis was not sufficient to induce insulin resistance. Thus, inflammatory MAITs in obesity likely act through both the gut and adipose as well as inter-organ crosstalk to produce systemic metabolic dysfunction. Future studies will be necessary to reveal the downstream regulators of MAIT-IL-17A-IEC gut permeability control, microbial homeostasis, and crosstalk with ILC3s.

In line with the complex interplay between diet, microbiota, and immune homeostasis, these immune axes are also sensitive to perturbations in nutrients. For example, mice fed a diet lacking Vitamin A exhibit a dramatic loss of ILC3 in the gut[95,96]. Similarly, the microbiota required to promote Vitamin A metabolism by intestinal myeloid cells maintain their niche via an immune regulatory loop. Microbial signals act to promote IL-1β by myeloid cells, which in turn activate ILC3 to produce GM-CSF[97]. ILC3 provision of GM-CSF in turn stimulates myeloid cells to produce retinoic acid from Vitamin A, as well as IL-10, to induce $FoxP3^{+}$ Tregs that ultimately maintain a tolerogenic state in the gut.

Tripartite circuits between myeloid cells, ILC3 and T cell subsets have increasingly been implicated in the maintenance of intestinal tissue homeostasis and suppression of inflammation against the diet or commensal microbiota. In addition to secreting IL-22 and IL-17A, ILC3 have increasingly been demonstrated to regulate barrier tissue health via other effector molecules. For example, ILC3 may additionally promote a regulatory environment in the gut via the provision of IL-2, which in turn supports intestinal Tregs which preferentially express the high affinity IL-2Ra[98], and antagonise inflammatory signals that drive epithelial cell death via production of heparin-binding epidermal growth factor (HB-

EGF)[99]. In addition to soluble factors, ILC3 are increasingly appreciated to fine-tune the priming, polarization, and activity of $CD4^+$ T helper cell subsets, most likely after primary antigen-presentation by classical antigen presenting cells such as DCs and macrophages. In this regard, a subset of $CCR6^+$ LTi-like ILC3 express major histocompatibility complex (MHC) II in the intestine and associated lymphoid where they are ideally co-localized within tissue microenvironments to modulate T cell responses[100–106]. In the absence of ILC3-intrinsic MHCII expression, $CD4^+$ T cells were found to become increasingly pro-inflammatory within the intestinal tract driven by response to the commensal microbiota, which resulted in colitis and contributed to progression of colorectal cancer[101,102,107]. ILC3 can further tune the adaptive immune response by providing auxiliary modulatory signals such as OX40L[108–111], or modulate interactions between DCs, T cells and B cells to regulate the induction of B cell responses and IgA responses to mediate tolerogenic control of the gut-resident microbiota[104,112–114]. Interestingly, recent advances have expanded on these findings to suggest a heterogeneous group of RORγt-expressing antigen presenting cells of both myeloid (cDC2 and Thetis cells) and lymphoid lineage (ILC3 and AIRE-expressing eTACs) act to induce Treg responses to the microbiota[115–120]. Together these findings reveal the layered nature of the regulatory immune system in the gut and highlight the resources dedicated by the host to maintaining mutualism with the commensal microbiota.

Adipose Tissue

Adipose tissue is an essential organ that regulates the storage of excess caloric energy in the form of lipid droplets, energy homeostasis and systemic insulin sensitivity. In mammals, adipose tissue mainly consists of both subcutaneous and visceral white adipose tissue (WAT) depots that are predominantly composed of white adipocytes, smooth muscle cells, endothelial cells, mesothelial cells, neurons, and fibroblast-lineage cells that are composed of a complex mixture of adipocyte progenitor and preadipocyte populations (hereafter called adipocyte progenitor cells). The primary function of these structural cells in the WAT is to coordinate signals influenced by systemic energy levels to regulate the balance of fatty acid uptake (lipogenesis) and fatty acid release (lipolysis), in addition to expansion or contraction of the total adipose tissue mass. As these topics have been recently reviewed in detail[121,122], we will not discuss adipose tissue metabolic function, structure, and adipocyte plasticity in greater depth.

Recent high parameter single-cell RNA sequencing studies from mice and human adipose tissues have significantly challenged the previously perceived simplicity of cellular composition of the WAT. These studies, in addition to mouse parabiosis and intravenous antibody labeling experiments, have shown that healthy lean WAT is composed of conserved populations of adipose-resident perivascular macrophages (PVMs), lipid-associated macrophages (LAMs), cDC1s, cDC2s, γδ T cells, Tregs, ILCs, and MAITs[123–128]. In this section, we will discuss our current knowledge of how these tissue-resident immune cell circuits collaborate to regulate critical functions of the WAT to promote systemic metabolic homeostasis and how these circuits are modified in settings of metabolic disease (Figure 3).

During ontogeny, yolk-sac derived myeloid progenitors and fetal monocytes populate peripheral mouse organs and become tissue resident macrophages[129,130]. In healthy lean adipose tissue of mice and humans, most adipose-resident macrophages have a transcriptional and cell surface phenotype consistent with PVMs[124,125,131,132]. Recent spatial sequencing analysis of the human WAT revealed that PVMs localize closely with adipocyte progenitor cells[123], suggesting that PVMs may form critical regulatory cell circuits with adipocyte lineage cells. Indeed, previous studies have shown that adipocyte lineage cells produce CSF-1 to maintain the CFSR-1$^+$ PVM niche[124,133,134], and adipocytes can release extracellular vesicles (EVs) containing lipids and mitochondria to regulate PVM function[135,136]. These results are supported by various mouse models of global macrophage deficiency or macrophage function which suggest that tissue-resident macrophages regulate weight gain, energy storage, and systemic metabolism[127,132,137–139]. Specifically, PVM-derived platelet-derived growth factor c (PDGFc) was found to promote WAT weight in newborn mice and mice fed a high fat diet through regulation of genes associated with lipid synthesis and storage in adipocytes, resulting in adipocyte hypertrophy[132]. However, whether this mechanism involves PVM to adipocyte progenitor signaling, or another responding cell type *in vivo* remains unclear. Single cell RNA sequencing analyses also suggest that human WAT PVMs express genes critical for efferocytosis (*MERTK*, *C1QA*)[124], and are likely the main cell type responsible for initiating the clearance of dead or dying adipocytes in the WAT during homeostasis. However, *in silico* trajectory analyses in obese human WAT and fate-mapping experiments in HFD-fed mice demonstrate that recruited monocytes can differentiate into TREM2$^+$ LAMs that express genes associated with lipolysis (*LIPA*, *LPL, PPARG*) to potentially “digest” cell membrane associated lipid from phagocytosed apoptotic cells[124,127]. Of course, further experiments will be necessary to more precisely define the cellular source of WAT LAMs during human obesity, and future experiments will be necessary to test the intrinsic functional capacity of adipose PVMs and LAMs for efferocytosis and lipolysis *in vivo*.

Studies from the past decade have also collectively revealed that a cell circuit consisting of adipose-resident ILC2s, PVMs, neurons and adipocyte progenitor cells regulate insulin sensitivity and adipose tissue homeostasis. Mechanistically, norepinephrine is produced in sympathetic neuronal circuits derived from the periventricular nucleus of the hypothalamus and prevertebral sympathetic ganglion. Norepinephrine-activated ADRB2-expressing adipocyte progenitor cells increase the expression of GDNF, which can activate RET$^+$ ILC2s to produce IL-13 and IL-5[140]. IL-13 acts as a critical upstream regulatory signal for PVM maintenance and function in addition to its direct effects on adipocyte progenitor cells[141–143]. IL-5 functions to enhance eosinophils survival and proliferation, leading to IL-4 production that regulates WAT PVM maintenance and function in addition to regulation of adipocyte progenitor cells[141,144,145]. Importantly, genetic loss of these pathways, or a reduction in WAT ILC2s or eosinophils in mice results in increased systemic metabolic dysfunction in mice fed a high fat diet[140,143–146]. However, whether these phenotypes are due to metabolic disruption in the adipose tissue versus other metabolic organs is difficult to dissect given the use of whole-body knockout mice. Given the critical importance of this adipose-resident cell circuit in WAT homeostasis and insulin sensitivity, future studies will be necessary to define additional ILC2 and PVM-derived signals that

can directly regulate adipocyte or adipocyte precursor function, and how this cell circuit is controlled by the sympathetic nervous system during feeding and fasting cycles, chronic stress, and fight or flight responses.

As adipocytes expand in response to increase dietary lipid storage, oxygen and essential nutrients become limiting, and stimulate enhanced vascularization of the adipose tissue to activate adipocyte progenitor differentiation to pre-adipocytes and mature adipocytes to expand the adipose tissue in a process called adipogenesis[122]. PVMs may serve as important regulators of adipogenesis by serving as sources of extracellular matrix components to provide a structural substrate for pre-adipocytes and newly formed adipocytes, in addition to expression of the pro-angiogenic factor VEGF-A[147,148]. In contrast, IL-17A derived from either WAT γδ T cells or MAITs has been shown to either inhibit or promote adipogenesis *in vivo*[149–151]. The discrepancies between these studies can likely be explained by the fact that IL-17A has complex role in regulation of systemic metabolism due to tissue and diet-dependent activities. For instance, while IL-17RA$^{-/-}$ mice weigh more than controls on a low fat diet[149], genetic deficiency of IL-17RA in ~50% of adipocytes leads to decreased weight gain during high fat diet feeding in mice[150]. These results suggest that WAT-resident sources of IL-17A may promote adipogenesis in the context of increased dietary fat intake. However, IL-17A-deficiency has been shown to limit lipid accumulation in the liver[75] and can lead to dysregulation of the commensal microbiota and resulting dysbiosis[152], suggesting that analysis of adipogenesis in whole body knockout mice has important caveats. Irrespective of these points, IL-17A has been shown to directly regulate the phosphorylation of PPARγ and can regulate the expression of genes associated with adipogenesis in adipocyte cell lines *in vitro*[150,153]. Thus, while IL-17A has been suggested to have a direct role in adipocytes, the role of IL-17A on adipogenesis *in vivo* is complex and will require more precise investigation to uncouple its tissue and diet-specific functions in systemic metabolism.

Subcutaneous WAT and brown adipose tissue (BAT) tissues undergo thermogenesis to increase energy expenditure in order to generate heat for the host after exposure to cold temperatures. This is achieved in part in the WAT by stimulating greater expression of uncoupling protein 1 (UCP-1) in white adipocytes to differentiate into beige adipocytes, as has been reviewed in detail previously[154]. In response to cold stress, IL-33 can be produced by endothelial cells, mesothelial cells, or adipocyte progenitor cells to increase adipose-resident ILC2 production of IL-13[142,155–157]. IL-13 in addition to IL-4 produced by eosinophils has been shown to directly promote the differentiation of PDGRα^{+} adipocyte progenitor cells into UCP-1^{+} beige fat cells[141]. In a separate proposed mechanism, IL-33-activated ILC2s can produce methionine-enkephalin peptides to directly increase the expression of UCP-1 in white adipocytes[158]. However, exogenous IL-33 treatment has also been recently shown not to increase UCP-1 expression in the WAT or BAT of adult mice[159], and IL-33 can directly regulate mitochondrial respiration of brown adipocytes in the absence of ILC2s[160]. These results suggest that further studies are necessary to more completely understand the role of these cell circuits in beige versus brown fat during thermogenesis. Similarly, the signals that regulate IL-33 production in structural cells during thermogenesis will require further investigation *in vivo*. However, it is tempting to speculate that sympathetic neuronal production of norepinephrine may also regulate the

IL-33 pathway, as this cell circuit is reported to be suppressed during cold exposure by experimentally induced sympathetic denervation in mice[161].

Although adipocytes have tremendous plasticity in their ability to accommodate excess energy as triglycerides, there are limits to their cell size. Once adipocyte size limits are surpassed because of chronic overnutrition during obesity, adipocyte-intrinsic stress and hypoxic responses occur and results in the production of inflammatory mediators and adipocyte cell death[162]. In obesity, chronic low-grade inflammation of the WAT is associated with systemic metabolic dysfunction that can lead to the development of type 2 diabetes[163]. The cellular composition of both the mouse and human WAT are dramatically remodeled during obesity, with increased density of cDC1s, cDC2s, MAITs, PVMs, $CCR2^+$ monocytes that can differentiate into inflammatory macrophages (IMs) and $CD9^+Trem2^+$ LAMs (collectively referred to as M1 in previous studies), and loss of ILC2s[124,125,127,158]. Visceral white adipose tissue ILC2s, MAITs and Tregs have been shown to be decreased during mouse models of obesity[94,158,164,165], supporting studies in healthy obese WAT predicting a loss of lean homeostatic communication networks *in silico*[124]. However, loss of WAT MAITs and Tregs during mammalian obesity is likely WAT depot specific, as healthy obese patients display an increase in subcutaneous WAT Tregs and MAITs[124]. While WAT-resident Tregs have been shown to have a metabolically protective phenotype during homeostasis in mice[164,166], likely through promotion of efferocytosis or inhibition of IL-1β processing in macrophages as shown in other mouse models[167,168], IL-10 derived from Tregs can drive systemic metabolic dysfunction during obesity through suppression of adipocyte beiging and decreased energy expenditure through IL-10R signaling in adipocytes[169,170]. Thus, further research will be necessary to determine the precise signals that lead to loss of WAT ILC2s during obesity, and to better uncouple the role of Tregs and Treg-derived signals in specific WAT depots and responder cells to regulate systemic metabolic dysfunction during obesity.

While the precise role of adipose-resident dendritic cell subsets remain unclear in the WAT during obesity[171], IMs largely drive chronic low grade inflammation in the WAT and contribute to systemic metabolic dysfunction in mice through production of TNF-α, IL-1β, and extracellular vesicles containing miRNAs[172–178]. IM differentiation is dependent on IFN-γ signaling in mice and humans, which is predominantly produced by adipose-resident ILC1 early during obesity and subsequently by infiltrating NK cells in response to increased levels of IL-12 and NKG2D ligands in the WAT[124,128,179,180]. $Trem2^+$ LAMs have been suggested to have a metabolically protective role during obesity, as $Trem2^{-/-}$ mice have increased metabolic dysfunction during diet-induced obesity[127]. However, given that Trem2 is required for efferocytosis by LAMs in the liver during NASH[56], the suggested protective effect of LAMs may be through limiting inflammation caused by defects in efferocytosis of dead or dying adipocytes during obesity. However, both IM and LAMs endogenously produce TNF-α and IL-1β in obese human WAT[124], which can inhibit efferocytosis through upregulation of CD47 on dead or dying cells or can signal directly in adipocyte lineage cells to decrease insulin signaling[178,181,182]. Thus, while inflammatory mediators produced by WAT macrophages, MAITs, and ILC1s have been shown to be detrimental to systemic metabolic homeostasis during obesity in mice, the relative contribution of adipose Tregs and LAMs to protective versus pathologic responses to systemic metabolic function will require further investigation.

Aging is associated with an increase in total fat mass accumulation and chronic low grade inflammation observed in various peripheral organs[183]. Inflammation of the WAT and systemic metabolic dysfunction are also associated with age in mice and humans[183,184]. While aged mouse WAT displays a similar increase in IMs as obesity[185], the frequency of PVMs is reduced[159]. Furthermore, aged PVM function in peripheral organs may be compromised by either induction of cellular senescence and acquisition of a pro-inflammatory senescence-associated secretory phenotype or aging-associated functional impairment in efferocytosis[186–188]. Similar to high fat diet-induced obesity in mice, aged WAT contains less ILC2s[159,189]. Aged WAT ILC2s were also found to be functionally deficient, with adoptive transfer of young ILC2s able to rescue aged mice from cold-stress induced mortality[159]. The proposed mechanism for decreased ILC2s was based on an observed increase in soluble IL-33R expression in aged WAT, likely limiting IL-33 bioavailability for ILC2 homeostasis. However, aged WAT shows an enrichment of IL-33R$^+$ Tregs that potentiate metabolic dysfunction in an unknown mechanism[190], and Tregs do not compete with ILC2s for available IL-33 in the WAT[159], suggesting that increases in soluble IL-33R may not fully explain the loss of ILC2s in the aged WAT. Together these studies suggest that key regulatory cell circuits consisting of WAT PVMs, Tregs, and ILC2s are functionally impaired during aging, and may contribute to aging-associated metabolic dysfunction.

Everything, everywhere, all at once: Inter-organ communication networks regulate systemic metabolism

The influence of tissue-resident immune circuits is not limited to regulating local metabolic activity. Increasingly, emerging evidence suggests that inter-organ crosstalk takes place alongside local communication, integrating resident immune networks across organs to coordinate systemic metabolism. Here, we discuss recent evidence supporting major immune-structural cell communication linking the adipose, liver, and intestinal tract.

The liver can modulate systemic glucose and lipid balance not only by regulating hepatocyte-intrinsic metabolism, but also by communicating with other tissues through the production of hepatokines. Of these hepatocyte-derived protein hormones, FGF21 is well studied. Recombinant FGF21 treatment has been shown to improve insulin sensitivity and glucose tolerance largely by targeting the adipose tissue, as adipocyte-specific loss of the FGF21 receptor abrogates the metabolic benefits of FGF21 treatment[191]. Mechanistically, FGF21 enhances the activity of PPARγ in the adipose tissue, modulating adipocyte lipolysis as well as the production of the adipokine adiponectin which exerts pleiotropic metabolic effects on peripheral tissues[191]. FGF21 production can be regulated by liver resident circuits in response to multiple stimuli. For example, bacterial components sampled from the gut microbiome can stimulate KC IL-1β production to suppress hepatocyte FGF21 production and subsequent lipolysis in the adipose tissue[192]. Accordingly, depletion of KCs resulted in hyperlipidemia and weight loss due to increased FGF21-driven lipolysis. Similarly, as discussed above, commensal bacteria immune circuits including IL-22 in the gut to regulate lipid uptake from the diet in the intestine[193], while changes to gut barrier integrity, commensal microbial composition or diet can precipitate inflammation in

the liver to alter metabolic function. These linked tissue-resident circuits may represent a method of coordinating lipid metabolism between the gut, liver, and adipose in specific bacterial contexts, perhaps in response to microbiota that specifically metabolize dietary fats or become enriched upon increased dietary fat availability. Conversely, KCs can stimulate hepatocyte FGF21 production during high fat diet-induced inflammation by increasing infiltration of circulating monocytes via KC-derived CCL2[194]. Heightened levels of MAPK-p38 signaling in infiltrating monocyte-derived macrophage were found to attenuate IL-12 production and maintain hepatic FGF21 expression, leading to increased brown fat thermogenesis in an attempt increase energy expenditure during increased dietary fat intake. While loss of myeloid p38 signaling inhibited FGF21 production and brown fat thermogenesis, overactive p38 activity promoted hepatic steatosis, suggesting that tight control of macrophage infiltration and activation is necessary for balancing systemic metabolic control against liver homeostasis.

In addition to regulating gut-intrinsic nutrient absorption and circadian rhythm, immune circuits in the gastrointestinal tract have been shown to coordinate multi-organ metabolic patterns. Diurnal patterns of microbial abundance in the gut mucosa correspond to circadian transcriptional patterns of intestinal epithelial clock genes and metabolic pathways[195]. These transcriptional rhythms are sensitive to diet-induced changes to microbiota, as mice fed HFD or transferred with HFD feces exhibited similar aberrations in normal intestinal circadian behavior[196]. Loss of commensal gut microbes disrupted these homeostatic rhythms systemically, as multiple studies show antibiotic-treated or germ-free mice exhibit disruptions in liver clock genes such as *Bmal1, Cry1, Rev-erba, Per1*, and *Per2* as well as altered transcriptional cycling of PPARγ-driven pathways involving amino acid and fat metabolism compared to mice bearing normal gut microbiome[195,197]. Moreover, modulation of the microbiota via the circadian production of the mucosal antibody IgA exerts immune pressure on the composition, rhythmicity and metabolic functions of the microbiota and can be dysregulated in mice fed HFD[198]. IgA also acts to determine nutrient uptake into systemic tissues such as the liver and adipose[199]. Disruptions in the microbial populations corresponded to abnormal circadian cycling of circulating molecules including free fatty acids, bilirubin, high density lipoprotein-bound cholesterol, and FGF21[197]. Furthermore, transfer of gut microbiota is sufficient to confer systemic metabolic changes associated with HFD. Fecal transplant of HFD mouse stool into chow-fed recipients induced increased fat mass and liver lipid content[200]. Analysis of liver *Bmal1, Rev-erba*, and *Per2* expression revealed shifts that were consistent with HFD mice without fecal transplant, and both HFD stool recipient and HFD mice exhibited drastic PPARγ-driven metabolic changes driving lipogenic pathway expression and hepatic lipid accumulation[200]. Dysregulation of the gut microbiota can also modulate cytokine-producing circuits in the liver, as the microbiome has been shown to regulate IL-17A-producing hepatic γδ T cells. During homeostasis, this was likely through commensal microbial production of lipid antigens presented to γδ T cells by $CD1d^+$ antigen presenting cells[18]. Alterations to the microbiome due to MAFLD or mutations in biliary transport proteins like *Mdr2* subsequently resulted in increased hepatic IL-17A production that exacerbated liver damage[201]. Increased hepatic IL-17A due to microbiome disruption would likely also increase hepatocyte lipid accumulation and insulin resistance, further worsening liver pathology. These gut-liver pathways suggest that

the type 3 intestinal immune circuits regulating barrier integrity and tolerance to commensal microbes are in fact critical for maintaining homeostasis of immune circuits that control liver metabolism.

In addition to its role in energy storage and release, the adipose tissue functions as a critical endocrine organ through the production of adipokines (e.g. leptin and adiponectin), lipids, metabolites, and EVs containing mitochondria and miRNAs that can regulate systemic metabolic homeostasis[136,173,202–206]. Recent studies have provided evidence that WAT macrophage-derived EVs can improve metabolic dysfunction when injected into obese mice by increasing insulin sensitivity in the WAT, muscle, and liver in an unknown mechanism[173]. In contrast, obesity associated changes in macrophage composition and activation changes the composition of miRNAs in macrophage-derived EVs, leading to miR-155-mediated suppression of insulin signaling through decreased PPARγ levels in peripheral tissues in recipient lean mice[173]. However, over 500 different miRNAs were detected in macrophage-derived EVs[173], suggesting that their effect on systemic metabolism is complex and will require further mechanistic investigation. During high fat diet feeding in mice, reduction of adipocyte iron levels through genetic deletion of the transferrin receptor in adipocytes can improve systemic metabolism by promoting iron uptake in the liver and limiting lipid uptake by enterocytes in the gastrointestinal tract[203]. Reduction of adipocyte iron levels led to both changes in the adipocyte secretome, composition of adipocyte-derived EVs, and the microbiome, suggesting that the underlying molecular mechanisms for this phenotype are likely complex. However, $CSFR1^+$ myeloid cells have recently been implicated in the control of adipocyte iron levels either through control of iron turnover in the WAT during high fat diet feeding or through direct control of iron release in adipocytes *in vitro*[207]. Although these results are derived from transgenic mice with overexpression of MitoNEET (an iron-binding outer mitochondrial membrane protein) in $CSFR1^+$ myeloid cells, WAT myeloid cell-adipocyte crosstalk through regulation of intracellular iron levels in adipocytes may serve as a critical feedback mechanism to the gastrointestinal tract in order to prevent nutrient overload in adipocytes. Of course, future studies will be necessary to fully understand how immune-structural cell crosstalk between metabolic organs can regulate systemic metabolism during homeostasis and disease (Figure 4).

Concluding Remarks

High-parameter single cell sequencing of mouse and human tissues has fundamentally altered the way we approach biological questions. Using single-cell sequencing datasets combined with computational tools to predict cell-cell interactions, unbiased and clinical evidence-based hypotheses can be generated for direct functional testing *in vitro* and *in vivo*[208–210]. While some studies have harnessed these tools to characterize cellular circuits involved in processes like dementia and cancer[211,212], future studies and analyses of existing datasets will be invaluable to address open questions in systemic tissue immunometabolism. For example, activating ligands upstream of ILC2s, γδ T cells, and MAITs in the liver have yet to be defined. Conversely, *in silico* cellular communication networks may also reveal shifts in signaling nodes from tissue-resident cells, such as KCs during homeostasis, toward infiltrating circulating immune cells that may provide more critical proinflammatory signals upstream of changes in gene expression during disease. Furthermore, the complete

molecular mechanisms that regulate adipose-resident cell circuits such as PVM-mediated adipogenesis, PVM or LAM-mediated efferocytosis of adipocyte lineage cells, and WAT beiging remain incomplete.

Future studies will also be required to clarify species-specific immune cell functions. For example, while extensive mouse studies reflect the importance of ILC3s in gut integrity and homeostasis, similar experiments using human tissue will be necessary to parse the differential contributions of human ILC3s versus Th17 to these type 3 circuits. While we have limited our discussion to circuits involving cell types conserved between mouse and human, these comparisons can be confounded by the interspecies differences such as species-specific transcriptional signatures in ILCs. Further clarification of these processes will depend on direct study of these rare cell types in humans to determine how mouse studies can be translated to treatment modalities for human metabolic diseases. Furthermore, the precise systemic metabolic effects of certain cytokines remain elusive. Increased IL-17A signaling is broadly detrimental to host metabolism, yet IL-17RA-null mice paradoxically accumulate more fat mass during development. Similarly, IL-10 production from Tregs can be protective or detrimental to host metabolism depending on certain contexts. For instance, Treg-derived IL-10 can promote the tolerance of commensal microbiota in the gut and liver, while Tregs can also exacerbate liver fibrosis and metabolic dysfunction in the aged adipose tissue. These results suggest that metabolic responses to the local cytokine milieu are complex and tissue-specific, as well as indicating a particular role for certain tissue-resident cytokine circuits in modulating local structural cell metabolism rather than exerting systemic control.

Beyond the local cytokine environment, the balance of metabolic control between central neuronal and endocrine signals versus local immune circuits remains to be examined deeply. Systemic metabolism is heavily determined by neuroendocrine feedback, but the relative contribution of immune regulatory circuits versus structural cells directly responding to neuroendocrine signals remains to be determined. However, neuroendocrine signaling likely represents a key mode of systemic metabolic integration between disparate organs in the body. As immune cells can respond to a repertoire of hormones and neurotransmitters, central control of metabolism must balance both direct signaling with structural metabolic cells as well as modulation of tissue-resident immune circuits[213–218]. It is possible that tissue-resident circuits in metabolic organs serve to fine-tune the broad systemic metabolic state established by central regulatory molecules, offering an additional layer of regulation in response to perturbations to metabolic homeostasis of the organism. In the future, *in vivo* models of cell-specific receptor knockouts will be necessary to parse the direct and indirect hormonal and neuronal signals that maintain metabolic function considering these tissue-resident immune regulatory cell circuits.

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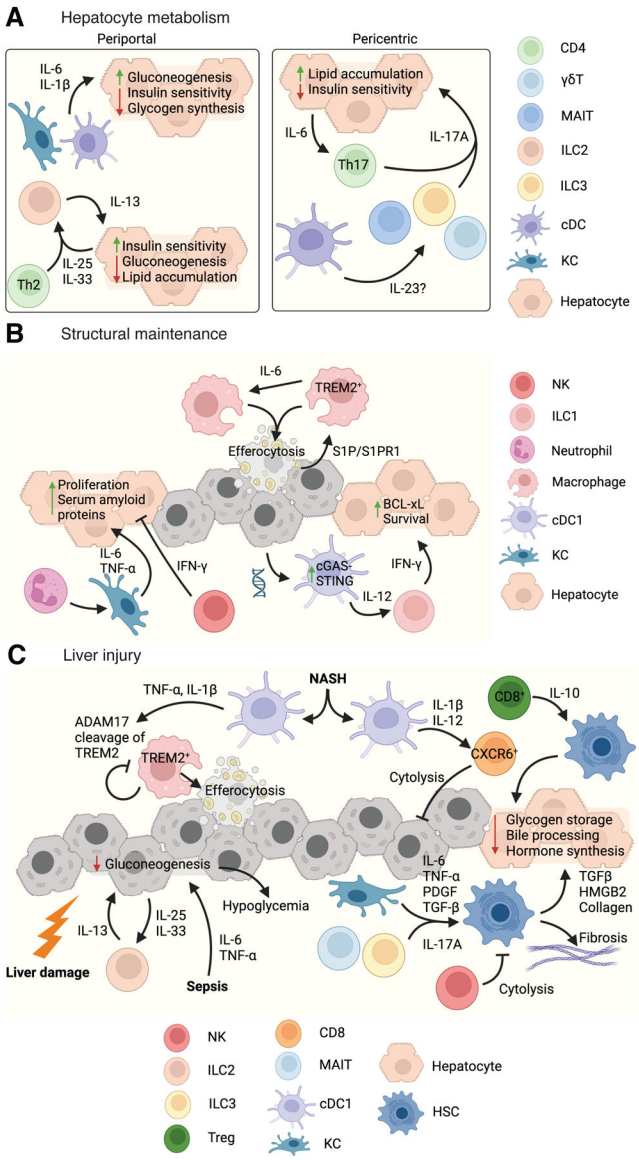

Figure 1. Liver-resident immune circuits regulate homeostasis and disease.

a) Hepatocytes and liver-resident immune cells are spatially heterogeneous in function. In the periportal zone, hepatocytes display higher levels of gluconeogenic enzymes and decreased glycogen synthesis. which may be controlled by IL-6 and IL-1β from KCs or cDCs, as well as IL-13 secretion from ILC2s. ILC2 activation may be mediated by hepatocyte or Th2 cell-derived IL-25 or IL-33. In lipogenic pericentric hepatocytes, lipid accumulation can be regulated by IL-17A from MAITs, γδT cells, or ILC3s, potentially by cDC-derived IL-23. Activated hepatocytes can secrete IL-6 and stimulate IL-17A from Th17 cells, generating a positive feedback loop. **b)** Hepatocyte integrity is maintained by immune cell regulation of proliferation, efferocytosis, and survival. Neutrophil-activated KCs secrete IL-6 and TNF-α to promote hepatocyte proliferation and serum amyloid protein production to support liver regeneration, which is inhibited by NK-derived IFN-γ. Apoptotic hepatocytes are cleared by $TREM2^{+}$ macrophages, which are activated by

S1P-S1PR interactions with dying hepatocytes. Activated efferocytotic macrophages may also secrete IL-6 to induce efferocytotic capacity in neighboring phagocytes. Hepatocyte DNA released after liver injury may also be detected by cGAS-STING activation in cDC1, resulting in cDC1 IL-12 production and stimulation of IFN-γ from ILC1s to promote hepatocyte pro-survival signaling. **c)** Disrupted immune cell-hepatocyte circuits result in metabolic imbalance during liver injury. In NASH, hepatic cDC1s produce TNF-α and IL-1β to upregulate ADAM17-mediated cleavage of TREM2 on efferocytotic macrophages, inhibiting clearance of lipid-laden apoptotic hepatocytes. cDC1s also stimulate killing of hepatocytes via autoreactive $CXCR6^{+}$ $CD8^{+}$ T cells. Liver damage induces inflammatory cytokines such as ILC2-derived IL-13 or systemic IL-6 and TNF-α during sepsis to inhibit hepatocyte gluconeogenesis, leading to systemic hypoglycemia. Additionally, HSCs are activated by cytokines produced by KCs, MAITs, ILC3s, and Tregs to secrete extracellular matrix and stimulate metabolic changes in hepatocytes to decrease glycogen, hormone, and bile synthesis.

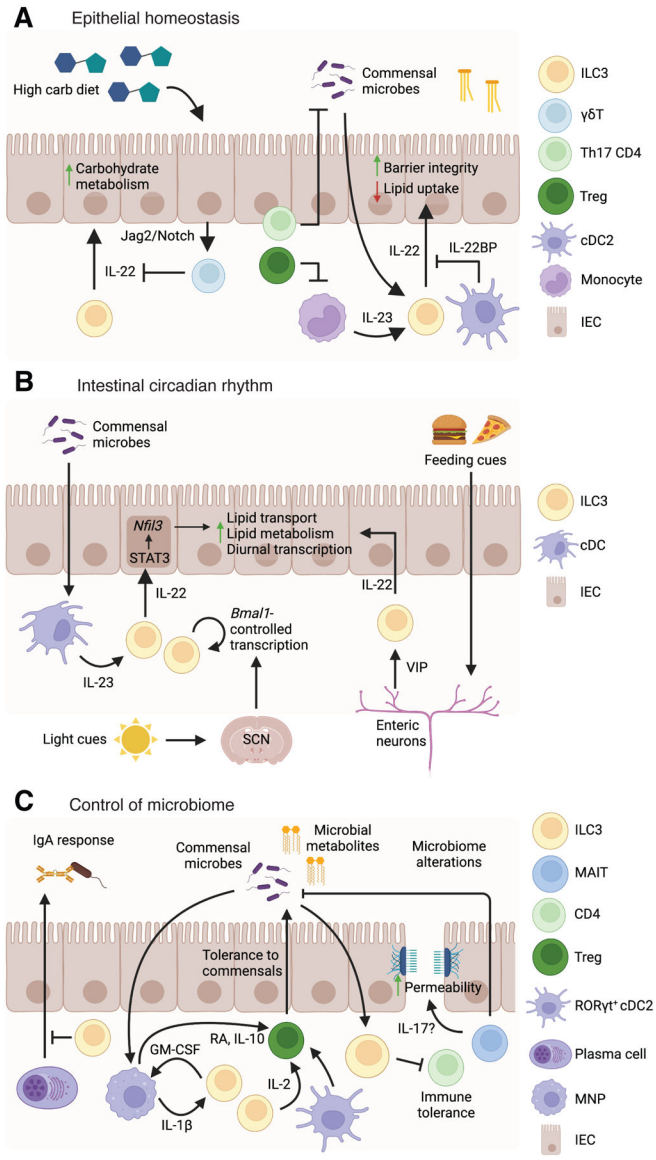

Figure 2. Gut regulation of intestinal barrier homeostasis and microbiota.

a) Dietary composition can activate Jag2-Notch interactions between intestinal epithelial cells (IECs) and γδT cells to inhibit IL-22 production from ILC3s. Decreased IL-22 leads to increased carbohydrate metabolism in IECs. ILC3 production of IL-22 can be stimulated by commensal microbiota or monocyte-derived IL-23 to inhibit expression of IEC lipid transporters and maintain barrier integrity. During dietary changes upon weaning, Tregs inhibit monocyte-derived IL-23 while Th17 cells regulate microbiota-induced activation of ILC3s, leading to inhibition of ILC3-derived IL-22 and increased lipid uptake. cDC2-derived IL-22 binding protein (IL-22BP) can also control local IL-22 levels by sequestering free IL-22, thereby increasing intestinal lipid uptake. **b)** ILC3-derived IL-22 maintains diurnal metabolic activity in IECs in response to microbes, light cues via the suprachiasmatic nucleus (SCN), feeding cues, and vasoactive intestinal peptide (VIP) from enteric neurons. Both *Nfil1*-driven IEC and *Bmal1*-driven ILC3 intrinsic circadian

signaling are required for metabolic homeostasis. **c)** Immune circuitry maintains tolerance to gut microbiota. Activated mononuclear phagocytes (MNPs) secrete IL-1β to stimulate GM-CSF production from ILC3s, signaling back to MNPs to produce retinoic acid (RA) and IL-10 to activate Tregs. RORγt^+ cells such as cDC2s also maintain Treg function to support local immune tolerance. ILC3s also directly activate Tregs via IL-2 production, supporting immune tolerance to commensal microbes, as well as inhibiting plasma cell secretory IgA responses against commensal microbes. Presentation of microbial antigens by $MHCII^+$ ILC3s to $CD4^+$ T cells in the absence of costimulation also inhibits immune response to commensals. Overabundance of MAITs can disrupt gut microbial homeostasis by increasing epithelial permeability and altering microbial content, possibly via IL17 secretion.

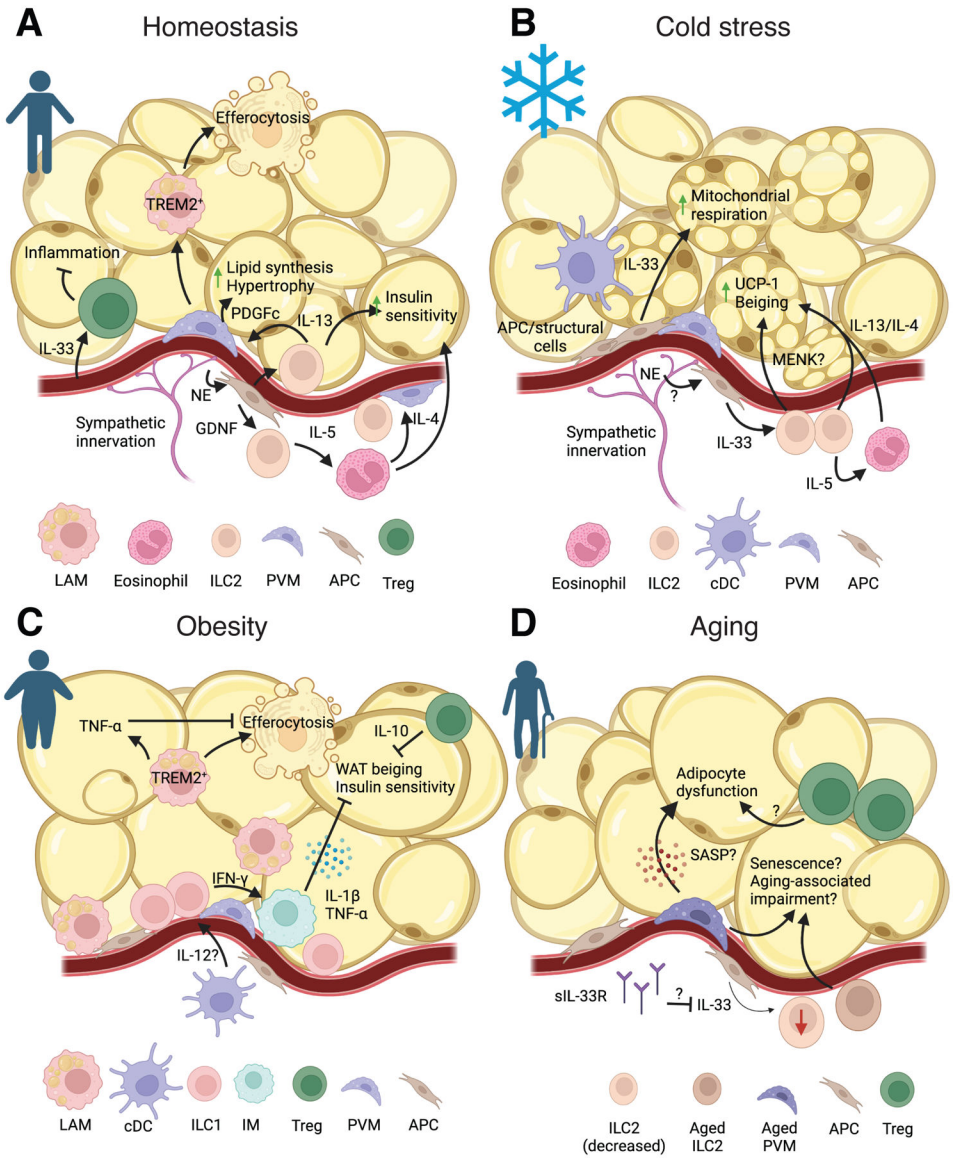

Figure 3. Adipose-resident circuits in homeostasis, cold stress, and obesity and aging.

a) In homeostasis, norepinephrine (NE) from the sympathetic innervation can activate adipocyte progenitor cells (APCs) to secrete GDNF, activating adventitial ILC2s to produce IL-13 and IL-5. ILC2-derived IL-13 as well as IL-4 from recruited neutrophils both directly support perivascular macrophage (PVM) maintenance and enhance adipocyte insulin sensitivity. PVMs additionally secrete PDGFc to support adipocyte growth and metabolism, and likely differentiate into TREM2^{+} lipid-associated macrophages (LAMs) to efferocytose apoptotic adipocytes. IL-33-activated Tregs also serve to suppress local inflammation under homeostatic conditions. **b)** Under cold stress, APCs and other structural cells secrete IL-33 to activate ILC2s and directly increase adipocyte mitochondrial respiration. ILC2-derived IL-5 recruits neutrophils, and both secrete IL-13 and IL-4 to support upregulation of uncoupling protein 1 (UCP-1) and beiging of white adipocytes. ILC2s may also secrete methionine-enkephalin peptides (MENK) to directly support beiging of white adipose. **c)**

In obese WAT, ILC1s are activated by IL-12 potentially from resident cDCs to produce IFN-γ, activating inflammatory macrophages (IMs). IM-derived TNF-α and IL-1β as well as IL-10 from Tregs inhibits WAT beiging and insulin sensitivity. Efferocytosis is also potentially disrupted in TNF-α- stimulated TREM2^{+} LAMs. **d)** Aged WAT displays decreased ILC2s, possibly due to sequestering of IL-33 by soluble IL-33 receptor, as well as the presence of senescent or dysfunctional aged ILC2s and PVMs. Aged PVMs may impair adipocyte function via acquisition and release of senescence-associated secretory phenotype (SASP) proteins. Increased Tregs may also augment adipocyte dysfunction by unknown mechanisms.

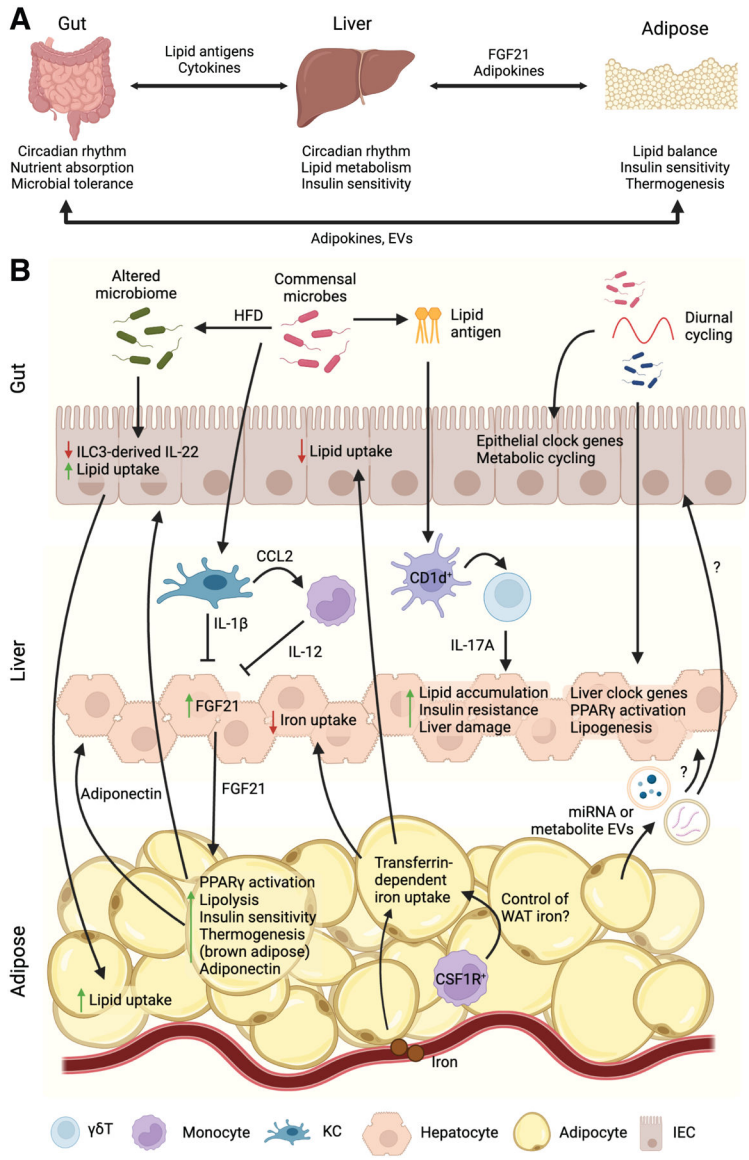

Figure 4. Inter-organ communication between immune-resident circuits.

a) Broadly, the gut, liver, and adipose communicate through circulating cytokines, lipid antigens, and adipokines and hepatokines to regulate overall systemic metabolism and circadian rhythms. **b)** Gut microbes directly modulate intestinal epithelial lipid uptake via IL-22 circuits as well as modulating hepatocyte FGF21 production through KC IL-1β production and monocyte IL-12. FGF21 has pleotropic effects on adipose tissue, broadly enhancing metabolic homeostasis. FGF21-stimulated production of adiponectin by the adipose additionally exerts varied effects on peripheral tissue metabolism. High fat diet (HFD)-induced alterations to the microbiome lead to decreased ILC3-derived IL-22 in the intestinal epithelium, increasing lipid uptake in both the gut and adipose tissue. Presentation of gut-derived microbial lipid antigens by $CD1d^{+}$ hepatic DCs to γδT cells stimulates IL-17A production detrimental to hepatic metabolic health. Intestinal lipid uptake may also be modified by WAT regulation of iron. Increased WAT iron uptake, modulated by

$CSF1R^+$ myeloid cells in the adipose, results in decreased hepatic iron uptake and intestinal lipid absorption. Adipose-derived EVs containing metabolites and miRNAs also influence peripheral metabolism in the liver and gut through unknown mechanisms. Finally, gut sensing of diurnal microbial cycles regulates both intestinal and hepatic circadian rhythms and metabolism.