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Review

Systemic Immunometabolism: Challenges and Opportunities

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SUMMARY

Over the past 10 years, the field of immunometabolism made great strides to unveil the crucial role of intracellular metabolism in regulating immune cell function. Emerging insights into how systemic inflammation and metabolism influence each other provide a critical additional dimension on the organismal level. Here, we discuss the concept of systemic immunometabolism and review the current understanding of the communication circuits that underlie the reciprocal impact of systemic inflammation and metabolism across organs in inflammatory and infectious diseases, as well as how these mechanisms apply to homeostasis. We present current challenges of systemic immunometabolic research, and in this context, highlight opportunities and put forward ideas to effectively explore organismal physiological complexity in both health and disease.

INTRODUCTION

In a seminal experiment, Urey and Miller demonstrated that simple metabolite precursors and conditions resembling the atmosphere of the early Earth can generate amino acids and RNA nucleobases (Ferus et al., 2017; Miller, 1953). Metabolites are biochemical intermediates or end-products of cellular metabolic pathways, represent cornerstones of life, and, as molecular basis of metabolism, are considered a driving force of evolution. Anabolic processes build up biomass, whereas catabolic processes generate energy and redox equivalents to catalyze thermodynamically unfavorable reactions. Next to their bioenergetic and biosynthetic roles, metabolites are key communication signals that are evolutionarily conserved from prokaryotes, including quorum sensing between bacteria, to complex multicellular eukaryotic organisms. Extracellular cues may shift the metabolic homeostasis of cells under certain environmental conditions. Such signals are sensed by central pathways like mTOR, which integrate available environmental information including nutrients and other stimuli to coordinate metabolic adaptations and proliferation of cells (Saxton and Sabatini, 2017). These environment-driven metabolic adaptations play particularly important roles for the immune system. The organism is estimated to spend up to 30% of its basal metabolic rate for the activation of the adaptive immune system alone (Muehlenbein et al., 2010; Straub et al., 2010). This demonstrates its evolutionary value for multicellular organisms to control pathogens, tissue repair, and many other vital functions (Bantug et al., 2018; Pearce and Everts, 2015).

The chemist Emil Fischer made fundamental discoveries in the field of carbohydrates and published the structures of glucose and its isomers in 1891 (Fischer, 1891). Three decades later, biochemist Hans Krebs described the first metabolic cycle in 1932, while physiologist Otto Warburg made seminal findings

about the peculiar metabolism of cancer cells (Krebs and Hensley, 1932; Warburg, 1956; Warburg et al., 1927). Around two decades later, Otto Warburg noted that increased cellular glycolysis was not only a hallmark of tumor cell development, but also for leukocyte activation (Warburg et al., 1958). Half a century of seminal discoveries about the immune system later (Doherty and Robertson, 2004), immunologists rediscovered metabolic adaptations as critical initial steps for immune responses (Febbraio et al., 2004; Hotamisligil et al., 1993; Pearce et al., 2009; Wieman et al., 2007). This eventually resulted in the establishment of the thriving research field of immunometabolism. Research in this field studies the metabolic control of the immune-regulated processes including infectious or tumorigenic diseases, tissue regeneration, and how these immune responses influence metabolic organs (Buck et al., 2017; Eming et al., 2017; Norata et al., 2015). Initial *in vitro* studies were instrumental to unravel cytokine-driven reprogramming of the metabolic network and the resulting switch from the reliance on mitochondrial respiration toward glycolysis in activated macrophages and dendritic cells (Jha et al., 2015; Pearce and Everts, 2015; Pearce and Pearce, 2013; Russell et al., 2019). Similarly, engagement of cognate antigen and T cell receptor (TCR) signaling alters metabolism in naive T cells, which is a prerequisite for subsequent rapid clonal expansion and effector function acquisition (Bantug et al., 2018; Sinclair et al., 2013). *In vitro* studies showed that T cell proliferation relies on increased oxidative phosphorylation (OXPHOS), glycolysis, and Warburg metabolism (Bantug et al., 2018; Chapman et al., 2020; Warburg et al., 1927). Glycolytic reprogramming of T cells also directly affects effector cytokine production (Chang et al., 2013), and multiple studies have explored the contribution of OXPHOS, fatty acid oxidation (FAO), and glycolysis on T cell memory formation (Klein Geltink et al., 2017; Pearce et al., 2009; Phan et al., 2016; Raud et al., 2018).



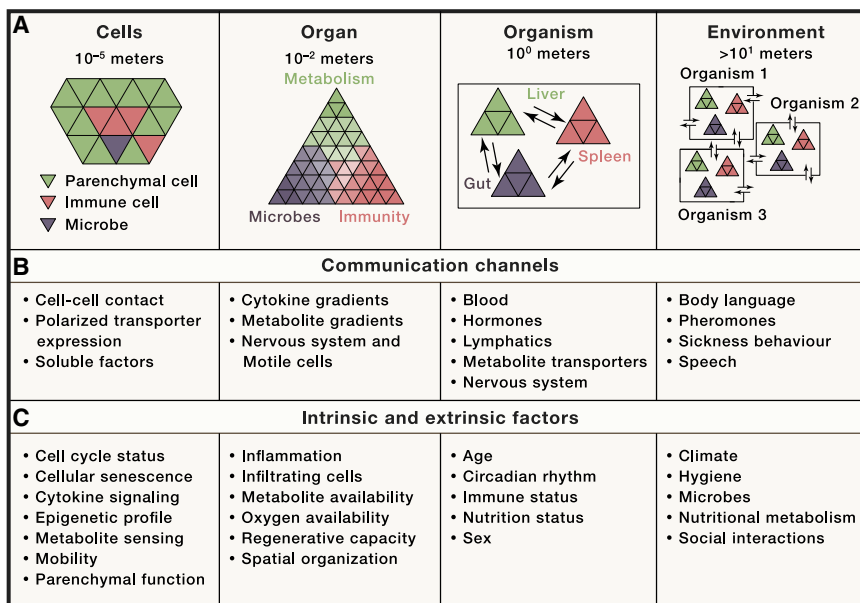


Figure 1. Communication Levels of Systemic Immunometabolism

(A) Organizational units of higher organisms ranging from the cellular level, to organs, to the whole organism, up to the environment and inter-individual relationships.

(B) Communication channels that are critically involved for communication within and/or between the individual organizational units.

(C) Intrinsic and extrinsic factors shaping the identity of the described organizational units.

bolic processes across organs and with the microbiota (Figure 1A). The crosstalk between immune and metabolic processes is conserved across the animal kingdom. A good example is the fat body in *Drosophila* that coordinates processes that are mirrored by the crosstalk between the immune system, adipose tissue, and liver in vertebrates (Beller et al., 2010; Hotamisligil, 2017; Padmanabha and Baker, 2014). This supports the notion that most organs, even if

Cell culture systems are indispensable for breaking new mechanistic grounds, but they cannot recapitulate the vast complexity of the organism. This is reflected by a recent study highlighting the differences between metabolic reprogramming of *in vitro*-activated T cells compared to their infection-activated counterparts *in vivo* (Ma et al., 2019). Metabolic parameters such as organ-specific pH, partial pressure of oxygen, nutrient gradients, and disease-dependent changes of the metabolic environment are not considered by standard cell culture conditions, but clearly influence T cell activation (Buck et al., 2017; Geiger et al., 2016; Johnson et al., 2018; Lercher et al., 2019; Ma et al., 2017; Murray, 2016; Nakaya et al., 2014; Roy et al., 2020; Sinclair et al., 2013). Similarly, tumor-associated fibroblasts have a high affinity for glucose and deplete the tumor microenvironment from glucose, resulting in metabolic competition that impairs the function of infiltrating tumor-specific T cells (Chang et al., 2015). Next to glucose, numerous other extracellular metabolites, including amino acids, may modulate T cell function in the tumor microenvironment or during chronic viral infection (Geiger et al., 2016; Lercher et al., 2019; Murray et al., 2015).

In this review, we will discuss recent advances and technological approaches to study immune-metabolic crosstalk at the organismal level, in between organs, and within tissues and provide examples of how these communication networks are shaped by pathogenic and/or commensal microbes. We conclude by providing examples of how research of systemic immunometabolism revealed therapeutic opportunities to target essential mechanisms at the tissue and organismal level.

THE MANY COMPONENTS OF SYSTEMIC IMMUNOMETABOLISM

Organs and specialized tissue-resident cells evolved to compartmentalize metabolic processes. This was accompanied by co-evolution of communication systems to coordinate meta-

specialized on metabolic tasks, may critically impact systemic immune responses.

Recent advances in single-cell sequencing technology vastly expanded our understanding of cellular heterogeneity of organs and how this correlates with organ-specific immune responses and composition (Aizarani et al., 2019; Han et al., 2020; Jaitin et al., 2019; Krausgruber et al., 2020; Stubbington et al., 2017; Zhao et al., 2020). For inter-organ coordination, mammals evolved blood, lymph, and nervous systems as communication channels (Figure 1B). Distal communication is achieved by tissue-specific sensing and production of soluble messenger molecules including hormones, neurotrophic peptides, cytokines, and metabolites (Chu et al., 2020; Hotamisligil, 2017; Krauss et al., 2012; Perry et al., 2015; Priest and Tontonoz, 2019). On a cellular level, metabolic processes are spatially organized, and intracellular nutrient distribution is important for organelle communication and function (Pareek et al., 2020; Sdelci et al., 2019). Tissue-specific and context-dependent expression of metabolite transporters and receptors form an additional versatile layer of inter-organ communication. While we are yet to de-orphanize many of these proteins, it seems clear that this will open a new era of increased understanding of how pathophysiological processes involving multiple organs are coordinated across cellular membranes (César-Razquin et al., 2015). Thus, such communication networks orchestrate and coordinate responses to environmental cues or immunological challenges such as infection-associated sickness behavior with symptoms of fever, lethargy, fatigue, social withdrawal, and/or anorexia (Hart, 1988). Organism-wide response programs are largely conserved across species, albeit there are differences such as febrile responses to viral infection between mice and humans (Dybing et al., 2000; Hart, 1988). These immune-metabolic programs are driven by cytokine signaling in the brain and impact pathogen clearance and disease-tolerance mechanisms (Ayres, 2020a; Dantzer et al., 2008; Hart, 1988). In case of bacterial

infection, reduced food intake and infection-associated anorexia can be beneficial and promote survival, whereas it aggravates pathology during influenza infection (Wang et al., 2016). A recently identified regulator of anorectic behavior is the neurotrophic peptide GDF15, which signals through its receptor GFRAL in the hindbrain (Borner et al., 2020; Johnen et al., 2007; Tsai et al., 2016, 2018). GDF15 is expressed by a wide range of cells, including macrophages (Fairlie et al., 1999; Hsu et al., 2017; Patel et al., 2019), and was shown to modulate systemic metabolism (Luan et al., 2019; Santos et al., 2019). Conversely, bacteria may interfere with anorexia-related response programs to promote host survival and ensure prolonged pathogen dissemination (Rao et al., 2017). The underlying endogenous regulation of feeding behavior during infection is thought to redistribute energy and balance the energetic demands of the activated immune system with the organism's core functions of maintenance, growth, and reproduction programs, known as the "life history programs" (Ganeshan et al., 2019; Muehlenbein et al., 2010; Schieber and Ayres, 2016; Straub et al., 2010). Related evolutionarily conserved mechanisms have been reviewed elsewhere (Wang et al., 2019).

Nutritional metabolism is a key determinant of body composition, systemic metabolism, and immune responses and linked to numerous diseases. Unbalanced diet leads to inflammation and influences systemic immune responses and co-morbidities (Cornier et al., 2008; Marcos et al., 2003). This is probably most extensively studied in obesity-associated chronic inflammation, metabolic syndrome, and type 2 diabetes (T2D) (Hotamisligil, 2017). Poor metabolic health is a risk factor for developing a more severe course during infectious diseases. Concurrently, diabetes and hypertension are among the most important risk factors for coronavirus disease 2019 (COVID-19) in the global SARS-CoV-2 pandemic (Ayres, 2020b; Lu et al., 2020; Shen et al., 2020; Zhou et al., 2020).

The adipose tissue is an important immune cell niche during homeostasis and an important immune-metabolic communication hub in metabolic syndrome (Hotamisligil, 2017; Schipper et al., 2012). Diet-induced obesity leads to the accumulation of a broad range of immune cells in the adipose tissue that can contribute to systemic metabolism (Aouadi et al., 2013; Jaitin et al., 2019). Particularly, the recruitment of macrophages in the adipose tissue augments systemic glucose intolerance via pro-inflammatory cytokines like TNF α (Aouadi et al., 2013; Weisberg et al., 2003). Adipocytes instruct tissue-resident macrophages toward intracellular lipid accumulation and degradation and thus contribute to overall adipose tissue lipolysis (Xu et al., 2013). Recent single-cell analyses highlighted a role of *Trem2*⁺ lipid-associated macrophages in counteracting adipocyte hypertrophy during obesity. Yet, it remains elusive whether macrophage-intrinsic *Trem2* is necessary and sufficient to ameliorate obesity-associated metabolic syndrome (Jaitin et al., 2019).

Beyond the adipose tissue, nutritional metabolism broadly affects immune responses in malignant and infectious diseases. Diet-associated obesity and increased availability of extracellular lipids rewires cellular metabolism of natural killer cells, leading to impaired anti-tumoral activity in animals and patients (Michelet et al., 2018). Ketogenic diet improves survival in a model of influenza infection in the presence of $\gamma\delta$ T cells in the lung, boosting protective mucus production by airway epithelial cells (Goldberg

et al., 2019). Perturbing nutritional metabolism by intermittent fasting promotes localization of pro-inflammatory monocytes (Jordan et al., 2019) and memory T cells (Collins et al., 2019) to the bone marrow, a nutrient-rich immune cell niche, and increases disease tolerance during infection (Ganeshan et al., 2019). Dietary restriction of the amino acid methionine proved beneficial in a model of autoimmune disease by repressing epigenetic remodeling and effector functions of T_H17 via intracellular S-adenosyl-methionine (SAM) levels (Roy et al., 2020). Additionally, dietary deficiency of glycine and serine blunts cytotoxic CD8 T cell responses, likely via reduced cell-intrinsic one carbon metabolism and *de novo* nucleotide synthesis (Ma et al., 2017). This corroborates previous *in vitro* studies that highlighted increased amino acid dependencies of activated T cells (Geiger et al., 2016; Murray, 2016; Van de Velde et al., 2016). Of note, pathogens themselves may trigger systemic metabolite changes and by that effect, immune responses (Balmer et al., 2016; Qiu et al., 2019), and vice versa, circulating immune cells can actively shape systemic metabolite levels (Fan et al., 2019; Miyajima et al., 2017). These cases exemplify that nutritional metabolism is an important regulator of homeostasis of systemic metabolism that shapes immunity and vice versa. Yet, the cellular responders and molecular basis for diet-induced effects, particularly during infectious diseases, remain to be fully understood.

Generally, studies of systemic immunometabolism in model organisms like mice are influenced by several fundamental metabolic cross-species variances. These include differences in surface-area-to-volume ratio, resting heart rate, relative food intake, or basal metabolic rate between mice and humans (Speakman, 2013). Additional confounding factors, which may be controlled for in experimental models, include sex, age, dietary habits, circadian rhythm, and the microbiome (Figure 1C) (Druzd et al., 2017; Dyar et al., 2018; Ferraro et al., 1992; Houtkooper et al., 2011; Lazzer et al., 2010; Rothschild et al., 2018; Weger et al., 2019).

Next, we will focus on selected metabolically active organs such as the liver, adipose tissue, and the gut to showcase how inflammation-induced local metabolic changes can affect systemic immunometabolism.

IMMUNOMETABOLISM BETWEEN ORGANS

Adipose tissue is connective tissue primarily formed by adipocytes and serves as a major energy store for the organism (Spalanzani et al., 2019). Adipocytes contain large lipid droplets and are actively involved in many systemic metabolic pathways including lipid metabolism and the regulation of glucose homeostasis. They communicate to other organs including the liver and muscle and contribute to systemic metabolism via secretion of fatty acids, adipokines, lipokines, and cytokines (Cao et al., 2008; Cawthorn and Sethi, 2008; Scheja and Heeren, 2019). A major research breakthrough was the revelation that adipose tissue itself can secrete the pro-inflammatory cytokine TNF α to modulate systemic glucose metabolism (Hotamisligil et al., 1993). This was also one of the first molecular studies to link metabolic and immunological processes, providing a pillar for the emerging research field of immunometabolism.

The adipose tissue is centrally involved in cachexia, a multifactorial syndrome leading to uncontrolled loss of body mass that is

accompanied by severe prognostic implications for patients suffering from cancer, chronic infections, and inflammatory diseases (Baracos et al., 2018). In this syndrome, weight loss is only partially mediated through anorexia (Ayres and Schneider, 2009; Murray and Murray, 1979; Wang et al., 2016). In general, pro-inflammatory signaling pathways trigger metabolic changes, resulting in a negative energy balance and a shift toward catabolism in a broad range of organs, including the adipose tissue. Specifically, cytokines like $TNF\alpha$, IL-6, and interferons are associated with cancer-associated cachexia, whereas pathogen-specific CD8 T cells are essential for cachexia in a model of chronic viral infection (Aner and Langin, 2014; Baazim et al., 2019; Cawthorn and Sethi, 2008; Fearon et al., 2012; Patel and Patel, 2017). Adipose tissue depletion is accompanied by release of energy in the form of increased free fatty acids (FFAs) into the circulation. FFAs directly contribute to energy distribution when they are taken up by other organs and fuel ATP production via oxidation and the tricarboxylic acid (TCA) cycle, or they may be re-esterified and stored as lipid droplets. FFAs can also instruct metabolic reprogramming in receiving tissues like the liver, where they facilitate a shift of glucose utilization and by that, shape systemic metabolism (Rosen and Spiegelman, 2006). During diet-induced T2D, macrophage-derived IL-6 boosts lipolysis in adipose tissue, which leads to increased glucose production in the liver via increased FFA-derived acetyl-CoA in hepatocytes (Perry et al., 2015). Apart from FFAs, the adipose tissue can communicate with distal organs via exosomal miRNAs, and, for example, modulates production of the hepatokine FGF21, a well-known regulator of systemic glucose metabolism (Thomou et al., 2017).

Such metabolic crosstalk between adipose tissue and liver highlights the communication networks to facilitate labor distribution across the organs within an organism. The liver evolved as a major hub for glucose, fatty acid, and amino acid metabolism and, as such, controls serum levels and homeostasis of the respective metabolites (van den Berghe, 1991; Trefts et al., 2017). Owing to its anatomical location, there is also extensive communication between the liver and intestine via the portal vein (Kubes and Jenne, 2018; Tripathi et al., 2018). Hepatocytes are the functional unit of the liver parenchyma and account for approximately 80% of total liver cells (Racanello and Rehermann, 2006). At the tissue level, hepatocytes are organized in hexagonal lobules with a central vein at the center and the portal triads, consisting of hepatic artery, hepatic portal vein, and bile duct, at the edges. The directed blood flow from the edges to the center, together with bile flow from center to the periphery, establishes nutrient and oxygen gradients that drive metabolic zonation. This phenomenon, whereby hepatocytes assume specific metabolic tasks depending on their anatomical position within a liver lobule, is best described in the liver (Ben-Moshe and Itzkovitz, 2019; Jungermann and Sasse, 1978; Kietzmann, 2017), but it is likely that metabolic zonation exists in most organs to varying extents. Single-cell transcriptome (single-cell RNA sequencing [scRNA-seq]) analyses combined with mathematical modeling and single-molecule fluorescence *in situ* hybridization (smFISH) identified marker genes of liver zonation during homeostasis (Halpern et al., 2017). Yet, so far it remains elusive how pathogens and/or immune responses influence metabolic zonation of the liver. Ongoing and future studies will aim to assess the

robustness and plasticity of metabolic zonation in liver pathologies. Next to their metabolic core functions, hepatocytes serve as immune signaling platforms during inflammation (Bénéchet et al., 2019; Crispe, 2016; Kubes and Jenne, 2018; Lercher et al., 2019; Rehermann and Nascimbeni, 2005; Zhou et al., 2016). Systemic pathogens and hepatotropic viruses enter the liver primarily via the hepatic artery and are thought to infect hepatocytes close to the blood vessel (Kubes and Jenne, 2018; Protzer et al., 2012; Robinson et al., 2016). Immune cell recruitment and pro-inflammatory cytokine signaling might lead to the establishment of an immunological gradient across the liver lobule. Virus-induced innate immune responses are dominated by the antiviral cytokine type I interferon (IFN-I). IFN-I induces an antiviral state in a broad range of target cells via interferon-stimulated genes (ISGs), but is also a modulator of cellular metabolism (Fritsch and Weichhart, 2016; McNab et al., 2015; Schoggins et al., 2011). IFN-I rewires cellular metabolism of innate immune cells to license optimal antigen presentation or boost the production of immune-modulatory metabolites like itaconate (Mills et al., 2016; O'Neill and Artymov, 2019; Pantel et al., 2014; Wu et al., 2016). Similarly, IFN-I modulates intracellular cholesterol homeostasis in non-immune cells to increase antiviral responses (York et al., 2015). In a model of metabolic syndrome, IFN-I shapes hepatic glucose metabolism via infiltrating T cells, corroborating data from non-alcoholic fatty liver disease (NAFLD) patients (Ghazarian et al., 2017). Apart from inducing a robust antiviral immune response, IFN-I modulates cellular redox homeostasis and central metabolic pathways in hepatocytes (Bhattacharya et al., 2015; Lercher et al., 2019; Schoggins et al., 2011). This initiates an endogenous regulatory circuit to modulate adaptive antiviral T cell responses and tissue damage via circulating metabolites in a murine infection that is similar to serum metabolite changes in patients with severe COVID-19 (Lercher et al., 2019; Shen et al., 2020). Conversely, inflammation-induced metabolic reprogramming of hepatocytes can influence systemic energy metabolism (Okin and Medzhitov, 2016). This highlights the important role of the liver as central modulator of systemic immunometabolism (Figure 1).

METABOLIC COMMUNICATION ACROSS KINGDOMS: IMMUNOMETABOLISM AND THE MICROBIOTA

Eukaryotes live with trillions of bacteria and, depending on the context, their relationship can be pathogenic, commensal, or symbiotic (Hooper and Gordon, 2001). The gut represents a large barrier surface, where a single layer of epithelial cells is a major mediator of crosstalk between gut microbes in the lumen and host cells, including immune cells in the lamina propria. Metabolism is at the center of many of these inter-kingdom interactions. Microbes harbor distinct metabolic pathways and thus can synthesize a vast diversity of small molecules that can be further metabolized (Visconti et al., 2019). Recent chemical and forward genetic screening approaches further highlighted the vast potential of microbiome-derived metabolites to initiate distinct signaling pathways in host cells (Chen et al., 2019; Colosimo et al., 2019; Visconti et al., 2019). Immune responses in the gut are coordinated by epithelial cells and intraepithelial lymphocytes (IELs). They are tightly regulated to adequately respond to pathogens, while avoiding excessive tissue damage

and detrimental responses to commensals or food antigens (Figure 1) (Olivares-Villagómez and Van Kaer, 2018).

From an evolutionary perspective, the metabolic labor division and crosstalk between eukaryotic host and prokaryotic microbiome appears highly advantageous (Figure 1A). Gut bacteria metabolize otherwise indigestible food components and by that, fuel metabolic processes of the host and contribute to serum metabolite levels (Cummings et al., 1987; McNeil, 1984; Uchimura et al., 2018; Weger et al., 2019; Wikoff et al., 2009). Yet, the metabolic flexibility of commensal bacteria can also be detrimental, as they can interfere with drug metabolism and associated pathologies (Pryor et al., 2019; Zimmermann et al., 2019). The microbiome affects local and systemic immune responses through the production of immune-reactive metabolites (Abt et al., 2012; Belkaid and Hand, 2014). Prime examples are short-chain fatty acids (SCFAs), which have a local effect in the gut to dampen immune responses toward commensal bacteria (Chang et al., 2014). Increased dietary fiber leads to elevated levels of systemic SCFA via the gut microbiome and is associated with altered bone marrow hematopoiesis. This is accompanied by ameliorated tissue damage in a model of influenza virus infection via increased lung infiltration of alternatively activated macrophages (Trompette et al., 2018). In addition, SCFAs facilitate the development of regulatory T cells (T_{reg}) in the periphery (Arpaia et al., 2013; Haghikia et al., 2015). Contrarily, gut-derived long-chain fatty acids (LCFAs) increase pro-inflammatory T cell responses and ameliorate autoimmune pathologies (Haghikia et al., 2015).

Non-classical T cells, including natural killer T (NKT) or mucosal-associated invariant T (MAIT) cells, specifically recognize microbe-derived metabolites via their TCRs. Microbe-derived metabolite antigens shape development, activation, and maintenance of these cells and are critical in mediating initial immune responses and tissue repair at barrier surfaces (An et al., 2014; Brennan et al., 2013; Constantinides et al., 2019; Legoux et al., 2019). During early life, gut microbe-derived riboflavins are critical for adequate MAIT cell development and skin wound healing in adult animals, yet the communication networks between gut and skin in humans remain elusive (Constantinides et al., 2019). These non-classical T cells represent yet another communication hub between commensal bacteria, the immune system, and individual organs. Of note, microbiome-related studies in laboratory mice are confounded by the controlled hygienic standards of animal facilities and inter-cage diversity, as well as inter-individual variability of the microbiome (Almeida et al., 2019; Pasolli et al., 2019). The microbial diversity is influenced by the genetic background of the host and, to a great extent, by environmental factors (Rothschild et al., 2018). In line, the microbiome of laboratory animals vastly differs from their feral counterparts (Rosshart et al., 2017). Not only is wild microbiome more resilient, but also profoundly affects the immune system, which appears closer to human in wild animals. This can be recapitulated by co-housing or fecal transplant experiments from wild to laboratory animals (Beura et al., 2016; Rosshart et al., 2017, 2019). Embryo transfer of laboratory mice into wild mothers results in mouse colonies that unify well-controlled genetics and a highly resilient microbiome and may, thus, provide a highly relevant model for translational research (Rosshart et al., 2019). This showcases that microbiome-related studies warrant

high standardization, meticulous documentation, and disclosure of information about microbiome composition by methods such as 16S RNA sequencing. Undoubtedly, germ-free or antibiotic-treated animals are important experimental models, but show altered immune responses toward pathogens and might not be ideal for studying immune-metabolic relationships (Abt et al., 2012; Kennedy et al., 2018). Reconstitution with a defined microbial community and working with gnotobiotic or isobiotic mice is a laborious alternative, but would allow even better experimental standardization across research groups (Hooper et al., 2012; Wymore Brand et al., 2015). Guidelines for optimization of microbiome-related study design have been reviewed elsewhere (Laukens et al., 2016).

At the tissue level, there are close interactions between IELs and epithelial cells, which themselves are immune signaling platforms that locally modulate IEL function. For example, innate immune signaling pathways in gut epithelial cells are critical for metabolic adaptation and function of IELs in bacterial infection (Hoytema van Konijnenburg et al., 2017). Further, single-cell transcriptome profiling of intestinal epithelial cells unraveled location-dependent heterogeneity and plasticity in homeostasis and following bacterial infection (Haber et al., 2017). Another related immune-regulatory mechanism is the proximal-to-distal gradient of T cell responses along the gut. Mesenteric lymph nodes (mLNs) drain anatomically distinct segments of the gut and by that, distribute inflammatory and tolerogenic immune responses to antigens (Esterházy et al., 2019). The mLNs are surrounded by white adipose tissue (WAT), which contributes to immune responses in the gut and is a reservoir for potent tissue-resident memory T cells (Han et al., 2017). Structural damage to the lymphatics disrupts the communication between microbiome and immune cells and microbes accumulating in the WAT lead to chronic inflammatory responses that cannot be resolved (Fonseca et al., 2015). The compartmentalization of pro- and anti-inflammatory responses along the gut correlates with distinct expression of metabolic genes in migratory dendritic cells, respective to the draining lymph node (Esterházy et al., 2019). Thus, in analogy to metabolic zonation of liver lobules, there is evidence of metabolic zonation along the gut (Quinn et al., 2020).

TECHNOLOGICAL APPROACHES TO STUDY SYSTEMIC IMMUNOMETABOLISM

Experimental dissection of immunometabolic relationships at the organismal level during homeostasis and disease remains challenging. Experimental animals can be housed in metabolic cages to longitudinally monitor energy expenditure, physical activity, indirect calorimetry based on oxygen consumption and carbon dioxide production, and food and water intake (Speakman, 2013; Tschöp et al., 2011). Time-resolved imaging techniques may provide strong complementary evidence for immunometabolic alterations within an organism. A functional imaging readout well suited to address such questions is positron emission tomography (PET). This non-invasive whole-body imaging technique is based on radioactively labeled tracers like ^{18}F -labeled deoxy-glucose (FDG) to identify tissues with high glucose demands in both animal models and patients (Lammertsma, 2017; Vaquero and Kinahan, 2015; Zhu et al., 2011). Complementary, heavy isotope tracing of ^{13}C -labeled

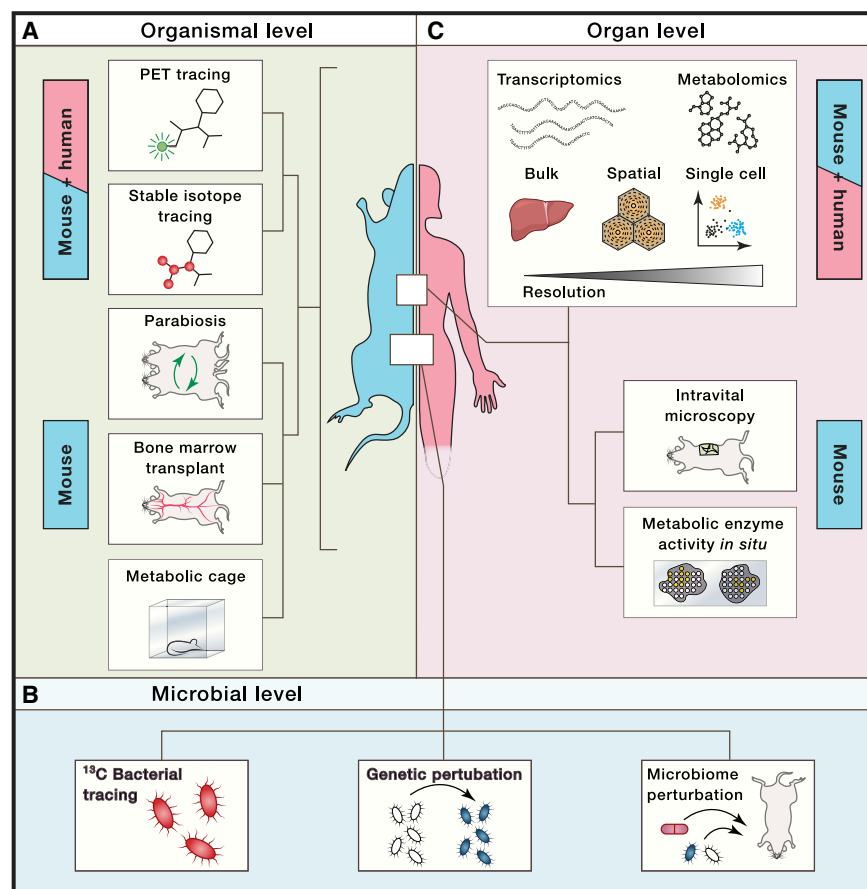


Figure 2. Technical Approaches to Study Systemic Immunometabolism

(A–C) Schematic depiction of selected complementary technical approaches to dissect immune-metabolic crosstalk and relationships in experimental model systems and patients at the (A) organismal (e.g., PET tracing, stable isotope tracing, parabiosis, bone marrow transplant experiments, or metabolic cages), (B) microbial (e.g., ^{13}C bacterial tracing experiments, genetic or microbiome perturbations), and (C) organ (e.g., bulk, spatial or single-cell transcriptomics and metabolomics, intravital microscopy, or measuring metabolic enzyme activity *in situ*) levels.

types and tissue-specific metabolic pathways. Widely used genetic systems like the Cre-*loxP* system are valuable genetic systems to specifically ablate genes in a cell-type-specific manner, but come with certain limitations as discussed elsewhere (Becher et al., 2018; Kurachi et al., 2019). Recombinant adeno-associated viral (AAV) vectors pose a versatile alternative to specifically manipulate gene expression in a wide range of tissues *in vivo* (Srivastava, 2016). Adoptive cell transfers and bone marrow transplants from genetically modified animals to wild-type animals or vice versa are another versatile tool to address the contribution of the hematopoietic immune cell compartment

metabolites by mass spectrometry, together with computational metabolic flux modeling, offers yet another powerful technique to assess *de novo* host metabolite synthesis and turnover *in vivo* (Jang et al., 2018). By transplanting ^{13}C heavy isotope-labeled bacteria and subsequent metabolite tracing, this methodological approach further allows dissection of microbiome- versus host-derived metabolites (Figure 2A) (Jang et al., 2018; Uchimura et al., 2018). Additionally, ^{13}C tracing of bacterial metabolites by mass spectrometry allows identification of unknown bacterial metabolites. Complementary, metabolic pathways of bacteria of the microbiome may be genetically perturbed *in situ* by engineering a donor strain with broad phylogenetic recipient range to harness horizontal gene transfer (Figure 2B) (Ronda et al., 2019).

To dissect immune-metabolic relationships at the cell and tissue level, imaging techniques visualizing cells via defined markers combined with functional well-established metabolic readouts to quantify, for example, mitochondria, reactive oxygen species, lipid droplets, or glucose, are widely used. This includes the quantification of metabolic enzyme activity *in situ* for research focused on certain metabolic pathways (Miller et al., 2017). Spatiotemporal resolution of cell-cell interactions and migration dynamics of immune cells within tissues *in vivo* could be achieved via intravital microscopy (Figure 2C) (Karreman et al., 2016).

A critical question for investigating communication networks *in vivo* relates to the specific sender-respective responder cell

to an observed metabolic phenotype. Parabiosis experiments may augment such approaches to examine the contribution of migrating immune cells and/or circulatory factors to systemic metabolism in homeostasis and disease (Han et al., 2017). These and other technologies, particularly when integrated with single-cell sequencing and methods providing spatial resolution (Stark et al., 2019), are expected to offer unprecedented new mechanistic insights into systemic metabolism and inflammation across and between both lymphoid and non-lymphoid organs.

Development and application of methods with spatial resolution gain increased momentum as exemplified by current advances toward spatial *in situ* transcriptomics (Moor and Itzkovitz, 2017; Stark et al., 2019). Multiplexed error-robust FISH (MERFISH) is an advanced imaging-based method with single-cell-transcript-level resolution that may be combined with single-cell sequencing (Figure 2B) (Chen et al., 2015; Moffitt et al., 2018). Other approaches are based on direct hybridization of RNA from tissue sections of interest to spatially barcoded probes immobilized either on a plane surface with the prospect of providing single-cell or even sub-cellular resolution (Rodrigues et al., 2019; Ståhl et al., 2016; Vickovic et al., 2019). Alternatively, multiplexed immunohistochemistry using DNA-bar-coded antibodies enable detection of protein abundances within tissues combined with a high throughput sequencing readout (Stoeckius et al., 2017). Multi-dimensional *in situ* imaging at high resolution is also achievable by using heavy

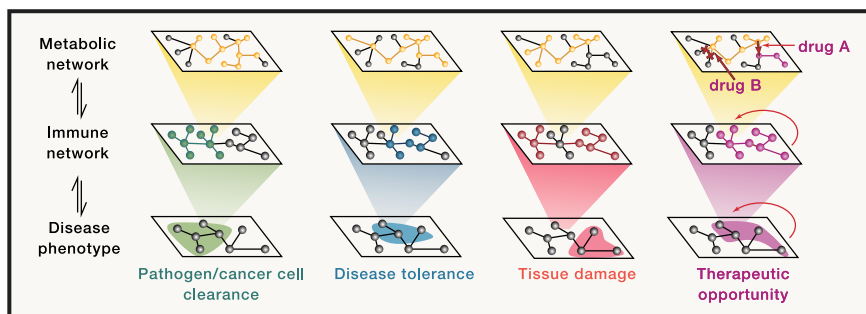


Figure 3. Reprogramming of Systemic Immunometabolism as Therapeutic Intervention Strategy

Schematic depiction of the hierarchical order of metabolic, immune, and disease pathology networks. The metabolic network of a cell or organism is the basal regulator of immune responses in different tissues or organs. The quality of the immune response, immune cell activation state, and cytokine signaling in turn shapes beneficial or detrimental disease pathophysiology. These outcomes include removal of the perturbation (e.g., pathogen or cancer cell) and disease tolerance (e.g., pathogen-host co-adaptations), but also extensive tissue damage

(e.g., viral hepatitis) that can be life threatening to the host. Specific therapeutic interventions at the level of the metabolic network bears the potential to effectively modulate immune-related disease pathologies.

metal-labeled antibodies for protein detection and subsequent tissue ablation via a laser and mass-cytometry-based (CyTOF) analyses of the liberated particles (Hartmann and Bendall, 2020).

To ultimately address spatiotemporal dynamics of immunometabolic processes at the tissue level, advances in spatial metabolomics will be instrumental (Miura et al., 2012). Methods for *in situ* spatial single-cell metabolomics integrating matrix-assisted laser desorption/ionization (MALDI) imaging mass spectrometry (IMS) with bright field and fluorescence microscopy are under development (Alexandrov, 2020). These methods deliver spatially resolved single-cell metabolite profiles and allow visualization of tissue sections via their metabolite distribution (Miura et al., 2012; Rappetz et al., 2019; Sun et al., 2019). A combination of spatial scRNA-seq and metabolomics is bound to open new perspectives for the immunometabolic relationships within organs and contribute to mapping inter-organ communication within an organism.

In summary, it is evident that studying systemic immunometabolism requires a broad complementary technological portfolio to investigate utilization, distribution, and immune-metabolic communication networks in space and time. The integration of spatial reorganization of cells within tissues and metabolic phenotype changes of an organ or organism will be of paramount importance to elevate our knowledge on systemic immunometabolism.

IMMUNOMETABOLISM IN THE CLINICS

The discovery of so-called antimetabolite drugs and the subsequent development of the folate pathway inhibitor methotrexate by Sidney Farber is considered the beginning of modern chemotherapy (Farber and Diamond, 1948; Miller, 2006). This and similar discoveries put metabolic pathways as attractive targets in the spotlight early on. Many chemotherapeutic drugs used in the clinics nowadays exploit the metabolic vulnerabilities of highly proliferative cancer cells (DeVita and Chu, 2008).

A common metabolic feature of proliferating cancer and activated immune cells is increased energy demand. This demand is generally met by upregulation of glycolysis and OXPHOS, but also depends on extracellular metabolite availability and import. A currently explored antitumoral strategy is the inhibition of glycolysis via 2-deoxy-glucose (2-DG), a competitive inhibitor of glycolysis (Wick et al., 1957). 2-DG is well tolerated in patients and showed beneficial effects in solid tumors (Raez et al., 2013;

Stein et al., 2010). Recent studies also suggested a beneficial effect of 2-DG treatment in systemic lupus erythematosus (SLE) and autoimmune disease mediated by glycolytically highly active T cells (Choi et al., 2018; Yin et al., 2015). Cancers and immune cells can upregulate *PKM2*, an inactive isoform of the glycolysis gene *PKM*, to activate hypoxic signaling, angiogenesis, and cytokine production (Luo et al., 2011; Palsson-McDermott et al., 2015). The small molecule TEPP-46 inhibits this process by restoring enzymatic activity of *PKM2* and yielded promising results in experimental models of cancer and infectious diseases (Anastasiou et al., 2012; Palsson-McDermott et al., 2015). Glycolysis produces pyruvate that is conjugated to coenzyme A (CoA) to be fed into the TCA cycle as acetyl-CoA. Reprogramming of the TCA cycle and associated genes and metabolites are linked to inflammatory processes or malignant transformation (Lampropoulou et al., 2016; Mills et al., 2016; O'Neill and Artymov, 2019; Yen et al., 2010). The TCA cycle gene *SDH* facilitates inflammatory processes by boosting OXPHOS and the accumulation of reactive oxygen species (ROS) (Mills et al., 2016). Dimethyl-malonate and 4-octylitaconate are small molecules targeting *SDH* and ameliorate inflammation in several experimental models (Chouchani et al., 2014; Mills et al., 2018). An isoform of isocitrate dehydrogenase, *IDH2*, is an oncogene and targeting of the mutant form with the drug Enasidenib appears as promising treatment option in acute myeloid leukemia patients (Stein et al., 2019; Yen et al., 2017). Dimethyl-fumarate is a derivate of the TCA metabolite fumarate, thought to interfere with the NRF2 pathway and glycolysis, and is currently used as an immunomodulatory drug to treat multiple sclerosis and psoriasis in patients (Gross et al., 2015; Kornberg et al., 2018; Mrowietz et al., 2017). These findings support the idea that cell-type-specific metabolic dependencies are an attractive therapeutic target to selectively modulate activity of any cell type of interest. An example thereof is the possibility to boost anti-tumoral activity of chimeric antigen receptor (CAR) T cell responses to tumor by genetic or pharmacological perturbation of CPT1A, the rate-limiting enzyme of FAO (Klein Geltink et al., 2017).

Research in the field of systemic immunometabolism helped to unveil metabolic dependencies of highly proliferating cells on the metabolic environment. This is particularly evident in rapidly proliferating T cells or malignant cells that are sensitive toward extracellular amino acid scarcity. This opens an opportunity to tune immune responses or interfere with cancer cell

progression and growth by modulating amino acid availability. A prime example is the *IDO1*-mediated depletion of the essential amino acid tryptophan and accumulation of the immunosuppressive metabolite kynurenine (Prendergast et al., 2017). Several clinical studies explored *IDO1* as a target to re-activate T cells and, after setbacks, inhibitors like Epacadostat and BMS986205 might be most effective in combination therapy against cancer (Van den Eynde et al., 2020; Komiya and Huang, 2018). A second example is the semi-essential amino acid arginine, whose extracellular availability is critical for both cancer and immune cells (Brunner et al., 2020; Feun et al., 2012; Geiger et al., 2016). The therapeutic potential of arginine depletion via recombinant enzymes, including arginine deiminase (ADI-PEG20) and recombinant arginase 1 (recARG1), was evaluated in clinical trials (Abou-Alfa et al., 2018; Ensor et al., 2002; De Santo et al., 2018). Since arginine-depletion seems to reduce pro-inflammatory immune cell activity, it could also provide a strategy to ameliorate inflammatory diseases. Analogously, the essential amino acid methionine is another limiting factor of cancer cell metabolism and malignant transformation and, concurring, dietary methionine restriction reduces cancer progression in humans (Gao et al., 2019; Hoffman and Erbe, 1976). Complementarily, the high glucose demand of tumors can be exploited by adhering to a ketogenic diet, which reduces circulating glucose availability (Champ et al., 2014). Preclinical patient data and small cohort trials suggest a beneficial effect of ketogenic diet and the associated blood glucose in several tumors (Fine et al., 2012; Weber et al., 2018). Apart from cancer, recent studies in animal models show that extracellular availability of amino acids or glucose influences immune responses in autoimmune or infectious diseases (Brunner et al., 2020; Goldberg et al., 2019; Lercher et al., 2019; Ma et al., 2017; Roy et al., 2020; Zhang et al., 2019). Specifically, extracellular amino acids are important regulators of the protective properties of T_{reg} cells and thus modulate pathophysiology of autoimmune diseases (Do et al., 2020; Ikeda et al., 2017; Shi et al., 2019). This shows a potentially broad applicability of the immune-metabolic intervention strategies that are currently predominantly explored in cancer. Further reviews discussing the potential of metabolic drugs and nutritional metabolism for the treatment of inflammatory diseases and cancer are provided elsewhere (Kanarek et al., 2020; Pålsson-McDermott and O'Neill, 2020).

Altogether, disease pathologies are the result of the interplay of multiple molecular processes (Menche et al., 2015). Similarly, cells and signaling molecules of the immune system are organized in complex network-like structures whose activity is modulated by the underlying metabolic program (Jha et al., 2015; Rieckmann et al., 2017). Targeted intervention with the metabolic networks bears the potential to tailor immune responses to ameliorate and/or prevent disease (Figure 3). As we keep discovering the whole breadth of crosstalk between immune-metabolic networks and disease pathophysiology, therapeutic interventions targeting specific organs and/or cell types are becoming increasingly in reach.

CONCLUDING REMARKS

Immune-metabolic relationships form the basis of life and are at the center of many diseases including cancer, immune-medi-

ated diseases, and metabolic syndrome. The field of immunometabolism is one of the most exciting interdisciplinary research areas. We expect fundamental new insights for our understanding of how the intricate regulation of the immune system interdepends on metabolism. Research will be propelled by the integration of sophisticated *in vitro* systems, disease-relevant animal models, and patient-derived data, exploiting the respective strengths of the approach while considering the existing limitations. Technological advances on all levels including imaging, single-cell analysis, and spatially resolved techniques will empower the immunometabolism research community in their quest. Conceptually, we are convinced to see an even stronger and more profound consideration of physiological processes, such as the core functions of parenchyma and connective tissue, spatial zonation of organs, and drainage by blood and lymph. This will open new dimensions that eventually result in a truly holistic understanding of immunology on the cellular, organ, and organism level. Systemic immunometabolism will be at the forefront to integrate hitherto rather neglected roles of non-immune cells and non-lymphoid organs, thereby filling important gaps in our understanding of how immune cells communicate with the organism to execute their diverse tasks most effectively.

There is already a surge in novel therapeutic strategies based on the exploitation of metabolic vulnerabilities and targeting of specific metabolic processes. Systemic immunometabolism will improve our mechanistic understanding of the inner workings of the human organism, promising to contribute to a stream of innovative (immuno-) therapeutic approaches for a great range of diseases.

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