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Dietary Regulation of Immunity

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SUMMARY

Integrated immunometabolic responses link dietary intake, energy utilization, and storage to immune regulation of tissue function and is therefore essential for the maintenance and restoration of homeostasis. Adipose-resident leukocytes have non-traditional immunological functions that regulate organismal metabolism by controlling insulin action, lipolysis, and mitochondrial respiration to control the usage of substrates for production of heat versus ATP. Energetically expensive vital functions such as immunological responses might have thus evolved to respond accordingly to dietary surplus and deficit of macronutrient intake. Here, we review the interaction of dietary intake of macronutrients and their metabolism with the immune system. We discuss immunometabolic checkpoints that promote healthspan and highlight how dietary fate and regulation of glucose, fat, and protein metabolism might affect immunity.

INTRODUCTION

The hominids that were destined to become humans evolved with larger and intensive energetic demands for brain function. Host survival thus required mechanisms that balance the energetic costs of essential functions such as successful immune response against infections and tissue repair. Accordingly, humans have developed an integrated immunometabolic response (IIMR) that involves sensing of nutrient balance by neuronal (sympathetic and sensory innervation) and humoral signals (e.g., hormones like insulin, incretins, FGF21, GDF15, ghrelin, and leptin) between the hypothalamus and peripheral tissues to allow the host to prioritize storage and/or utilize substrates for tissue growth, maintenance, and immune responses. The evolutionary pressure to maintain healthy adiposity concurrently with tissue-protective inflammatory responses to injuries and infections is important drivers of IIMR. It has been hypothesized that because energy-rich nutrients have been scarce throughout most of human evolution, dominant genetic pathways evolved to favor increasing intake of calorie-rich diets and storage of energy as triglycerides in adipose tissue. Within this evolutionary pressure to store calories, consumption of energy-rich diets in the modern world has given rise to obesity. Excessive adiposity or obesity with a body mass index (BMI) of >30, is a multisystem disorder resulting from chronic caloric intake and perturbation of IIMR. A large body of literature suggests that altered IIMR in obesity causes a chronic proinflammatory state that is linked to diseases such as type 2 diabetes, non-alcoholic steatohepatitis, and cardiovascular disease (Christ et al., 2019). In addition, obesity impairs adaptive immune responses and is a major risk factor for mortality and morbidity from H1N1 influenza (Van Kerkhove et al., 2011).

In opposition to obesity, negative energy balance without malnutrition is induced by restriction of calories and is one of the most effective means for lifespan and healthspan extension in multiple species (Anderson et al., 2017; Weindruch and Sohal, 1997). Caloric restriction (CR) limits glucose availability, and therefore the host must engage fatty acid oxidation to generate ATP. The effector immune functions that rely on glucose as their primary substrates are most likely modulated by such dietary interventions, and these interventions could be promising avenues to prevent or treat diseases that involve hyperinflammatory responses. It is recognized that severe reduction in nutrient and energy intake might cause tradeoffs in non-essential functions. As posited by the disposable soma theory, this involves diversion of resources from host growth and reproduction toward cellular maintenance, and when nutrients become available again, energetically costly pathways dedicated for host defense can be re-engaged (Kirkwood et al., 2000). Which scenarios induce such a tradeoff and whether the immune system is indeed dispensable when energy is limiting are open questions. However, emerging evidence suggests that immune response to infectious challenges is maintained during moderate dietary restriction (Collins et al., 2019; Jordan et al., 2019; Nagai et al., 2019) and is boosted when carbohydrate deficient, high-fat diet (HFD) intake induces ketogenesis (Goldberg et al., 2019). Surprisingly, restriction of proteins, including the restriction of essential amino acid methionine in adult life extends lifespan in rodents by almost 40%–50% (Orentreich et al., 1993; Solon-Biet et al., 2014). The biochemical metabolic pathways engaged by such dietary alterations could hold the keys to identifying as of yet unknown mechanisms that could be harnessed to control reparative responses, inflammation, and immune surveillance. In this review, we discuss the interaction of dietary intake of macronutrients and their metabolic fate on immune system including adipose-tissue-resident leukocytes in regulation of inflammation and organismal metabolism.

IMMUNE DEFENSE IN DIET-INDUCED OBESITY

Modern diets are rich in saturated fats and processed carbohydrates, such as high fructose corn syrup, and are deficient in...
fiber, vitamins, and minerals, while containing high levels of salt. These diets are a leading cause of the emergence of obesity-associated chronic diseases, the majority of which are linked to chronic inflammation (Bray et al., 2017). A vast number of studies have described a predominant role of inflammation, originating from visceral adipose tissue and lipotoxicity, in engaging innate immune cells that lead to development of type 2 diabetes through their production of tumor necrosis factor-$\alpha$ (TNF-$\alpha$), interleukin-1$\beta$ (IL-1$\beta$), and IL-6 (Donath and Shoelson, 2011; Hotamisligil, 2006; Saltiel and Olefsky, 2017). There is however, also increasing evidence of obesity as an independent risk factor for dysregulated adaptive immune response against various infections. The retrospective analyses after the 2009 H1N1 pandemic across the globe revealed obesity to be co-morbid with influenza in nearly one-third of hospitalized patients with increased fatality after infection (Van Kerkhove et al., 2011). The mechanisms by which obesity disrupts immune response and recovery from influenza are manifold and represent the effect of chronic metabolic perturbation on multiple cell types. Diet-induced obese (DIO) mice have reduced amounts of H1N1-specific antibodies as well as lower neutralization response during influenza infection (Honce et al., 2020). Whether obesity affects germinal center reactions, class-switching of antibodies, or the B cell repertoire remains unknown. There are data that suggest that obesity restricts T cell receptor (TCR) repertoire diversity (Yang et al., 2010) and decreases the number of T cell receptor excision circles (TRECs) in the blood of obese and diabetic individuals, suggesting reduced thymic generation of naive T cells (Yang et al., 2009b).

In addition, the differentiation of naive T cells (CD4 and CD8) into an effector state upon antigen recognition is dependent on glucose and glutamine (Jacobs et al., 2008; Michalek et al., 2011; Pearce et al., 2009; Wang et al., 2011). It is thus likely that hyperglycemia and dyslipidemia seen in obesity affects T cell immune activation against influenza infection. Interestingly, HFD feeding expands $\gamma\delta$ T cells in the lungs that are IL-17 competent but lack a tissue-protective transcriptional profile and fail to confer protection against influenza (Goldberg et al., 2019). Whether altered lipid versus glucose metabolism drives dysfunctional $\gamma\delta$ T responses in obesity remains to be characterized.

Furthermore, effective memory T cell response relies on efficient transition from glycolytic to a more oxidative metabolism (Pearce et al., 2009), although this distinction might not be binary in vivo. Recent studies using $^{13}$C-based stable isotope labeling techniques in T cells highlight that glucose use by CD8$^+$ cells is dynamically regulated during the course of an immune response to Listeria infection and identified that glucose-dependent serine biosynthesis as a key metabolic program for optimal T cell expansion in vivo (Ma et al., 2019). How diet-induced obesity affects the metabolic reprogramming of T cells in vivo in bacterial or viral infection requires further investigation. Initial analyses suggest that indeed altered glycolytic and oxidative respiration in memory T cells of obese animals is a likely mechanism influencing influenza disease susceptibility (Rebeles et al., 2019). In addition, Mauro et al. (2017) found that metabolic stress induced by saturated fatty acids affects T cell differentiation and causes preferential trafficking of CD4$^+$ T cells to non-lymphoid effector sites in obesity. Palmitate drove CD4$^+$ T cells to acquire a specific CD44$^+$CCR7$^+$CD62L$^+$CXCR3$^+$LFA1$^+$ pro-inflammatory dysfunctional phenotype via the activation of a PI3K p110$\alpha$-Akt-dependent pathway (Mauro et al., 2017). Interestingly, adipose tissue serves as a reservoir of memory T cells specific to several viruses including but not limited to lymphocytic choriomeningitis virus (LCMV) and HIV (Damouche et al., 2015), as well as bacteria like Yersenia and protozoa like Toxoplasma (Han et al., 2017). It is possible that antigen-specific T cells might enter the adipose tissue to potentially resolve the infection but then remain as a memory population distinct from memory T cells in classical sites of immune response. Formal studies would be required to test the hypothesis that the adipose microenvironment shapes the specific transcriptional signatures of memory phenotype that is compromised in obesity. It is, however, known that in obese mice, upon re-challenge to infection, adipose memory T cells up-regulate lipases and cause severe disease including calcification of adipose tissue, pancreatitis, and reduced survival (Mismi et al., 2019). Concernedly, data from the COVID-19 pandemic has identified obesity and diabetes as a major risk factor in disease severity and mortality (Drucker, 2020) (Box 1). Given that in the US, over one third of adults are obese, urgent research efforts are needed to determine immunoregulatory mechanisms that affect immune response, disease tolerance, treatment, and potential vaccination failure in this large high-risk population.

ADIPOSE TISSUE AS AN IMMUNOLOGICAL ORGAN

Of the metabolic organs responding in the IIMR during chronic positive energy balance (Figure 1), adipose tissue has been best characterized and strongly contributes to the pathogenesis of obesity. Obese adipose contains approximately 2 to 5 million stromal-vascular cells per gram, of which approximately 60%–70% are immune cells. In severe obesity, adipose tissue can expand to constitute up to 30%–50% of total body mass (Kaneganti and Dixit, 2012). Thus, the adipose tissue represents an underappreciated immunological organ that harbors distinct subpopulations of immune cells that localize to specific niches to perform potentially unique functions.

Even before it was recognized that immune function could be regulated by cellular metabolism (Buck et al., 2015; Waurwuth et al., 2009; O’Neil et al., 2016), the discovery that obesity-induced insulin resistance was directly caused by elevated TNF levels in adipose tissues launched the field of immunometabolism, pioneering the association of the immune system with metabolic processes (Hotamisligil et al., 1993). Although, initially thought to be derived from adipocytes, later studies clarified that accumulation of macrophages in the adipose were the main drivers of inflammatory cytokine production (Lumeng et al., 2007; Weisberg et al., 2003). It has now been elucidated that during obesity, in addition to macrophages, there are large changes in the adipose immune landscape as certain cells are recruited and activated while other cell types are depleted and replaced, leading to a more pro-inflammatory environment that drives type 2 diabetes and chronic disease progression (Figure 2). Mechanistically, pro-inflammatory cytokines such as TNF, IL-6, and IL-1$\beta$ have been shown to block insulin receptor signaling through inhibition of insulin receptor substrates (IRSs), by increasing their serine phosphorylation (Hotamisligil et al., 1996; Werner et al., 2004). Conversely, gain of function of
inhibitor of nuclear factor-κB kinase (IKK) in the liver was found to reduce endoplasmic reticulum (ER) stress by elevated X-box binding protein 1 (XBP1) activity leading to an actual improvement in insulin sensitivity (Liu et al., 2016). Additional studies are needed to determine the delicate balance of chronic pro- and anti-inflammatory cytokine signaling required to repair and restore metabolic homeostasis.

**ADIPOSE TISSUE MACROPHAGES IN OBESITY**

It is now understood that macrophages are resident immune cells found in almost every tissue and play key roles in maintaining homeostasis (Lavin et al., 2014; Okabe and Medzhitov, 2014). In healthy adipose tissue, macrophages are thought to constitute about 10% of the hematopoietic cell composition. However, it is possible that enzymatic digestion protocols of adipose tissue can be divided into various populations of diverse lineages and functionality that respond dynamically to local metabolic cues within their unique niches. Although these macrophage subsets are still being defined, careful examination of the transcriptional profiles of different ATM groups have clarified that there are numerous ways to define macrophage subsets and most infiltrating macrophages in adipose tissue in chronic inflammation do not fit a simple M1/M2 polarization model (Camell et al., 2017; Kratz et al., 2014).

In lean adipose tissue, macrophages are a mixed heterogeneous population of yolk-sac-derived, self-maintaining macrophages and bone marrow (BM)-derived monocytes and macrophages that are continuously replenished (Amano et al., 2014; Hassnain Waqas et al., 2017; Schulz et al., 2012; Silva et al., 2019). Silva et al. (2019) have recently described four different groups of lean visceral ATMs. The group of macrophages that make up the majority of ATMs in lean adipose tissue express high amounts of CD206 and are CD11b+MHCII+Tim4+. Through BM chimera experiments, these macrophages were found to be largely tissue resident with minimal replenishment from the periphery (Amano et al., 2014; Silva et al., 2019). Surprisingly, these macrophages were found to be laden with lipids even in the lean state (Silva et al., 2019). One of the roles of macrophages in lean adipose is to clear dead adipocytes. ATMs form CLSs around dying adipocytes to clear the dying cell and lipids in a contained manner (Murano et al., 2008). Because adipocytes are too large to be engulfed by macrophages, ATMs release

### Box 1. Immunometabolic Regulators of COVID-19 Severity

In addition to old age, metabolic syndrome, diabetes, and obesity are independent risk factors for increased severe acute respiratory syndrome coronavirus 2 (SARS-COV-2)-induced mortality and morbidity. Given the prevalence of obesity is 10% among younger adults aged 20-39, 45% among adults aged 40–59 years, and 43% among older adults aged 60 and over (Hales et al., 2020), there is urgent need for studies that define the mechanism of aberrant immune response that promotes predisposition to infection and disease. Recent analyses show that 47% of cases of COVID-19 hospitalization represented obese patients with BMI >30. Moreover, 85% of patients above the BMI of 35 developed hyperinflammatory response in lungs that required mechanical ventilation to boost oxygen saturation (Simonnet et al., 2020). Macrophage activation and neutrophil influx mediate a hyperinflammatory response in the lungs in COVID-19 (Zhou et al., 2020). Given obesity’s known effects on increasing inflammation, future studies will be needed to determine the immunological mechanism of diet-driven complications of SARS-COV-2 viral infection. Of note, NLRP3 inflammasome, a myeloid-cell-expressed multiprotein complex that senses pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) to cause IL-1β and IL-18 release, is activated in obesity, type-2 diabetes, atherosclerosis, and aging (Camell et al., 2015; Goldberg and Dixit, 2015). There is increasing evidence that SARS-COV-2 infection activates the NLRP3 inflammasome (Siu et al., 2019) with increased levels of IL-18 and lactate dehydrogenase (LDH) because of inflammasome-mediated pyroptotic cell death (Lucas et al., 2020; Zhou et al., 2020). Interestingly, SARS-COV-2 open reading frame 3a (ORF3a) and ORF8b activates the NLRP3 inflammasome (Siu et al., 2019) by inducing ER stress and lysosomal damage (Shi et al., 2019), mechanisms that are independently shown to be elevated in obesity. It is now known that increased glycolysis, which also induces transcriptional upregulation of inflammasome machinery, causes aberrant activation of myeloid cells, and worsens COVID-19 (Codo et al., 2020). This raises the question whether dietary approaches that mimic a glucoprivic state by feeding of a low carbohydrate, high-fat diet, which necessitates the switch from glycolysis to production of ketone metabolites, can be employed to stave off COVID-19. Indeed, ketone bodies inhibits the NLRP3 inflammasome (Youm et al., 2015) and ketogenic diet protects against influenza-induced lethality in mice by expanding γδ T cells (Goldberg et al., 2019). Thus, raising the possibility that harnessing specific immunometabolic checkpoints, such as glycolytic-to-ketogenic switch, maybe relevant to several infections, including SARS-COV-2.
acidic exosomes laden with lysosomal enzymes that can take up and degrade large adipocyte fragments, which can then be taken up by the macrophages in a process called exophagy (Haka et al., 2016). This process allows for macrophages to internalize large amounts of lipids. During obesity, this process becomes increasingly overburdened because there is an increase in the number of dying adipocytes and CLSs. The accumulation of macrophages in response to an HFD is mostly attributed to an influx of peripheral BM-derived monocytes that quickly differentiate and proliferate locally (Amano et al., 2014; Hill et al., 2018; Jaitin et al., 2019; Nagareddy et al., 2014; Oh et al., 2012; Silva et al., 2019). The macrophages that accumulate with obesity are also heterogeneous and further studies might clarify the specific roles of each subset in disease progression (Hill et al., 2018; Jaitin et al., 2019). Most of the infiltrating macrophages are found at CLSs and proliferate locally. They are largely CD9+ and are enriched with signatures for lipid metabolism, lysosomal biosynthesis, and phagocytosis (Hill et al., 2018; Jaitin et al., 2019; Xu et al., 2013). Transcriptomic profiling has identified that CD9+ macrophages that accumulate with diet-induced obesity also express CD163 and Trem2. Because of their association with enlarged adipocytes at CLSs, these macrophages have been named lipid-associated macrophages, or LAMs (Jaitin et al., 2019). Depletion of TREM2+ LAMs led to reduced lipid uptake by macrophages and increased adipocyte hypertrophy and weight gain and a worsening of glucose homeostasis, challenging the idea that infiltrating ATMs during obesity purely cause disease progression, but also play critical protective roles in the adaptation to metabolic stresses that occur during obesity (Jaitin et al., 2019).

Adipose tissue is highly vascularized. As adipocytes increase in size and number via hypertrophy and hyperplasia to store excess calories as triglycerides, hypoxia ensues as the diffusion limit of oxygen is reached. Pockets of local hypoxia leads to angiogenesis to meet the oxygen demands required for hypertrophy and increased mitochondrial respiration. Lyve1+ macrophages express MMP-7, MMP-9, and MMP-12 to remodel the extracellular matrix (ECM) and promote angiogenesis (Cho et al., 2007). In lean adipose, macrophages are found tightly wound around blood vessels as a subset of perivascular macrophages, or PVMs (Hilgendorf et al., 2019; Silva et al., 2019). These self-maintaining PVMs that are in direct contact with the vasculature make up a large proportion of macrophages in healthy adipose and express high amounts of CD206 (Silva et al., 2019). Surprisingly, PVMs store lipid droplets even in the lean state, and rapidly take up dextran and ovalbumin (OVA) from the circulation, suggesting that they are constantly surveilling and buffering lipids within the adipose circulation and might play important roles in presenting antigens and maintaining T cells within the adipose tissue (Silva et al., 2019). During obesity, PVMs change in morphology from an elongated shape to a rounded shape and have a reduction in their capacity to take up dextran, suggesting that their homeostatic functions are diminished in response to HFD (Silva et al., 2019). Given that PVMs might play important roles as antigen-presenting cells (APCs), how this might affect the interaction of PVMs with other immune populations during DIO remains to be elucidated.

Adipose tissue is also densely innervated by both sympathetic and sensory nerves, which are important in controlling lipolysis and thermogenesis (Bartness et al., 2014; Chi et al., 2018; Slavin and Ballard, 1978). Density of innervation varies among different fat depots, with brown adipose tissue (BAT) having the most, then subcutaneous adipose tissues (SFAT), and various visceral adipose tissues such as the mesenteric adipose and gonadal

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adipose tissues. Release of catecholamines such as norepinephrine (NE) by sympathetic nerves is essential for hydrolysis of triglycerides into fatty acids, a process called lipolysis that provides substrates for energetic and synthetic purposes. (Barthness et al., 2010). Interestingly, macrophages also reside on nerves in the adipose tissue as nerve-associated macrophages, or NAMs (Camell et al., 2017; Pirzgalska et al., 2017; Wolf et al., 2017). Although a significant portion of brown adipose NAMs are self-maintaining, long-lived resident macrophages, white adipose NAMs are more frequently replenished by BM-derived macrophages (Pirzgalska et al., 2017; Wolf et al., 2017). NAMs lack tyrosine hydroxylase and therefore do not produce catecholamines (Fischer et al., 2017; Pirzgalska et al., 2017; Spadaro et al., 2017). Instead, they express the canonical catecholamine transporter, Slc6a2, allowing for the uptake of catecholamines from the local environment and express catecholamine degradation enzymes such as monoamine oxidase A (MAOA) and catechol-O-methyl transferase (COMT) to control local availability of catecholamines (Camell et al., 2017; Pirzgalska et al., 2017). Furthermore, the expression of MAOA and COMT in NAMs is upregulated by NLR family pyrin domain containing 3 (NLRP3)-mediated inflammation during obesity and aging, leading to increased catecholamine degradation by NAMs to contribute to metabolic dysregulation (Camell et al., 2017). How NAMs integrate metabolic and immune sensing in adipose tissue in response to different diets is not well understood and is likely to reveal important non-traditional functions of macrophages in maintaining tissue homeostasis.

**EFFECT OF DIET-INDUCED OBESITY ON ADIPOSE LEUKOCYTES**

Besides macrophages, many other immune cell types have been described in adipose tissue and in the context of obesity. Adipose tissue is relatively enriched with innate immune cells such as eosinophils, innate lymphoid cells (ILCs), invariate natural killer T (iNKT) cells, and γδ T cells and have been well described in other reviews (Kane and Lynch, 2019; Mraz and Haluzik, 2014). In brief, mast cells, ILC1s, γδ T cells, and neutrophils all increase in adipose tissue with obesity and are associated with inflammation. Mast cells increase in the visceral adipose tissue (VAT), particularly around CLSs and actively degranulate to release TNF-α, IL-6, and interferon-γ (IFN-γ) to promote obesity and diabetes (Altintas et al., 2011; Liu et al., 2009). Recently, Zhang et al. (2019) have demonstrated that dietary cholesterol leads to activation of mast cells, suggesting mast cells might be directly sensing and responding to dysregulated metabolites. Neutrophils are transiently increased during obesity and are one of the earliest cells to infiltrate adipose tissue and secrete elastase to contribute to pathology (Elgazar-Carmon et al., 2008; Talukdar et al., 2012). ILC1s or NK cells were found to contribute to obesity by producing IL-2 and IFN-γ to promote M1 skewing in
macrophages, and displayed higher killing activity toward M2-like macrophages over M1-like macrophages (Boulenour et al., 2017; O’Sullivan et al., 2016). In humans, CD1c^+CD11c^+CD83^+ dendritic cells (DCs) increase in obese adipose tissue and induce Th17 differentiation (Bertola et al., 2012).

γδ T cells are tissue resident and increase in proportion to fat mass during diet-induced obesity (Mehta et al., 2015). Mice lacking γδ T cells have reduced accumulation of pro-inflammatory macrophages and significant reductions in systemic insulin resistance, suggesting that γδ T cells play a role in driving the pro-inflammatory response during diet-induced obesity (Mehta et al., 2015). However, γδ T cells might also serve homeostatic functions in healthy adipose tissue given that IL-17A production by γδ T cells stimulates the secretion of IL-33 in stromal cells to maintain the expansion of Treg cells in adipose tissue during development (Kohlgruber et al., 2018). Conversely, iNKT cells, ILC2s, and eosinophils are reduced in the adipose tissue during obesity and their presence is associated with a reduction in metabolic inflammation, increased insulin signaling and promotion of thermogenesis (Lynch et al., 2016; Lynch et al., 2009; Molofsky et al., 2015; Wu et al., 2011).

Besides innate immune cells, B and T cells also become dysregulated during obesity. B cells in healthy adipose tissue are thought to express IL-10 to negatively control adipose tissue inflammation (Nishimura et al., 2013). During obesity, although adipose B are fewer than T cells, their overall numbers are increased and contribute to insulin resistance by secreting autoimmune, pathogenic immunoglobulin G (IgG) antibodies and cytokines that drive inflammatory macrophages, Th17 polarization, and CD8^+ T cell cytotoxicity (DeFuria et al., 2013; Duffaut et al., 2009; Winer et al., 2011). Cytotoxic CD8^+ T cells increase with an HFD even before macrophages accumulate (Rausch et al., 2008) and along with increased Th1 cells contribute to insulin resistance during obesity (Nishimura et al., 2009; Pacifico et al., 2006; Winer et al., 2009). The expansion of T cells before infiltration of peripheral monocytes and macrophages occurs through antigen expression of resident ATMs, especially within CLSs, but the increase in T cells might not be exclusively through clonal expansion during obesity (Morris et al., 2013). Regulatory T cells and iNKT cells largely contribute to the homeostasis of adipose tissue and produce anti-inflammatory factors such as IL-10, IL-4, and transforming growth factor-β (TGF-β) to promote metabolic homeostasis (Feuerer et al., 2012; Lynch et al., 2012; Schipper et al., 2012). During obesity, both Treg cells and iNKT cells are reduced in adipose tissue (Feuerer et al., 2009; Lynch et al., 2009). How many of these immune cells are sensing metabolic dysregulation and macronutrient availability remains to be established.

**IMMUNE CELLS REGULATE THERMOGENESIS**

Maintenance of core body temperature in homeotherms through heat production is a high-priority metabolic event that is crucial for survival. The invaginations of the inner mitochondrial membrane that forms cristae are the sites of oxidative phosphorylation (OXPHOS) complexes that generate ATP (Kozak and Harper, 2000). In addition to ATP synthesis, mitochondrial OXPHOS generates heat as an energy byproduct. To enhance adaptive thermogenesis, adipocytes upregulate the expression of uncoupling protein 1 (UCP1) that forms pores in the inner mitochondrial membrane to allow protons to pass through without producing ATP (Kozak and Harper, 2000). Therefore, in the uncoupled mitochondria, the rate of OXPHOS is significantly boosted and releases heat instead of ATP. Although UCP1 was long thought to be the primary mediator of non-shivering thermogenesis, the discovery that UCP1^-/- mice are able to adapt to long-term cold exposure uncovered the possibility of alternative thermogenic mechanisms independent of UCP1 (Ukropce et al., 2006). More recently, studies have revealed that other mechanisms such as futile creatine cycling, sarcoplasmic reticulum Ca^2+-ATPase (SERCA)-mediated calcium cycling, and UCP3 can also contribute to fat thermogenesis (Ikeda et al., 2017; Kazak et al., 2015; Riley et al., 2016).

Macrophages control thermogenesis by controlling the bioavailability of catecholamines. Inhibition of MAOA in macrophages increases NE content in adipose tissue, leading to increased lipolysis and thermogenesis by upregulation of UCP1 (Camell et al., 2017). Moreover, ILC2s, eosinophils, iNKT, and γδ T cells have also been implicated in increasing thermogenesis and upregulating UCP1 (Brestoff et al., 2015; Hu et al., 2020; Lynch et al., 2016; Qiu et al., 2014). Notably, fibroblast growth factor 21 (FGF21), which gets induced during dietary restriction, can promote the expression of C-C motif chemokine ligand 11 (CCL11) by adipocytes to recruit eosinophils, suggesting that immune cells are actively regulated during adaptive adipose tissue remodeling (Huang et al., 2017). Future studies are needed to determine whether immune cells directly affect UCP1 and alternative thermogenic pathways, differentiation of de novo brown or beige adipocytes, or regulate the sympathetic nervous system to control heat production. Identification of such mechanisms could reveal strategies to divert the fate of dietary lipids from storage to heat production through increased mitochondrial uncoupling, thus reducing metabolic diseases emanating from lipotoxicity and obesity.

**INFLAMMATION AND ADIPOSE TISSUE FIBROSIS**

Metabolic perturbations such as diet-induced obesity or dietary restriction lead to rapid remodeling of the adipose tissue, where alterations in ECM proteins play an important role in maintaining adipose tissue homeostasis. During obesity, there are dynamic changes in the deposition of ECM components such as collagens, fibrillins, proteoglycans, and specific matrix metalloproteases. Although obesity is associated with an excessive accumulation of hypoxia-driven fibrosis that directly leads to poor metabolic output (Halberg et al., 2009), the regulation and interaction of the adipose ECM and the immune system is still being established. Chronic inflammation had been thought to be the main driver of fibrosis and metabolic dysfunction during obesity, but studies have revealed that fibrosis might precede and occur independently of tissue inflammation (Halberg et al., 2009). Furthermore, repression of fibrosis alone can improve metabolic parameters without largely affecting inflammation (Hasegawa et al., 2018; Khan et al., 2009). However, immune cells might contribute to the continued pathologic fibrosis during chronic obesity. Wang and colleagues have demonstrated that IFN-γ-producing ILC1s can increase TGF-β output by macrophages to increase fibrosis, whereas sensing of dying
adipocytes and hypoxia by Mincle and hypoxia-inducible factor 1-α (HIF1-α) in macrophages within CLSs can further drive adipose tissue fibrosis (Henegar et al., 2008; Tanaka et al., 2014; Wang et al., 2019). Recent studies suggest that Mincle might potentially be sensing cholesterol moieties released by dying adipocytes, given that human Mincle can bind crystalline cholesterol and Mincle was shown to sense cholesterol sulfate in mouse skin (Kiyotake et al., 2015; Kostarnoy et al., 2017). Further understanding of how different ECM components interact with the immune system to mediate adipose homeostasis and pathology remains to be elucidated.

**OBESITY IS NOT ACCELERATED AGING OF THE ADIPOSE RESIDENT IMMUNE SYSTEM**

Both obesity and aging are characterized by NLRP3 inflammation-driven, low-grade chronic inflammation and metabolic dysregulation. Despite these shared similarities, obesity is not an accelerated model of aging. Although aging is commonly associated with visceral obesity, there are distinct immunological changes that underlie the pathological disease progression of each condition (Figure 2).

In adipose tissue, obesity leads to an increase in most of the defined macrophage subsets (Jaitin et al., 2019; Silva et al., 2019). During aging, however, the opposite trend is observed where macrophage numbers modestly decline (Camell et al., 2017; Lumeng et al., 2011). Age-associated VAT ATMs are enriched for NLRP3-dependent senescence and catecholamine catabolism gene signatures, with growth differentiation factor 3 (GDF3) being the most highly upregulated gene with age (Camell et al., 2017). Although an accumulation of senescent pre-adipocytes, endothelial cells, and T cells have been described with age in adipose tissue, these signatures have yet to be highlighted in highly proliferative obese ATMs (Salvestrini et al., 2019). Careful investigation of how these newly defined subsets of macrophages and their niches change with age might help identify therapeutic targets in ameliorating metabolic pathogenesis in aging.

In contrast to the reduction of innate macrophage populations with aging, adaptive B and T cells increase in fat with age (Camell et al., 2019; Lumeng et al., 2011). Although there is also an increase in T and B cells in obese adipose tissue, during aging these cells accumulate in specific niches called fat-associated lymphoid clusters (FALCs). Therefore, FALCs increase their size and number with age (Lumeng et al., 2011). FALCs are a form of non-classical lymphoid structures that are not encapsulated like traditional lymph nodes but can form germinal centers and respond to immunological challenges (Cruz-Migoni and Caamaño, 2016). Although sterile peritoneal inflammation induced by zymosan increases the size and numbers of FALCs in visceral adipose depots, an increase in FALC formation is not associated with inflamed obese fat (Bénézech et al., 2015).

During aging, there is an NLRP3-dependent accumulation of adipose-tissue-resident B cells within FALCs that produce inflammatory mediators such as IL-1β and CCL2. Depletion of adipose B cells in aged mice improves lipolytic signaling and insulin sensitivity, identifying aged adipose B cells as important mediators of age-associated insulin resistance, lipolysis resistance, and adipose dysfunction (Camell et al., 2019).

Treg cells play important regulatory roles in protecting metabolic homeostasis in the adipose of young animals and their dramatic reduction during obesity contributes to pathology (Feuerer et al., 2009). Conversely, Treg cells accumulate in adipose with age (Bapat et al., 2015; Lumeng et al., 2011). Unlike young Treg cells, the accumulation of aged adipose Treg cells drive insulin resistance and depletion of Treg cells in aged animals improves metabolic health (Bapat et al., 2015). However, when aged animals are challenged with an HFD to induce obesity, metabolic homeostasis is not maintained by depletion of Treg cells, confirming that distinct mechanisms drive the pathophysiology of age- and obesity-associated insulin resistance (Bapat et al., 2015).

Other adipose-resident immune cells, which have been characterized in healthy and obese adipose tissue, still require additional examination in the context of aging. Although eosinophils, which are associated with promoting homeostasis in healthy adipose, are decreased in obese fat, there seem to be no substantial changes during aging (Bapat et al., 2015; Wu et al., 2011). Intra-T lymphocytes such as iNKT cells are decreased during obesity, whereas iNKTs significantly increase with age, and although γδT cells increase during obesity in the visceral adipose tissue, whether they are altered during aging still remains to be elucidated (Mehta et al., 2015). Surprisingly, ILC2s, which reside in visceral adipose tissues, including in FALCs, and produce IL-5 and IL-13 to recruit and maintain eosinophils, are also reduced with aging (Molofsky et al., 2015; Moro and Koyasu, 2010). In fact, many of the age-associated immunological changes that drive metabolic pathology predominantly occur within the visceral adipose. Although immune composition remains to be characterized within the BAT, the depletion of macrophages, and accumulation of FALCs and Treg cells with age occur mainly in the visceral adipose depots. Similarly, during obesity, changes in pro-inflammatory subsets such as macrophages are much stronger in visceral adipose depots than in subcutaneous adipose tissue (Weisberg et al., 2003). These depot-specific immune perturbations most likely drive tissue differences given that visceral adiposity is strongly associated with increased risk for metabolic dysfunction and disease, whereas SFAT has been considered to be more beneficial by acting as a metabolic sink that can buffer daily influx of nutrients to prevent ectopic lipid storage in visceral organs (Chusyd et al., 2016). As the immune system within adipose continues to be explored, it is becoming clear there are complex crosstalk between different immune cell types. How these homeostatic interactions become dysregulated during obesity and aging, and their specific tissue niches, remain to be carefully investigated.

**DIETARY PROTEIN AND AMINO ACID RESTRICTION**

Although the mechanisms of CR are not completely understood, protein quality and amino acid composition of diet have been more strongly associated with metabolic and age-associated health. Independently of caloric intake, low-protein and high-carbohydrate diets were found to have the strongest extension of lifespan (Solon-Biet et al., 2014). In addition to dietary protein restriction (PR), some studies suggest it is the restriction of essential amino acids (EAs) that drive beneficial effects, given that supplementing dietary restriction with EAAs but not
non-essential amino acids were sufficient to reverse longevity effects (Grandison et al., 2009; Yoshida et al., 2018). Restriction of specific EAAs, such as the restriction of sulfur-containing amino acids (SAAs), methionine and cysteine, or methionine restriction (MR), and deficiency of the branched chain amino acids, leucine, isoleucine, and valine, or branched chain amino acid restriction (BCAAR), have been extensively characterized to increase metabolic homeostasis and promote healthy aging (Fontana et al., 2016; Lee et al., 2016; Solon-Biet et al., 2014). These dietary interventions commonly lead to reduced adiposity and inflammation, increased insulin sensitivity, and lipolytic gene signatures, and reduction of lipogenesis in adipose tissue and liver (Kitada et al., 2019). Although much less characterized, restriction of tryptophan can also lead to increased lifespan and increases recovery to cold stress, suggesting an increase in thermogenic capacity (Segall and Timiras, 1975, 1976; Zapata et al., 2018). Surprisingly, these studies indicate that deficiencies of specific essential amino acids drive remodeling and programming of metabolic tissues to promote health. Despite numerous studies investigating the mechanisms driving increased longevity during these dietary interventions, alterations to the immune system and their role in tissue reprogramming have been lacking.

One of the pathways that are induced with CR, PR, and amino acid restriction, is the transsulfuration pathway (TSP) (Hine et al., 2015; Mitchell et al., 2016). The TSP involves the metabolism of SAAs and involves the catabolism of methionine to generate intermediates such as the methyl donor S-adenosylmethionine (SAM), S-adenosylhomocysteine (SAH), homocysteine, and cystathionine. The TSP also allows for the generation of cysteine through the action of cystathionine-γ lyase (CSE), which can further provide important metabolites and byproducts such as glutathione, pyruvate, and hydrogen sulfide (H2S) (Figure 3). Some TSP metabolites such as SAM and homocysteine are increased with obesity and aging and have been implicated with inflammation and disease risk (Elshorbagy et al., 2013; Obata and Miura, 2015; Rodríguez et al., 2006; Vayá et al., 2012).

Another exciting, relevant byproduct of the TSP is H2S. H2S is a gaseous signaling molecule produced by three mammalian enzymes, CSE, cystathionine-β synthase (CBS), and mercaptopyruvate sulfurtransferase (MPST), but some studies have shown that H2S might be produced via non-enzymatic reactions (Glorieux et al., 2020). Of note, lifespan extension induced by CR in Drosophila was abolished when treated with the inhibitor of CSE, propargylglycine (PPG) (Kabil et al., 2011). Overexpression of another TSP enzyme, CBS, and treatment with H2S increased median lifespan in C. elegans and yeast, respectively, highlighting TSP-mediated H2S production as an important mediator of dietary benefits (Hine et al., 2015). Interestingly, a role for H2S in immune responses is emerging. In T cells, H2S is needed for the differentiation of regulatory T cells by promoting demethylation at the Foxp3 locus by Tet1 and Tet2 (Yang et al., 2015). An anti-inflammatory role for H2S has been implicated by its action on nuclear factor kappa B (NF-kB) to regulate its transcriptional activity in macrophages (Sen et al., 2012) and its action on antioxidant gene regulation (Yang et al., 2013). These studies highlight that H2S might generally promote a more anti-inflammatory phenotype in immune cells. In myeloid cells, H2S can act specifically to inhibit inflammasome activation (Castelblanco et al., 2018; Lin et al., 2018), which might act as an important mechanism to reduce inflammation and initiate tissue remodeling during dietary interventions. However, studies with H2S have been...
largely limited to in vitro studies using H$_2$S donors, inhibitors, or whole-body deletions of TSP enzymes, particularly CSE. CBS deficiency in mice leads to neonatal lethality (Gupta et al., 2009), further complicating the investigation of the role of H$_2$S in immune cells. These complications have led to numerous contradictory reports of the action of H$_2$S on immune cells, such as the action of H$_2$S in regulating leukocyte adherence and tissue infiltration or NLRP3 activation (Basic et al., 2017; Spiller et al., 2010; Zanardo et al., 2006). Cell-specific and tissue-specific genetic deletion could allow for careful dissection of the role of the TSP in modulating immune response in physiological contexts.

Another pathway that is increased during protein and amino acid restriction is autophagy mediated by the integrated stress response. The integrated stress response allows for adaptive responses to various stresses such as starvation and ER stress. Stressors are sensed by four different sensors: general control nonrepressible 2 (GCN2), protein kinase R (PKR), heme-regulated inhibitor (HRI), and PKR-like endoplasmic reticulum kinase (PERK) (Pakos-Zebrucka et al., 2016). GCN2 senses amino acid depletion by sensing the accumulation of uncharged transfer RNAs (tRNAs) (Gallinetti et al., 2013). HRI recognizes heme deficiency, and PKR senses viral infection through activation by double-stranded RNA (Pakos-Zebrucka et al., 2016). Finally, PERK is activated by ER stress (Pakos-Zebrucka et al., 2016). Activation of these sensors are integrated by the activation and phosphorylation of eukaryotic initiation factor 2 (eIF2α), leading to global translational arrest (Pakos-Zebrucka et al., 2016). One central component of the integrated stress response is autophagy (Kroemer et al., 2010). In addition to GCN2 sensing of uncharged tRNAs, depletion of EAAs leads to interaction of their specific sensors such as SAMTOR (a SAM sensor), sestrin 2 (a leucine sensor), and CASTOR (an arginine sensor) with GATOR1 or GATOR2 to prevent mammalian target of rapamycin complex 1 (mTORC1) activation and promote autophagy (Kim and Guan, 2019) (Figure 3). Interestingly, autophagy and amino acid sensing also regulates immune function. It is now well established that autophagy inhibits inflammasome activation (Sun et al., 2017). In a model of colitis, PR and leucine restriction were able to reduce inflammation through the inhibition of NLRP3 inflammasome-mediated inflammation and reduction of Th17 differentiation. This response was dependent on amino acid sensing through GCN2 (Ravindran et al., 2016). Furthermore, treatment with halofuginone, which activates starvation responses by inhibiting prolyl tRNA charging, also inhibits Th17 cell differentiation (Sundrud et al., 2009). These studies highlight the induction of amino acid starvation responses in immune cells as potential strategies against inflammation-driven pathological states such as obesity, aging, and autoimmunity.

Although these different dietary amino acid restrictions might be inducing some common pathways, specific amino acids might target different pathways. Unlike leucine or BCAA diets, MR also induces hepatic FGF21 and lipolytic gene signatures independently of GCN2 (Lees et al., 2017). Instead, MR-specific hepatic changes are driven by PERK and glutathione depletion (Wanders et al., 2016). Thus, different mechanisms might drive adaptations to specific amino acid deficiencies in tissues and immune cells (Figure 3). Despite numerous studies investigating the broad metabolic adaptations that occur during PR, insight into how immune cell function is being altered has been lacking. A plethora of early studies have investigated immune defense in the context of protein malnutrition, suggesting alterations in both macrophage and lymphocytic responses to infection. However, these studies were conducted prior to the classification of broad immune subsets and advancement of technological tools, and they need to be revisited to properly understand how the immune system might be responding during PR without malnutrition in the context of both tissue adaptation and immune defense.

### INTEGRATED IMMUNOMETABOLIC RESPONSE TO CARBOHYDRATE AND CALORIC RESTRICTION

In an event of low glucose availability, such as food restriction, the limited glycogen reserves in the liver and muscle cannot sustain non-essential metabolic demand. Instead, triglycerides undergo fatty acid oxidation, ketogenesis, and ketolysis to support ATP production.

It is known that long-term CR lowers inflammation and protects against thymic lipatrophy and maintains T cell repertoire during aging (Yang et al., 2009a). Intriguingly, however, CR causes a major redistribution of circulating leukocytes. A two-year multicenter randomized controlled trial where healthy humans achieved approximately 14% CR (CALERIE-II) provided evidence that CR reduces the number of circulating lymphocytes and monocytes without compromising vaccine responses or increasing susceptibility to infections (Meydani et al., 2016). Similarly, studies from Jordan et al. (2019) found that 19 h of fasting in humans led to reduction of monocytes and DCs in blood but instead increased retention of pro-inflammatory Ly6C$^{hi}$ monocytes in the BM. In agreement with prior studies (De Rosa et al., 2015), fasting reduced systemic inflammation in a mouse model of multiple sclerosis. Importantly, monocytes could still respond and control Listeria monocytogenes infection during fasting in a peroxisome proliferator-activator receptor α (PPARα)-dependent manner (Jordan et al., 2019). Similarly, negative energy-balance-mediated reduction in mTOR also led to CXCL13-driven homing of naive B cells from Peyer’s patches to BM. Moreover, Collins et al. (2019) found that mice subjected to 50% dietary restriction for 3 weeks caused a loss of peripheral memory CD8 T cells and their surprising accumulation in the BM. Markedly, this redistribution of B and memory T cells led to enhanced protection against secondary bacterial infection (Collins et al., 2019). It is intriguing that during energy deficit, memory T cells do not prefer adipose tissue that is undergoing enhanced lipolysis with abundant fatty acids as energy substrates and home instead to BM. CR’s salutary effects on the immune system and control of inflammation require further characterization. From the current evidence, switch from glycolysis to fatty acid oxidation appears to be an important immunometabolic checkpoint affected by CR. For example, production of ketone bodies like β-hydroxybutyrate downstream of fatty acid oxidation, inhibits NLRP3 inflammasome-mediated inflammation and protects against influenza infection by expanding tissue-protective γδ T cells in lung and adipose tissue (Goldberg et al., 2019). Whether a low-carbohydrate, high-fat ketogenic diet that increases fatty acid oxidation and beta-hydroxybutyrate (BHB) can be harnessed to protect against inflammatory damage, as in COVID-19 immunopathology, requires careful testing. The endogenous immunometabolic mediators that drive CR...
salutary effects thus offer a promising avenue to regulate inflammation and enhance healthspan.

CONCLUDING REMARKS

Significant progress over the last decade has firmly established that reciprocal interactions between immune and metabolic systems are needed for the host to maintain homeostasis. Immunometabolism, not only encompasses immune-cell-intrinsic regulation of glycolysis, tricarboxylic acid (TCA) cycle, pentose phosphate pathway, and fatty acid metabolism to affect inflammation and effector functions, but also entails immune regulation of systemic whole-body metabolism and coupling of positive and negative energy balance to successful immune response. As outlined in this review, the integrated immunometabolic response is in fact vital for regulation of organismal metabolism and host defense. A major influencer of IIMR is the diet. It is evident that metabolic fate of fat, protein, and carbohydrates is important for immunologic function. However, how macronutrient intake elicits specific pathways in a host to either induce disease or promote health and longevity is only beginning to be understood. In addition, both immune response and metabolism are regulated by the autonomic nervous system, which are not under our conscious control. The neural regulation of immunometabolism, by which the autonomic nervous system integrates the central nervous system, immune system, and metabolic organs to maintain essential functions and prepare the host for mounting stressful challenges, is not well understood. Thus, study of neuroimmunometabolism could reveal new mechanisms to promote health and understand disease. Identification of immune cells like macrophages in sympathtetic nerve niches in adipose tissue represents one mode of neuroimmunometabolic crosstalk that controls inflammation and lipolysis setpoints. These advances have set the stage for the next era of immunometabolism studies where regulation of diet-driven metabolic checkpoints are likely to be revealed and potentially implemented in clinical practice to promote health.

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