

The Role of the Immune System in Metabolic Health and Disease

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In addition to the immune system's traditional roles of conferring anti-infectious and anti-neoplastic protection, it has been recently implicated in the regulation of systemic metabolic homeostasis. This cross-talk between the immune and the metabolic systems is pivotal in promoting “metabolic health” throughout the life of an organism and plays fundamental roles in its adaptation to ever-changing environmental makeups and nutritional availability. Perturbations in this intricate immune-metabolic cross-talk contribute to the tendency to develop altered metabolic states that may culminate in metabolic disorders such as malnutrition, obesity, type 2 diabetes mellitus (T2DM), and other features of the metabolic syndrome. Regulators of immune-metabolic interactions include host genetics, nutritional status, and the intestinal microbiome. In this Perspective, we highlight current understanding of immune-metabolism interactions, illustrate differences among individuals and between populations in this respect, and point toward future avenues of research possibly enabling immune harnessing as means of personalized treatment for common metabolic disorders.

Introduction

In most living multi-cellular organisms, metabolic homeostasis and the immune system influence each other in multiple manners. As early in the phylogenetic tree as *Drosophila*, immunity and metabolism are tightly linked structurally via the “fat body.” This organ is homologous with the mammalian liver, adipose tissue, hematopoietic and immune systems (Hotamisligil, 2006), and is hallmarked by Toll signaling-mediated immune activation suppressing growth and nutrient storage (DiAngelo et al., 2009) through transcriptional switching (Clark et al., 2013). In higher organisms and mammals, immune responses greatly vary between individuals (Brodin et al., 2015; Pulendran, 2014; Tsang et al., 2014), genders (Reardon, 2016), and genetic makeups (Boyd and Jackson, 2015; Li et al., 2016; Netea et al., 2012) and are modified throughout life (Kollmann et al., 2012), starting from birth and continuing throughout the course of pediatric and adult life into the elderly period. In each of these periods, immune-related processes impact metabolic processes through multiple mechanisms. The intimate interactions between these two seemingly unrelated systems have been puzzling scientists for years. One consideration governing immune-metabolic interactions includes sharing versus competition for energetic resources. This represents a trade-off between potentially conflicting processes such as the drive, on the one hand, for metabolic conservation of energy, versus the need, on the other hand, to implement energy-draining anti-infection immune defense mechanisms. Intriguingly, the relationship between the immune and metabolic systems is not only confined to resource sharing, but also includes interfaces in which cellular stress driven by metabolic perturbation also manifests as an inflammatory response putatively aimed at restoring homeostasis by adjusting broader biological functions, including endocrine and metabolic processes (Medzhitov, 2008).

In this Perspective, we portray principles of immune-metabolic interactions, and elaborate on the molecular mechanisms by which diet, the host genome, gut microbiome, and immune responses intertwine to influence metabolic homeostasis. We further discuss the broad clinical aspects by which aberrant immune activation may predispose the host to pathological metabolic states, ranging from features of the metabolic syndrome to malnutrition. As one of the focuses of this Perspective, we highlight examples demonstrating how person-specific environmental, genetic, and microbiome features may regulate complex immune-metabolic interactions. Finally, we suggest ways to harness the current knowledge in devising personalized interventions to manipulate the immune system as means of improving the host metabolic status and propensity to develop metabolic diseases.

Immune Contribution to Host Metabolic Physiology

Life comprises a dynamic succession of homeostatic equilibria, which entail physiological responses to ever-changing environmental exposures. In all of these physiological states, the immune and metabolic systems react to the changing environment and to the ensuing organismal need of adaptation. As part of this “dynamic equilibrium,” it is increasingly recognized that the immune and metabolic systems have co-evolved to signal to each other, thereby forming a complex network of interactions that determine the host's flexibility in response to shifting conditions. In the following section, we exemplify some of the interactions between the immune system and metabolism in common physiological states and showcase how they contribute to these important physiological responses (Figure 1).

The Neonatal Period

Early life is a critical phase in shaping of the developing immune and metabolic systems, a process substantially influenced by

	PREGNANCY / EMBRYONIC LIFE	INFANCY	ADULT	ELDERLY
Physiologic Conditions				
Immunity	• Mother (3rd Trimester): IFN-γ, IL-2, IL-6, TNF-α↑	• Infant: - Ig production - Inflammation↓ - Healthy Microbiome • Milk: IL-1, TNF-α, IL-6, IL-10, IL-18, MCP-1	• Adipose tissue: - Th2 cells - Tregs, eosinophils, M2 MΦ - IL-10, IL-4, IL-13	• TNF-α, IL-6↑ $\Rightarrow$ NFκB↑ • NLRP3 inflammasome activation, autophagy↓ HPA↑, Cortisol↑
Metabolism		Weight gain, bone maturation Liver, muscle, brain metabolism Insulin sensitivity	Insulin sensitivity	Insulin resistance, atherosclerosis
Pathologic Conditions				
Immunity	• Mother: - CRP, IL-6↑ • Adipose tissue: CD68+ MΦ, TNF-α, IL-6, IL-18 • Placenta: - TLR4↑ - IL-1β, IL-6, IL-8, MCP-1, CXCR-2↑ • Embryo: - IL-1, TNF-α, IL-6↑ • Adipose tissue: CD68+ MΦ, TNF-α↑, CCR2↑, GLUT-4↓ • Liver: Hepatic steatosis, lipogenesis↑, FFA oxidation↓, ROS↑, altered hepatic immunity	• Inflammation↑ • CD163↑, iNKT↓, TNF-α↑ IL-6↑, IgG↑, IgA↑ • Adipose tissue: - TLR↑ - Lephin↑, adiponectin↓ • HPA activation, microgliosis • Hypothalamic TLR4, IL-6, NF-κB↑ • Milk: TGF-β2↓, sCD14↓, IL-6↓	• TNF-α, IL-6, IL-1β, CCL2, CRP↑ $\Rightarrow$ NF-κB↑, JNK↑ • Adipose tissue: - ATM↑ - MCP-1, LTB4↑, M1 MΦ↑, Tregs↓, Teff↑, B cells↑, mast cells↑, eosinophils↓ - IL-4↓ - Adiponectin↓, leptin↑, lipolysis↑, FFA↑, TG synthesis↓	• TNF-α↑, IL-6↑, IL-8↑, CRP↑
Metabolism	Childhood obesity, HTN, insulin resistance, T2DM	Insulin resistance	Insulin resistance	Sarcopenia

Figure 1. Immune-Metabolic Interactions throughout Life in Physiological and Pathological Conditions

The immune-metabolic cross-talk is characterized by plasticity throughout the lifespan of an organism, as it adapts to intrinsic and extrinsic cues. The top panel delineates typical immune alterations and their complementing metabolic manifestations in physiological states of pregnancy, embryonic life, neonatal period, adulthood, and senescence. The bottom panel presents pathological metabolism in the corresponding states, i.e., obesity in pregnancy, embryonic life, neonatal period, adulthood, and frailty in old age.

dietary alterations and signaling by the gut microbiome. At this period, consumption of breast milk furnishes the newborn with passive protection through maternal antibody transfer (Gordon et al., 2012) and provides an armamentarium of immune functions including the maturation and repair of intestinal mucosa, promotion of immunoglobulin (Ig) A production, oral tolerance induction, secretion of cytokines and chemokines (Böttcher et al., 2000), prevention of pathogen colonization, and regulation of inflammatory gene expression (*Irf1*, *Slc26a3*, *Vdr*, *Zmiz1*, *Pla2g2a*) (Rogier et al., 2014; Wacklin et al., 2014). In parallel, human milk contributes to the establishment of metabolic homeostasis. As one example, sialylated human milk oligosaccharides promoted weight gain and bone maturation and impacted liver, muscle, and brain metabolism, and their

reduced abundance in breast milk was associated with stunted infant growth.

Intriguingly, these effects on host metabolism may be mediated by milk-driven modulation of host immune system and the gut microbiome (Charbonneau et al., 2016). For example, Lacto-N-fucopentaose III (LNFP III), an immunomodulatory glycan found in human milk, improved glucose tolerance and insulin sensitivity in mice fed with high-fat diet (HFD) partially by increasing interleukin (IL)-10 secretion by macrophages and dendritic cells, thereby reducing white adipose tissue inflammation and potentiating insulin response and decreased hepatic lipogenesis. These inter-connected immune and metabolic effects were mediated by the extracellular signal-regulated kinase (Erk)-Ap1 pathway (Bhargava et al., 2012). Additionally, a link has

been found between cytokine levels in breast milk and maternal weight, as lower levels of transforming growth factor (TGF)- β 2, soluble CD14, and IL-6 were exhibited in milk obtained from mothers with higher weights, and these findings were correlated to specific alterations in the gut microbiome configuration (Collado et al., 2012). Similarly, polyamines, which contribute to intestinal intraepithelial lymphocyte maturation, were found in lower concentrations in breast milk obtained from obese mothers and were partially corrected by dietary intervention (Ali et al., 2013). Moreover, the microbiome may integrate the newborn's metabolic wellness (Blanton et al., 2016; Schwarzer et al., 2016; Trasande et al., 2013) and immune maturation (Fagarasan et al., 2002; Gaboriau-Routhiau et al., 2009; Macpherson and Uhr, 2004; Zhang et al., 2016). Microbiome modulation in the neonatal period may have long-standing effects on the newborn's metabolic outcomes. For example, antibiotic administration, in both mice and humans, was suggested to impact weight gain later in life (Cho et al., 2012; Trasande et al., 2013), a phenotype transferable by microbiota transplantation into germ-free mice (Cox et al., 2014).

Together, these findings underscore the significance of breast milk to the developing infant in terms of immune priming, which in turn dictates its metabolic phenotype. In light of these observations, one open, currently unresolved issue includes the prospect and mechanisms by which metabolic traits may be transferred from mothers to infants by immunomodulation through breastfeeding and possible means by which they can be externally manipulated. One such putative intervention may include breast milk immune components, including cytokines, which, if found to metabolically impact the developing infant, could be supplemented to the maternal or infant diet. Additionally, the gut microbiome configuration may be amenable to manipulation by targeted antibiotic or probiotic interventions in reprogramming immune-metabolic interactions in the developing gut.

Pregnancy

Mammalian pregnancy constitutes another physiological context exemplifying the importance of immune-metabolic interactions for both the mother and the embryo. It constitutes a unique physiological state, in which immune tolerance to the developing fetus coincides with immune activation in order to induce relative insulin resistance necessary to meet the needs for higher energy uptake by the mother, coupled with an increased demand for glucose by the embryo. Pre-gravid metabolic status contributes to metabolic inflammation manifesting during pregnancy, as obese pregnant women featured enhanced systemic, adipose tissue, and placental inflammation, including increased circulating C-reactive protein (CRP) and IL-6, adipose tissue and placental accumulation of CD68⁺ macrophages (Basu et al., 2011), and enhanced expression of Toll-like receptor (TLR)-4, IL-1 β , IL-6, IL-8, monocyte chemoattractant protein (MCP)-1, and CXC motif chemokine receptor (CXCR)-2 (Roberts et al., 2011). Furthermore, cross-generational transfer of metabolic properties between the mother and her offspring may be modified via immune programming occurring in utero. Fetuses exposed to limited nutrient availability and the resultant low birth weight feature an increased risk for metabolic diseases as adults (Barker, 1998) and impaired fetal immune development through alteration of T cell epigenetic regulation (Martino and Prescott, 2010), an effect potentially mediated by increases in the embryo's

immune system exposure to glucocorticoids (Lesage et al., 2001). Conversely, maternal obesity lead to embryonic accumulation of specific subsets of macrophages and expression of pro-inflammatory cytokines (IL-1, tumor necrosis factor [TNF]- α , IL-6) (Challier et al., 2008), some of which (CRP) were apparent even at the age of 12 (Leibowitz et al., 2012). Indeed, pups of mice fed HFD featured impaired metabolic profile, including increased hepatic steatosis and epigenetic changes typical of non-alcoholic fatty liver disease (NAFLD), augmented lipogenesis, and decreased free fatty acid oxidation (Brumbaugh and Friedman, 2014). These changes were coupled to an aberrant hepatic immunity, including activation of hepatic macrophages and natural killer T (NKT) cells (Thorn et al., 2014), increased Kupffer cell numbers, impaired phagocytic function and raised reactive oxygen species (ROS) synthesis, reduced NKT cells and overexpression of hepatic IL-12 and IL-18 (Mouralidharane et al., 2013), and an aberrant systemic immunity, manifesting as enhanced susceptibility to infections, increased intestinal inflammatory responses and enhanced autoimmunity and allergic reactivity.

Interestingly, these changes were associated with intestinal dysbiosis (Myles et al., 2013). As such, functional microbiome alterations, including enhanced energy harvest, were suggested to associate with the stage of pregnancy and levels of pro-inflammatory cytokines (interferon [IFN]- γ , IL-2, IL-6, and TNF- α), possibly implying that the microbiome may contribute to the relative state of pregnancy-induced insulin resistance, by driving a state of persistent low-grade mucosal inflammation (Koren et al., 2012). However, these findings were contested by another study (DiGiulio et al., 2015), a discrepancy meriting further studies.

Aging

The aging process entails the inevitable decline in various body systems and physiological processes at advanced stages of an organism's lifespan. While this process, involving pronounced immune and metabolic changes, is considered physiological, it also predisposes to a number of aging-related pathological conditions including neurodegenerative diseases and sarcopenia (López-Otín et al., 2013). The term "inflammaging" describes the low-grade pro-inflammatory shifts in innate and adaptive immunity (Franceschi et al., 2000). These aging-related immune changes manifest in increased expression of pro-inflammatory genes, elevated pro-inflammatory cytokine levels, such as TNF- α and IL-6, and activation of the transcription factor nuclear factor (NF)- κ B, in concert with elevation of anti-inflammatory agents, such as cortisol and upregulation of the hypothalamic-pituitary-adrenal (HPA) axis (Salminen et al., 2012).

These immune-related changes are often tightly linked to an enhanced propensity for developing features of the metabolic syndrome. For example, age-associated over-activation of NF- κ B induced "signal 1" for NOD-like receptor family pyrin domain containing (NLRP)-3 inflammasome activation (Salminen et al., 2012; Youm et al., 2013) leading to IL-1 β -driven impairment of insulin signaling (Wen et al., 2011) and weight gain (Vandamagsar et al., 2011).

Another hallmark of "inflammaging" is the progressive decline in autophagy, ultimately leading to an increase in ROS production and inflammasome activation (Green et al., 2011; Rubinstein et al., 2011). Impaired autophagy in the hypothalamus activated the hypothalamic I κ B kinase β pathway and induced

local inflammation, which contributed to obesity and insulin resistance in mice consuming HFD (Meng and Cai, 2011). Similarly in yeast, flies and worms exogenous administration of spermidine, a polyamine whose intracellular concentration diminishes with aging, was found to enhance autophagy and promote longevity through induction of hypoacetylation of histone H3 (Eisenberg et al., 2009). Furthermore, aging-related impaired intestinal barrier function has been correlated with a reduced lifespan and associated, through unknown mechanisms, with impaired insulin signaling (Rera et al., 2012).

The microbiome may also be linked to the aging process. In *Drosophila*, gut dysbiosis was associated with a decline in intestinal barrier integrity (Clark et al., 2015). In humans, features of the aging microbiome were significantly correlated with “inflammaging” markers (serum TNF- α , IL-6, IL-8, and CRP) and with metabolic readouts such as blood pressure and calf circumference, a marker of sarcopenia (Claesson et al., 2012). Moreover, the strain *Faecalibacterium prausnitzii* was reduced in the gut microbiome of centenarian population and was negatively correlated with levels of pro-inflammatory cytokines (IL-6 and IL-8) (Biagi et al., 2010). Replenishment of *Bifidobacterium* in elderly subjects resulted in altered TNF- α and IL-10 levels (Ouwehand et al., 2008).

With the increase in life expectancy and the proportion of elderly population in Westernized societies, alleviating the burden of metabolic morbidity associated with aging will become an inevitable challenge to health economies. Achieving this by means of immunomodulation, promotion of autophagy, or microbiome manipulation holds great promise; however, they might introduce risks of infection and carcinogenesis. Pursuit of this exciting prospect is expected to take a center stage in immunology research in coming years.

Mechanisms of Environment-Microbiome-Host Immune Interactions in Regulating Metabolic Homeostasis

Immune-metabolic homeostasis involves a set of complex interactions between the host immune and “non-immune” organs (such as adipose tissue, liver, and pancreas), its microbiota, and multiple related environmental factors, such as nutrition, antibiotics treatment, and pathogenic infections. Factors such as enhanced industrialization and urbanization, profound dietary alterations, increased usage of antibiotics, and improved hygiene altered the immune-metabolic crosstalk, thereby potentially contributing to the emergence of both immune- and metabolic-mediated disorders (“the hygiene hypothesis”). In the following sections we will highlight notable examples of environmental, dietary, and genetic factors impacting immune-metabolic interactions and how they may affect homeostasis and the propensity for metabolic derangements.

Nutrition in Immune-Metabolic Interactions

The “diet hypothesis” suggests that dietary composition and feeding timing constitute a major factor contributing to immune regulation of metabolism (Maslowski and Mackay, 2011). Diet modulates immune activity in multiple manners. As exemplified below, commonly consumed food ingredients may impact immunity either directly by interacting with immune cells via receptor-mediated signaling, or indirectly via interactions with the gut microbiota by modulating metabolites, which in turn signal to the host and may affect its metabolic homeostasis (Figure 2).

Aryl Hydrocarbon Receptor Modulators. Nutrients obtained by consumption of cruciferous vegetables (Kiss et al., 2011; Li et al., 2011) and associated chemicals such as indole-3-carbinol are converted into aryl hydrocarbon receptor (AhR) ligands following gastric passage and impact immune cells through signaling to AhR (Kewley et al., 2004). Intestinal intraepithelial lymphocytes (IELs), highly expressing AhR, are located in close vicinity to gut epithelial cells and play an important role in promoting epithelial repair (Chen et al., 2002) and preventing epithelial invasion by gut bacterial populations (Ismail et al., 2011). Signaling to AhR on IEL dictates the localization of IELs in the epithelium and in this way promotes normal immune function along the intestinal mucosa (Kiss et al., 2011; Li et al., 2011). Moreover, dietary AhR ligands can signal to RAR-related orphan receptor gamma (ROR γ t)-expressing innate lymphoid cells (ILC) leading to production of IL-22, which in turn regulates metabolism by improving insulin sensitivity, promoting gut barrier integrity, and by modulating lipid metabolism in adipose tissue and the liver (Wang et al., 2014).

Vitamin D. Vitamin D is obtained from diet in its inactive form, followed by a series of biochemical conversion steps involving the liver, skin, and kidneys, including hepatic hydroxylation into 25(OH)D3 followed by renal hydroxylation into 1,25(OH) $_2$ D3, the most active vitamin D isoform. Vitamin D regulates mineral metabolism and maintains a healthy mineralized bone structure, but it also plays important immunomodulatory roles. As such, vitamin D hydroxylation can also take place enzymatically in dendritic cells, B cells, and T cells. The produced 1,25(OH) $_2$ D3 binds heterodimers of vitamin D receptor and retinoid X receptor, which then bind nuclear vitamin D response elements leading to regulation of cellular differentiation and proliferation (Chen et al., 2007). Vitamin D has been shown to be important in the proliferation capacity of IELs, as its deficiency results in decreased IEL numbers (Bruce and Cantorna, 2011), and in tight-junction stabilization (Fujita et al., 2008). It therefore plays a crucial role in maintaining immunologic homeostasis and gut barrier integrity, processes impacting metabolic homeostasis.

Lipids. Metabolism of dietary lipids leads to the production of fatty acids that constitute a major source of biological lipids, playing important roles in structuring cell membranes and providing energy stores. Western diets are high in saturated fatty acids that are preferentially deposited into adipose tissue. Consumption of high saturated fatty acid diet leads to adipocyte and circulating immune cell activation through TLR4 signaling, resulting in TNF- α and other pro-inflammatory cytokine secretion (Rocha et al., 2016). The resultant subclinical inflammation involves adipose tissue recruitment of pro-inflammatory M1 macrophages, which contributes to the emergence of insulin resistance (Lumeng et al., 2007b). Polyunsaturated fatty acids, in contrast, are mainly derived from fish and plant-derived foods and are utilized in the synthesis of compounds such as steroid hormones. Omega-3 polyunsaturated fatty acids, richly available in the Mediterranean diet, play a role in suppressing inflammation (Endres et al., 1989) by directly interacting with adipose tissue immune cells exerting anti-inflammatory effects (Oh et al., 2010). As such, omega-3 polyunsaturated fatty acid binding the G protein-coupled receptor 120 (GPR120), highly expressed in pro-inflammatory M1 macrophages, activates the β -arrestin2 signaling pathway leading to an anti-inflammatory effect by

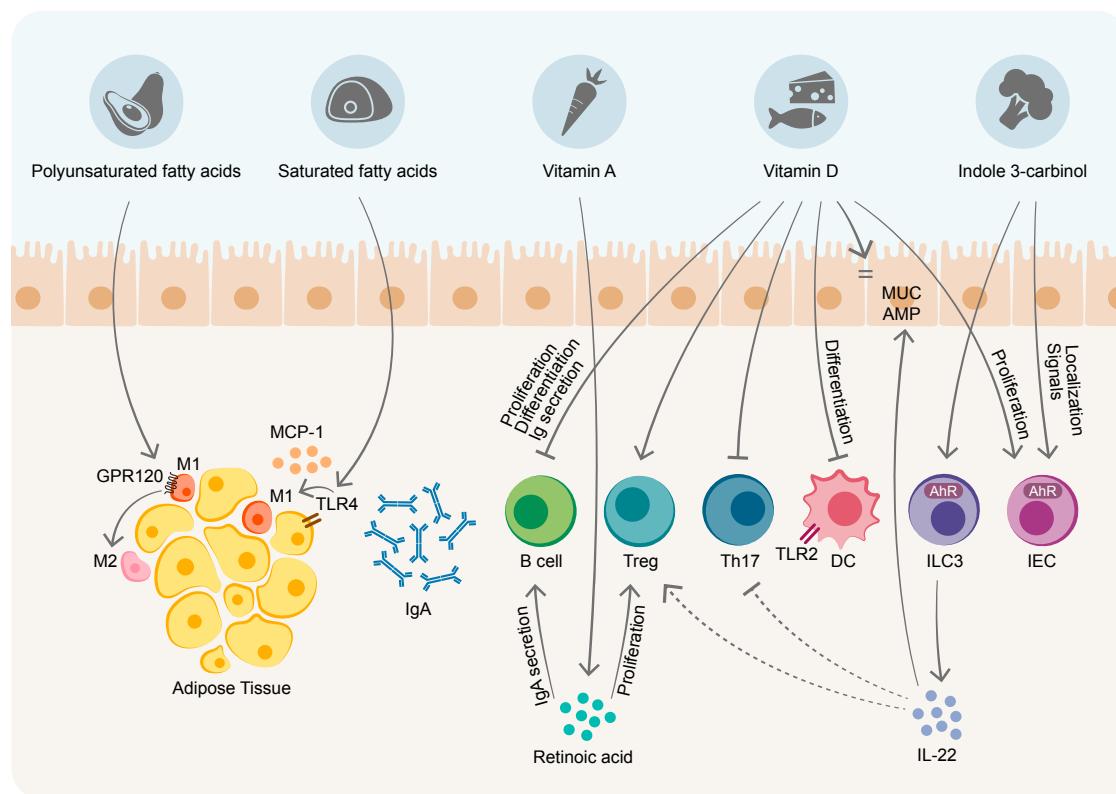


Figure 2. Nutrients and Their Immune and Metabolic Effects

Consumption of various nutritional constituents exert metabolic effects by modulating the immune system, some mainly by activating local hematopoietic cells and maintaining the gut mucosal barrier integrity (indole-3-carbinol, vitamin D, and vitamin A), and others by interacting with adipose tissue immune cells (saturated and polyunsaturated fatty acids).

inhibition of cytokine- and TLR-mediated pathways (Oh et al., 2010). This results in an infiltration of adipocytes with anti-inflammatory M2 macrophages that protect adipose cells by mitigating inflammation and maintaining adipocyte insulin sensitivity (Lumeng et al., 2007a). Lipoxin, resolvins, and protectins, metabolites of polyunsaturated fatty acids, have also been implicated in the resolution of inflammation due to their anti-inflammatory properties. Additionally, dietary fibers metabolized exclusively by the gut microbiome into short-chain fatty acids (SCFAs), such as acetate, butyrate, and propionate, mediate immune responses, such as cytokine and chemokine production in intestinal epithelial and mononuclear cells (Kim et al., 2013; Masui et al., 2013), neutrophil chemotaxis (Vinolo et al., 2011), immune cell differentiation, anti-inflammatory processes (Singh et al., 2014), and inflammasome activation (Macia et al., 2015); and impact the hematopoietic repertoire (Trompette et al., 2014) through their signaling via G protein-coupled receptors, such as GPR41, GPR43, and GPR109A (Thorburn et al., 2014). In parallel, SCFAs suppress appetite (Psichas et al., 2015), regulate leptin production and lipolysis in adipocytes (Ge et al., 2008; Xiong et al., 2004), and protect against insulin-mediated fat accumulation (Kimura et al., 2013). Although the association between the inflammatory and the metabolic properties of SCFAs is not fully elucidated, one may speculate that in the absence of dietary fibers, SCFAs are depleted in the gut and the epithelial barrier integrity is compromised, thereby resulting in systemic endotox-

emia, leading to adipose tissue inflammation and insulin resistance (McKenzie et al., 2015). Alternatively, SCFAs may confer a direct role in inflammatory processes through their regulation of adipokine production by adipose tissue (Lord et al., 1998) (Figure 3).

Host Genetics in Immune-Metabolic Interactions

In addition to diet, host genetics constitute an important host-intrinsic contributor to the induction and maintenance of immune-metabolic homeostasis. Large genomic-scale candidate gene approaches identified genetic contributions to metabolic diseases (Chen et al., 2008; Voight et al., 2010), among them a number of immune-related genes. A large-scale meta-analysis approach identified the immune-cell receptor *CD44* as a candidate gene implicated in T2DM (Kodama et al., 2012). *CD44* encodes an immune-cell receptor that regulates immune cell migration and may be involved in adipose tissue inflammation leading to insulin resistance. Another (Arora et al., 2011) cross-sectional study encompassing 6,720 individuals identified significant associations between single nucleotide polymorphisms (SNPs) and predisposing metabolic readouts. Specifically, the *IL6* variant rs7801406 was associated with lower fasting insulin levels, and the *TNFA* variant rs3039662 was associated with elevated fasting insulin levels. Additionally, SNPs in the *TNFA* and *CRP* genes were found to be associated with serum HDL-C levels. The *TNFA* variant rs1800630 was associated with lower serum HDL-C levels, and the *CRP* variant rs1205

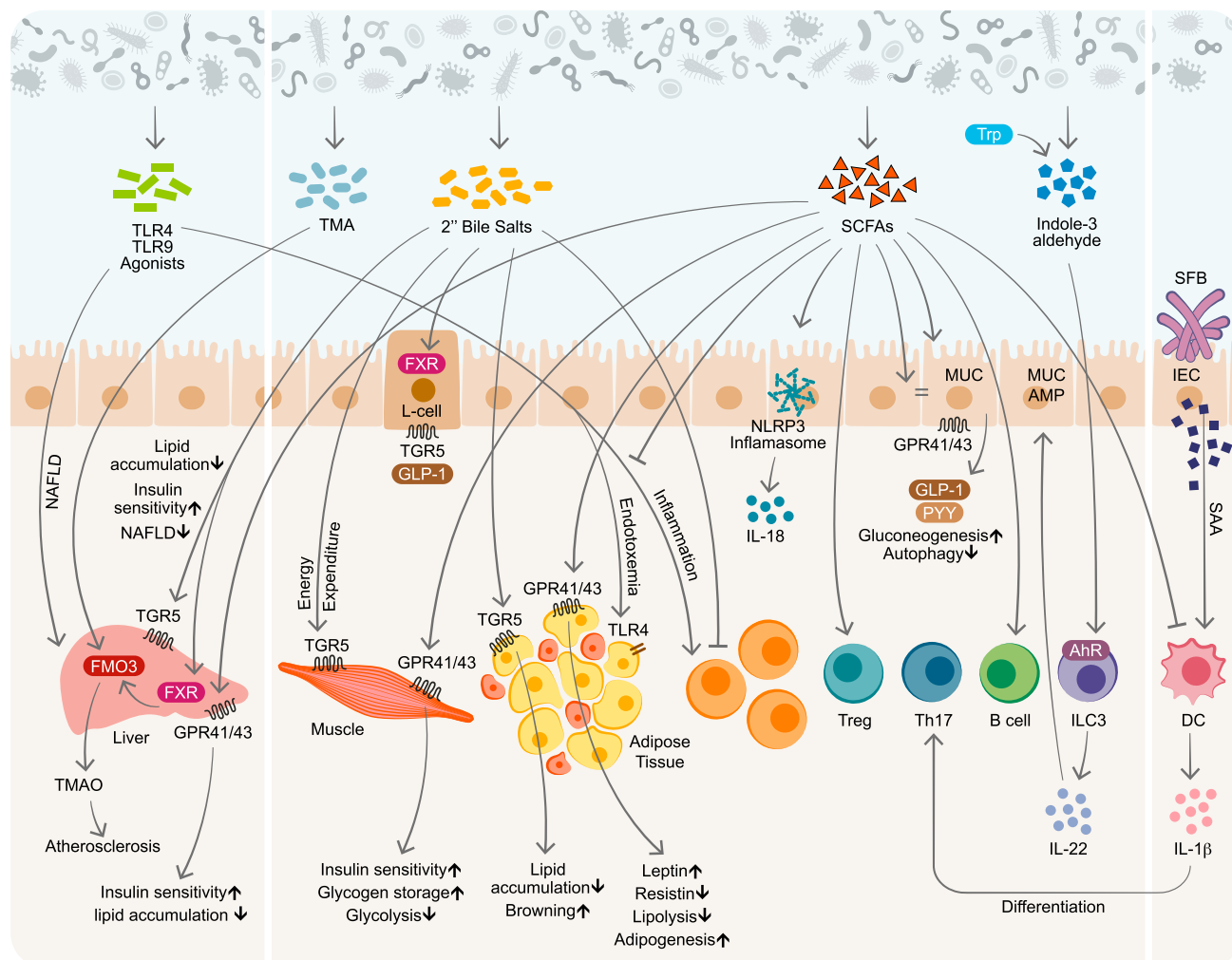


Figure 3. The Microbiome and the Immune-Metabolic Cross-Talk

The microbiome interacts with the host immune system to regulate metabolism by various mechanisms: direct physical contact, production of metabolites, and shedding of structural components. These affect metabolic homeostasis by local mucosal immune modulation and by remote alteration of metabolic organs, such as adipose tissue, muscle, and the liver.

was associated with lower serum HDL-C levels. In addition to highlighting genetic contributions linking immunity and metabolic homeostasis, these findings present an interesting prospect for identification of potentially usable genetic biomarkers for early detection of T2DM.

Host Epigenetics in Immune-Metabolic Interactions

Epigenetics constitute an important mechanistic link, by which environmental cues may impact the host gene expression, and thus contribute to immune and metabolic system cross-regulation. For example, a study investigating epigenetic changes in peripheral blood leukocytes in obese individuals identified an alteration in methylation of two genes that modulate T cells and macrophages (Waterland and Michels, 2007). The *UBASH3B* and *TRIM3* genes were found to feature higher and lower levels of methylation, respectively. Similarly, methylation in the *TLR2* and *TLR4* genes was linked to obesity and correlated with certain microbiome compositions (Remely et al., 2014a). Moreover, methylation markers in genes related to inflammatory

pathways (such as *TNFRSF4*, *MAP3K2*, and *IL5RA*) have been elucidated in obese individuals in a recent epigenome-wide association study (Wahl et al., 2017). However, causality was not established, and it is therefore not clear whether changes in methylation levels indeed altered immune function. Interestingly, it has been proposed that hyperglycemia can trigger persistent epigenetic activation of inflammatory genes, such as NF- κ B-p65, through alteration in the histone methylation landscape (Brasacchio et al., 2009). On a more global level, increased methylation levels in B cells were found in obese and T2DM patients (Simar et al., 2014), while increased global methylation levels were found in natural killer (NK) cells of T2DM patients (Simar et al., 2014). These global increases in the methylation epigenetic map of specific immune cells correlated to insulin resistance and may be indicators of immune cell functional alterations leading to metabolic dysfunction. Obesity involves polarization of adipose tissue macrophages (ATMs) from an anti-inflammatory M2 state to a pro-inflammatory M1-like state

(Mantovani et al., 2004). In these cells, de novo methylation is carried out through DNA methyltransferase 3a and 3b (DNMT3a and DNMT3b). Saturated fatty acids (characteristic of obesity) resulted in increased DNMT3b leading to M1 polarization, a hallmark of adipose tissue in obesity, and adipose tissue inflammation (Yang et al., 2014b).

The gut microbiome plays an important part in epigenetic alterations pertaining both to metabolism and immunity, namely through SCFAs, which act as histone deacetylase inhibitors to regulate the expression of immune-related genes and thereby attenuate inflammation (Aoyama et al., 2010; Berndt et al., 2012). Intriguingly, many nutrients and microbiome-derived compounds, including SCFAs, readily cross the placenta and have therefore been implicated in epigenetic immune reprogramming and long-term metabolic perturbations in the offspring of susceptible mothers (Wesolowski et al., 2017). Other epigenetic mechanisms, such as methylation in the promoter region of genes involved in inflammation and metabolism, have been exhibited in obese or diabetic individuals (Remely et al., 2014b; Rönn et al., 2015) and have been associated with certain microbiome compositions (Kumar et al., 2014).

Immune-Metabolic Interactions in Metabolic Perturbations

The importance of the above intricate interactions between the immune and the metabolic systems is best exemplified in several defined states of metabolic disturbances, ranging from over- or under-nutrition to overt manifestations of the metabolic syndrome. In most instances of perturbed metabolism, inflammation is a contributing or a regulating factor and involves immune signaling either in bona fide hematopoietic-derived immune cells or in tissue resident cells.

Obesity and the Metabolic Syndrome

The metabolic syndrome is comprised of closely associated, co-occurring, and highly prevalent disorders, including obesity, T2DM, hypercholesterolemia, non-alcoholic fatty liver disease, and their multiple complications (Després and Lemieux, 2006). In recent years it has become evident that systemic low-grade inflammation in the liver, muscle, and adipose tissue is a major contributor to the development of obesity and insulin resistance (Cai et al., 2005; Itani et al., 2002; Lumeng and Saltiel, 2011; Weisberg et al., 2003; Xu et al., 2003). The term “para-inflammation” was coined by Ruslan Medzhitov (Medzhitov, 2008) to characterize immune responses in which persistent tissue stress by a variety of stimuli, such as advanced glycation end products (AGEs) and oxidized lipoproteins, triggers maladaptive chronic non-resolving immune activation, which is capable of resetting homeostatic set-points and thereby inhibiting insulin signaling pathways and prompting the development of insulin resistance, ultimately driving all components of the metabolic syndrome. Hence, insulin resistance could serve as a transient adaptive mechanism, diverting blood glucose to leukocytes and other cell types required for preservation of homeostasis and tissue repair upon acute infection. However, the long-term consequences of such adaptive mechanism may be metabolically detrimental, particularly in cases of chronic non-resolving inflammation.

Multiple lines of evidence link chronic activation of pro-inflammatory pathways to obesity-related insulin resistance. Cytokines

and chemokines such as IL-6, IL-1 β , MCP-1, macrophage migration inhibitory factor (MIF), and TNF- α are released by both adipocytes and immune cells, thereby contributing to the development of obesity (Scherer, 2006). Furthermore, TNF- α neutralization improves insulin sensitivity (Hotamisligil et al., 1993; Uysal et al., 1997), and deletion of IKK- β protects mice from the development of insulin resistance (Arkan et al., 2005; Yuan et al., 2001). Similarly the JNK pathway is over-activated in the liver, muscle, and adipose tissue in mouse models of obesity, while its absence results in reduced adiposity and improved insulin sensitivity (Hirosumi et al., 2002). Anti-inflammatory cytokine levels are also altered in obesity, including upregulation of IL-1 receptor antagonist (IL-1Ra) (Juge-Aubry et al., 2003) and downregulation of secreted frizzled-related protein 5 (SFRP5) (Ouchi et al., 2010). Concordantly, obesity in humans has been associated with an increased risk for autoimmune diseases (Versini et al., 2014). Additionally, in vivo administration of IL-10 prevents IL-6 induced insulin resistance (Kim et al., 2004; Schottelius et al., 1999). Thus, the balance between pro- and anti-inflammatory cytokines seems likely to impact metabolic homeostasis.

Hematopoietic Mediators of the Metabolic Syndrome

Obesity is associated with increased numbers of ATMs, which comprise up to 40% of obese adipose tissue cells (Weisberg et al., 2003). ATM-mediated inflammation is one of the causes of insulin resistance (Lumeng et al., 2007b; Weisberg et al., 2003; Xu et al., 2003), by secretion of cytokines suppressing insulin signaling through local, paracrine and endocrine (systemic) pathways (Li et al., 2015b; Osborn and Olefsky, 2012; Spite et al., 2011).

Following adipocyte secretion of MCP-1 and leukotriene B4 (LTB4), monocytes are recruited to adipose tissues where they differentiate into ATMs, which secrete TNF- α , IL-6, and IL-1 β that attract additional macrophages, which lead to the activation of JNK and IKK- β (Hirosumi et al., 2002), and increased transcription of inflammatory genes. Genetic deletion of inflammatory pathways in macrophages, such as IKK- β , JNK1, or fatty acid-binding protein 4 (FABP4), was shown to protect from obesity-induced insulin resistance (Arkan et al., 2005; Mauer et al., 2010). In contrast, deletion of peroxisome proliferator-activated receptor- γ (PPAR- γ), a transcription factor mediating anti-inflammatory and insulin-sensitizing effects, increased insulin resistance and glucose intolerance (Hevener et al., 2007; Odegaard et al., 2007).

In addition to macrophages, other immune cells feature differential adipose tissue infiltration during obesity, thereby contributing to insulin resistance. For example, monocytes migrate to adipose tissue, polarize to the inflammatory M1 state, and secrete pro-inflammatory factors such as TNF- α . Furthermore, adipose tissue Tregs are reduced and effector T cells and B cells are expanded during obesogenic conditions, collectively contributing to the inflammatory process (Deiuliis et al., 2011; Feuerer et al., 2009). In the absence of T lymphocytes, RAG-1 deficient mice developed insulin resistance when fed HFD, while CD4+ T cell transfer normalized glucose tolerance in these mice, suggesting a protective metabolic role for lymphocytes against insulin resistance (Winer et al., 2009). Similar to T cells, B cells also accumulated in visceral adipose tissue under HFD conditions, where they promoted T cell activation that

further contributed to M1 polarization of macrophages and insulin resistance (Winer et al., 2011).

In addition to ATMs, other immune cells take part in the metabolic syndrome. Conflicting reports highlighted possible roles of mast cells in adipose tissue inflammation (Gutierrez et al., 2015; Liu et al., 2009). Deletion of NK cells in obese mice prevented macrophage accumulation and ameliorated insulin sensitivity (Wensveen et al., 2015). Regulation of macrophage activation is further maintained by eosinophils, whose levels were reduced in adipose tissue in obesity, while their absence resulted in adipose tissue IL-4 deficiency, leading to attenuated M2 activated macrophages, ultimately leading to enhanced inflammation and insulin resistance (Wu et al., 2011). Similar cellular changes have been observed in humans (Cancello et al., 2006; Dalmás et al., 2014). A pro-inflammatory intestinal environment was also suggested to contribute to obesity and metabolic syndrome, as the prevalence of inflammatory bowel disease (IBD) was increased in obese individuals (Calle and Kaaks, 2004). Furthermore, obesity was shown to trigger small intestinal inflammation characterized by increased T cell density and pro-inflammatory cytokines, possibly contributing to local insulin resistance in enterocytes (Johnson and Olefsky, 2013; Monteiro-Sepulveda et al., 2015).

Non-hematopoietic Mediators of the Metabolic Syndrome

In addition to bona fide immune cells, adipocytes secrete adipokines, among which are leptin, adiponectin, resistin, and visfatin, which provide an important link between obesity, insulin resistance and inflammation (Kusminski et al., 2005; La Cava and Matarese, 2004). Apart from its orixogenic effects and direct correlation to insulin resistance, leptin modulates the function of neutrophils (Caldefie-Chez et al., 2001; Mancuso et al., 2002), NK cells and macrophages, increases the expression of adhesion molecules and the secretion of pro-inflammatory cytokines such as IL-6, IL-12, and TNF- α , enhances naive T cell proliferation and contributes to maturation and survival of thymic T cells (Howard et al., 1999; Lord et al., 1998; Martín-Romero and Sánchez-Margalet, 2001).

Adiponectin levels are inversely correlated with insulin resistance, and high-molecular weight adiponectin was suggested to be protective against insulin resistance (Bobbert et al., 2005). Adiponectin has also been suggested to possess an anti-inflammatory role, as adiponectin-deficient mice showed higher adipose tissue TNF- α levels (Maeda et al., 2002), while treatment with adiponectin induced the production of the anti-inflammatory cytokines IL-10 and IL-1Ra and inhibited macrophage phagocytic activity (Wolf et al., 2004; Yokota et al., 2000).

Likewise, hepatocytes secrete liver-specific or restricted cytokines (termed hepatokines) that include macrophage-stimulating protein (MSP) and hepatocyte growth factor (HGF). MSP suppresses inflammation by inhibiting NF- κ B signaling and activating the PI3-kinase and AMPK-SHP pathways, which in turn reduce inducible nitric oxide synthase (iNOS) production in macrophages and cyclooxygenase-2 and inhibit the expression of pro-inflammatory cytokines, such as IL-12. HGF exhibits anti-inflammatory effects and promotes glucose uptake, insulin sensitivity and suppression of hepatic lipid accumulation and steatosis (Li et al., 2015a). Additional hepatokines include fetuin-A, an adaptor for binding of saturated fatty acids to

TLR4, which stimulates adipose tissue inflammation and results in insulin resistance (Pal et al., 2012), TGF- β (Yang et al., 2014a), and MCP-1 (Baeck et al., 2012). Less-studied hepatokines include fibroblast growth factor 21 (FGF21) (Vernia et al., 2016), leukocyte cell-derived chemotaxin 2 (LECT2) (Lan et al., 2014), selenoprotein P (Misu et al., 2010), angiopoietin-related growth factor (Oike et al., 2005), and Tanis (Walder et al., 2002).

Microbiome-Immune Contribution to the Metabolic Syndrome

The intestinal microbiome is a key regulator of host immune and metabolic functions and suggested to be a central factor contributing to inflammation in the context of the metabolic syndrome (Figure 3). Obesity is associated with reduced microbial diversity and altered microbial composition and metagenomic function, including an augmented ability to harvest energy from diet and increased host fat storage (Bäckhed et al., 2004; Ley et al., 2005; Turnbaugh et al., 2009, 2008, 2006). Additionally, obesity-related low bacterial richness and dysbiosis are associated with greater adiposity, dyslipidemia, insulin resistance, and an enhanced inflammatory potential.

Likewise, dysbiosis has been associated with symptomatic atherosclerosis, one of the notable complications of the metabolic syndrome (Karlsson et al., 2012). Specifically, peptidoglycan biosynthesis genes enriched in gut metagenomes of patients with atherosclerosis were postulated to prime the innate immune system leading to inflammation further contributing to atherosclerosis. Additionally, enhanced microbial production of choline and trimethylamine (TMA) from dietary phospholipid phosphatidylcholine (PC) and subsequent hepatic production of TMAO (Wang et al., 2011) contribute to progression of atherosclerosis through yet unclear mechanisms that may involve upregulation of the macrophage scavenger receptors CD36 and SRA1, leading to an increase in foam cell formation (Wang et al., 2011).

While the dialogue between immunity, metabolism, and the microbiome in the metabolic syndrome has not been fully deciphered, it seems to involve increased gut permeability (Cani et al., 2008), allowing for a closer interface between the microbiome and the host. As such, enhanced influx of bacterial components into the portal circulation may lead to inflammatory pathway activation exacerbating metabolic diseases, such as non-alcoholic fatty liver disease (NAFLD) (Henao-Mejia et al., 2012; Thaiss et al., 2014). Similarly, obese and insulin resistant mice featured high systemic levels of endotoxin and displayed adipose inflammation. Antibiotic treatment reduced endotoxemia and ameliorated adipose tissue inflammation, indicating possible links between systemic lipopolysaccharides (LPS), adipose tissue inflammation, and microbiome involvement in this process (Cani et al., 2008).

Malnutrition, Starvation, and Cachexia

On the other end of the metabolic spectrum, under-nutrition, defined as a deficiency in nutrients required to fulfill the energetic needs of the organism, poses a major public health concern and is associated with significant morbidity and mortality in developing countries and underprivileged populations, most prominently in regions of Asia and Africa. According to the WHO (<http://data.unicef.org/nutrition/malnutrition/>), close to one in four children under the age of 5 worldwide suffers from stunted growth as a long-term sequela of under-nutrition, and nearly

half of all deaths in children in that age group are attributed to under-nutrition.

Nutritional deprivation associated with acute starvation normally elicits a leptin-mediated immunosuppressive effect (Lord et al., 1998), potentially directed toward diversion of the limited energy reserves to vital functions. However, chronic under-nutrition often leads to a well-described albeit idiopathic inflammatory condition in malnourished populations called “environmental enteropathy” (also known as “tropical sprue”), which is characterized by structural and functional changes in the intestinal mucosa resulting in malabsorption and impaired barrier integrity (Gordon et al., 2012). The immune system reflects these alterations by increase in intraepithelial lymphocytes and lamina propria T cells with a predominant Th1 phenotype (Campbell et al., 2003). Recently, Brown et al. provided evidence that the etiology for this condition could be orchestrated by early-life dietary shortage combined with repeated exposure to specific bacterial strains, which together conduce to a phenotype similar to environmental enteropathy in a murine model, i.e., increased intestinal permeability, typical histological changes, and inflammatory changes, namely influx of intraepithelial lymphocytes and cytokine production (TNF- α and IFN- γ) (Brown et al., 2015). Kwashiorkor, a severe form of malnutrition, is also linked to dietary and microbiome alterations. Fecal transplantation of microbiome from Malawian twins discordant for kwashiorkor into gnotobiotic mice transferred the malnutrition phenotype in recipient mice, which were fed a Malawian diet (Smith et al., 2013), suggesting that diet-microbiome interactions play important roles in mediating kwashiorkor. Immune contributions and manifestations of this disorder remain elusive and warrant further studies.

Dietary Restriction

Intermittent fasting or periodic fasting without progression into full malnutrition is suggested to promote general health and metabolic benefits and enhance lifespan in various organisms, ranging from yeasts to mammals (Brandhorst et al., 2015; Fontana et al., 2010; Longo and Mattson, 2014). In humans, intermittent caloric restriction improved fasting insulin and insulin resistance and ameliorated blood pressure, serum cholesterol, and lipid levels (Harvie et al., 2011). These metabolic alterations were paralleled by distinct immune alterations, as dietary restriction attenuated immunosenescence and the age-related alterations in hematopoiesis (Cheng et al., 2014) and conferred anti-inflammatory effects, manifesting in the reduction of inflammatory biomarkers and lymph nodes, liver, and skin inflammation (Brandhorst et al., 2015). Immunomodulatory effects of this dietary routine were also suggested in models of inflammation, in which intermittent caloric restriction was associated with reduced sickness behavior, decreased circulating IL-6 and increased IL-10 levels, and upregulation of the HPA axis (MacDonald et al., 2014). Mechanistically, this dietary regimen was associated with a shift from mitochondrial fatty acid oxidation into ketogenesis and ketolysis and induced an elevation in plasma β -hydroxybutyrate levels, which in turn inhibited the NLRP3 inflammasome (Youm et al., 2015) and activated the GPR109A receptor on subsets of monocytes and macrophages (Rahman et al., 2014).

Interestingly, it has been suggested that caloric-restriction may drive a shift in the gut microbiome configuration with expansion of strains such as *Lactobacillus*, which was correlated with health benefits and enhanced lifespan in mice (Zhang et al.,

2013). Corroboration of these findings and mechanistic elucidations of immune, metabolic, and microbiome-related effects merit further studies.

From Molecular Mechanisms to Clinical Applications

The realization that inflammatory and metabolic signals are closely inter-related in multiple facets suggests that a broad anti-inflammatory strategy may be useful in treatment of insulin resistance and associated metabolic disturbances. Multiple anti-inflammatory treatments have been attempted as means of improving metabolic diseases. These include blockade or neutralization of inflammatory cytokines such as TNF- α and IL-1 (Donath and Shoelson, 2011). Antibody-mediated TNF- α inhibition in obese individuals was proven ineffective in improving insulin sensitivity, although it reduced blood glucose levels (Stanley et al., 2011). Blockade of IL-1 β signaling improved insulin secretion and glucose homeostasis and modestly reduced hemoglobin A1c and fasting glucose levels (Cavelti-Weder et al., 2012). Salicylates, which were shown over a century ago to reduce glucose levels of diabetic patients by inhibiting the IKK β /NF- κ B axis (Kopp and Ghosh, 1994; Pierce et al., 1996; Smith et al., 2016; Williamson, 1901; Yuan et al., 2001), lowered HbA1c levels and improved glycemic markers in T2DM patients (Goldfine et al., 2010). However, in follow-up human studies, salicylate treatment had a positive effect only in a subset of diabetic patients (Hundal et al., 2002). Thiazolidinediones, acting through activation of the nuclear receptor PPAR γ (Hauner, 2002), altered the transcription of genes involved in energy balance, glucose, and lipid metabolism and reduced HbA1c and insulin resistance in the liver, muscle, and adipose tissue. Moreover, thiazolidinediones were shown to reduce adipose tissue inflammation, lower the number of ATMs, enhance the beneficial Treg activity, and increase adiponectin levels and FGF21, which improved lipid metabolism (Ahmadian et al., 2013; Cipolletta et al., 2012; Dutchak et al., 2012; Koppaka et al., 2013). Dietary supplements possessing anti-inflammatory effects, such as the fish oil omega-3 fatty acids, eicosapentaenoic acid and docosahexaenoic acid, which signal through GPR120, decreased macrophage chemotaxis and improved insulin sensitivity and glucose tolerance, yet their beneficial effect in humans and effective dosing remain controversial and merit further studies (Oh et al., 2014; Spencer et al., 2013; Tousoulis et al., 2014).

Personalization of Immune-Metabolic Interactions

In recent years, mounting evidence highlighted a marked inter-individual variability in both the immune response and metabolic features, possibly explaining the variable and often disappointing efficacy of “silver bullet” interventions in large populations of patients suffering of the metabolic syndrome. This inter-individual variability prompted the need for a personalized approach when seeking to diagnose, characterize, and possibly cure such “multi-factorial” disorders (Carr et al., 2016; Liston et al., 2016). As such, understanding inter-personal variations in immune-metabolic interactions may enable us to better comprehend the poorly understood complex factors contributing to the metabolic syndrome, and how they may be influenced by personal variations in the composition and function of the microbiome. Indeed, personalized differences in the microbiome contributed to varying host responses to identical

food exposures (Cho et al., 2017; Kovatcheva-Datchary et al., 2015; Suez et al., 2014; Zeevi et al., 2015) and likewise contributed to individual differences in the systemic immune responses to pathogens (Li et al., 2016).

Personally tailored dietary interventions may enable us to modulate the composition and function of the microbiota, thereby impacting metabolic and immune alterations that alleviate the metabolic syndrome. As a proof of concept for such an approach, personalized machine-learning algorithm-based diets were recently shown to improve glycemic responses to dietary products (Zeevi et al., 2015). Other personalized therapeutic utilizations of the dietary-immune-metabolic axis include probiotic supplementation (Everard et al., 2013) or dietary planning based on microbiome profiles. For instance, consumption of barley kernel-based bread was suggested to induce improved glucose metabolism and glycogen storage in subjects whose microbiome was enriched with *Prevotella* (Kovatcheva-Datchary et al., 2015). Consumption of eggs and beef, on the other hand, yielded a greater increase in TMAO production in subjects featuring low microbiome diversity and high *Firmicutes:Bacteroidetes* ratio, both associated with a greater risk for atherosclerosis.

Conclusions and Future Prospects

We stand upon the beginning of a fascinating era in which personally collected “big data” allows us to better characterize “metabolic health” and immune contributions to metabolic risks, as determined in various physiological stages of life and nutritional availability. Despite a formidable leap in our comprehension of the links between the immune and the metabolic systems and the identification of key new players, which modify these interactions, these intricate relationships are still only illustrated in broad brush strokes. Future prospects will focus on deepening our molecular understanding of the immune-metabolic cross-talk, environmental and microbiome-associated influences on these interactions, and studying their relevance to humans in homeostatic or disease conditions.

Harnessing this knowledge will aid us in all aspects of health maintenance and disease prevention. Detailed profiling of immune markers, host genetics, epigenetics, and microbiome configurations could be of use for prophylaxis and early diagnosis in individuals susceptible to metabolic diseases. Likewise, interventions targeting key hubs in immune-metabolic interactions may be utilized to modify immune contributions to metabolic diseases. With that said, caution should be practiced when contemplating such interventions, as immune modulation may carry unwanted and unexpected “off-target” consequences ranging from susceptibility to infections, to autoimmunity, to altered tumor immune surveillance. Molecular-level understanding of immune-metabolic cross-talk, and the environmental- and microbiome-related modifications of this communication network, may enable a better grasp of the shaping forces determining immune and metabolic homeostasis and the pathogenesis of immune-mediated or associated metabolic diseases.

AUTHOR CONTRIBUTIONS

N.Z., S.B., and M.L. contributed equally to literature search, integration of data, and the writing of this Perspective. E.E. supervised data gathering and integration and headed the writing of the Perspective.

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