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Foundations of Immunometabolism and Implications for Metabolic Health and Disease

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Abstract

Highly ordered interactions between immune and metabolic responses are evolutionarily conserved and paramount for tissue and organismal health. Disruption of these interactions underlies the emergence of many pathologies, particularly chronic non-communicable diseases such as obesity and diabetes. Here, we examine decades of research identifying the complex immunometabolic signaling networks and the cellular and molecular events that occur in the setting of altered nutrient and energy exposures and offer a historical perspective. Furthermore, we describe recent advances such as the discovery that a broad complement of immune cells play a role in immunometabolism and the emerging evidence that nutrients and metabolites modulate inflammatory pathways. Lastly, we discuss how this work may eventually lead to tangible therapeutic advancements to promote health.

Impact of Immunity on Metabolism

Energy management is required for every biological function, and thus metabolism is an essential component of life. In addition, since the emergence of the first unicellular organisms, there has been a need for protection from environmental insults, leading to the evolution of the immune system. Thus, metabolism and immunity have been interwoven since the beginning of life, and, in the broadest manner, one could say that the timeline of immunometabolism is ancient, at least a few billion years old (Figure 1). The contemporary study of this intimate relationship dates to the end of the 19th century, when physicians recognized metabolic pathologies associated with infections. As early as 1884, it was noted that patients with meningitis exhibit a transient diabetic syndrome, and in fact the frequency of diabetes was so high that meningitis diagnoses were sometimes overlooked and patients treated only for hyperglycemia (Fox et al., 1947). Loss of secretion or action of insulin is a critical component of diabetes. Insight into the mechanism at play was missing until experiments carried out in the 1980s, when it was shown in dogs that treatment with lipopolysaccharide (LPS) from gram-negative bacteria caused resistance to insulin by abrogating the ability of insulin to induce glucose uptake in the muscle (Raymond et al.,

1981). In the same period it was recognized that acute infection in human patients was associated with decreased binding of insulin to the insulin receptor of isolated blood cells (Drobny et al., 1984).

Similarly, in the 1960s it began to be understood that obese subjects are simultaneously hyperinsulinemic and display insulin resistance; although glucose is rapidly taken up into muscle in lean subjects following insulin infusion, this effect is blunted in obese patients (Rabinowitz and Zierler, 1962). This state of chronic insulin resistance is a central component of metabolic syndrome, and predisposes individuals to developing type 2 diabetes. Thus, by the early to mid 1900s, two concepts were emerging independently: that obese subjects have insulin resistance and are predisposed to diabetes; and that insulin resistance, glucose intolerance, dyslipidemia and other metabolic problems occur in the setting of infection. The possibility of the existence of a “non-antibody antagonist” of insulin action causing diabetes was also raised during this period, however, there were no indications that such molecule may be an immune mediator (Berson and Yalow, 1958).

It had previously been observed that some diabetic patients treated with aspirin exhibited rapid improvements in glucose homeostasis (Ebstein W, 1876); however, this occurred well before the understanding that aspirin functions as an anti-inflammatory agent and inhibitor of the cyclooxygenase enzymes (Vane, 1971). These observations later inspired studies connecting the anti-diabetic effects of high dose salsalate with inflammatory signaling (discussed below). In addition, careful pathologists examining tissues of animal models of obesity in the 1960s had reported the infiltration of immune cells, such as macrophages and mast cells, into the adipose tissue (Hausberger, 1966; Hellman, 1965), but this mostly escaped the attention of scientists, including myself, until much later. Hence, despite all of these early observations and lines of evidence, the potential for an immunological nature of metabolic disease and its relation to obesity was largely disregarded for decades, and the cellular and molecular mechanisms that lead to abnormal insulin action, production, and glucose metabolism in obesity remained elusive. In the past thirty years, however, research defining the molecular and cellular players that connect immunity to metabolism in this respect has rapidly expanded, and together with the metabolic impact on immune cell function that will be discussed later in this article, yielded an exciting new field of study now dubbed “immunometabolism” (Figure 2).

Signaling pathways connecting immunity and glucose metabolism- a brief history

Some of the most important early insights into the molecular connections between immunity, metabolism, and insulin action came from the discovery in the mid-1980s that conditioned medium from macrophages incubated with LPS could induce resistance to insulin-induced glucose uptake and lipoprotein lipase expression in adipocytes (Mahoney et al., 1985; Pekala et al., 1983). These noteworthy observations made by Anthony Cerami and colleagues not only indicated a connection between the immune response and insulin responsiveness, but also were among the first to show an interaction between macrophages and adipocytes, to propose the presence of mediators exchanged between these cells, and to

biochemically define the locus of insulin resistance as a post-receptor signaling defect (Mahoney et al., 1985; Pekala et al., 1983). This seminal work represents an important cornerstone in the contemporary timeline of the field of immunometabolism. One of the macrophage-produced factors that may be responsible for this effect was later identified as the inflammatory cytokine tumor necrosis factor (TNF) (Beutler et al., 1985) which had previously been described as a cytotoxic factor (Carswell et al., 1975; Helson et al., 1975) linked to severe metabolic phenotypes in cancer, including dyslipidemia and cachexia (Oliff et al., 1987). During this period, Kenneth Feingold and Carl Grunfeld, as well as Charles Lang and Gregory Bagby, performed critical experiments to illustrate the *in vivo* metabolic effects of TNF, laying the foundation of our understanding of the metabolic impact of cytokines, particularly on glucose and lipid homeostasis (Feingold et al., 1989; Lang et al., 1992).

The critical observations of the inflammatory origin of obesity and diabetes came from studies in the early 1990s, from which evidence began to emerge that the adipose tissue of obese rodents exhibited inflammatory changes and expressed increased levels of TNF in both the adipocyte and stromal-vascular fractions (Hotamisligil et al., 1993). Soon after, similar observations showed increased TNF expression in the adipose tissue of obese humans, as reported by two simultaneous and independent publications (Hotamisligil et al., 1995; Kern et al., 1995), and subsequently it was shown that TNF expression was also elevated in the muscle tissue of obese humans (Saghizadeh et al., 1996). Many groups also demonstrated that neutralization of TNF in obese rats or mice resulted in increased insulin sensitivity and improved glucose metabolism (Borst and Bagby, 2002; Hotamisligil et al., 1993; Liang et al., 2008) (for a complete list, see www.metaflammation.org), whereas publications from the Grunfeld group, Jerry Olefsky's group, and Nawfal Istafan and colleagues all showed that administration of TNF caused insulin resistance and impaired glucose metabolism in animal models (Feingold et al., 1989; Ling et al., 1994; Miles et al., 1997). These studies identified differences in glucose fluxes between acute and chronic TNF exposures, as well as the target tissues responsible for impaired insulin action, increased glucose production, and alterations in disposal. Similarly, induction of insulin resistance and modulation of lipid metabolism was also demonstrated when TNF was infused into healthy human subjects (Plomgaard et al., 2005; Plomgaard et al., 2008; Van der Poll et al., 1991).

At this point in the early 1990s, many groups were pursuing the mechanisms underlying impaired insulin resistance and glucose metabolism in the inflammatory setting. Before the discovery that obesity features inflammation in adipose tissue, Jacqueline Stephens and Phillip Pekala had reported the suppression of glucose transporter 4 (GLUT4) in adipocytes by TNF in a series of elegant studies (Stephens and Pekala, 1991). Earlier work had also shown the stimulation of GLUT1 in cells that did not express GLUT4 upon TNF treatment, which explained the acute increase in glucose uptake in certain contexts upon exposure to inflammatory stimuli such as TNF (Cornelius et al., 1990). These studies illustrated a complex pattern of regulation of glucose fluxes by TNF in which immune, metabolic or stromal cells respond differently to inflammatory signals with temporal dependencies, as had been demonstrated in vivo (Spitzer et al., 1989). However, none of these findings were sufficient to explain how inflammatory mediators impacted systemic insulin action and how those relate to impaired glucose metabolism in obesity and diabetes. The next set of critical

studies illustrated that TNF can inhibit signaling cascades downstream of the insulin receptor, as first reported by Feinstein et al., in liver cells in 1993 (Feinstein et al., 1993). This was also shown in adipocytes (Hotamisligil et al., 1994) and upon chronic exposure, resembling what was seen in adipose tissue in obesity. Further efforts to understand the mechanisms by which TNF blocked insulin signaling were inspired by the findings from Yannick Le Marchand-Brustel's lab showing that blocking phosphatase action by okadaic acid treatment led to increased serine phosphorylation of IRS1 and blocked insulin action in cells (Jullien et al., 1993). Serine phosphorylation of insulin receptor substrate 1 (IRS1) was demonstrated upon cytokine stimulation, as first reported by Kanety et al. in liver cells (Kanety et al., 1995), in our studies with adipocytes and other reconstituted cell types (Hotamisligil et al., 1996), and subsequently in vivo in metabolic tissues.

The key evidence linking immunity to metabolism came a year later, in 1997, when two independent studies with independent mouse lines reported that genetic absence of TNF function resulted in reduced insulin resistance and improved glucose tolerance (Uysal et al., 1997; Ventre et al., 1997). These findings were supported by many other independent studies in multiple experimental models over time (for example, see (da Costa et al., 2016) and a complete list at www.metaflammation.org). While less definitive human genetics associations in which TNF polymorphisms have been linked to obesity, diabetes and other aspects of metabolic syndrome, including polycystic ovary syndrome and sleep apnea also started to emerge (Huang et al., 2012a; Sookoian et al., 2005). Many other inflammatory cytokines and mediators such as interleukin 1β (IL-1β) have since been implicated in the pathogenesis of insulin action or secretion (Maedler et al., 2002), leading to thousands of publications. These aspects have been reviewed in depth elsewhere (Donath, 2014; Feve and Bastard, 2009; Hotamisligil, 2017; Tack et al., 2012), and are not detailed here.

Thus, in the early 2000s the field began to understand that in obesity, hundreds of immune mediators are abnormally produced or regulated which contribute to altered metabolic status. Consistent with this complexity, most individual manipulations in mouse models have produced partial results in terms of resolution of disease, or in few occasions, produced differing and even conflicting results. For example, independent investigators have observed conflicting findings regarding the effect of loss of function of a component of inflammatory signaling on systemic metabolism (Hotamisligil, 2017). Similarly, type 1 diabetes research features highly instructive experiences of seemingly contrasting conclusions from which many important lessons can be drawn (Green and Flavell, 1999; Jacob et al., 1990; Koulmanda et al., 2012). This challenge is of course not limited only to immunological pathways and applies to other models and mechanisms that have been examined (for example, (Jornayvaz et al., 2011; Monetti et al., 2007), and may, at least in part, be related to the nature of cytokine actions on glucose metabolism, and to inadvertent flaws in the nature of genetic models and other external modifiers. Interestingly, more consistent results have been observed upon antibody, chemical, or RNAi-mediated suppression of inflammatory mediators than in genetic models ((Hotamisligil, 2017) and www.metaflammation.org). It is now widely recognized that physiological studies in mice are subject to many modifying effects emanating from the diet, genetic background, gut microbiota, circadian considerations, environmental conditions and enrichment, and others (Eisenbarth et al.,

2016; Jornayvaz et al., 2011; Thurmond et al., 2015; Woods and Begg, 2015), and we should all practice caution and humility when interpreting or re-interpreting phenotypic results.

Nevertheless, it was clear at the time that there was need to explore the intracellular signaling pathways that regulate the expression of and response to proinflammatory cytokines, and the mechanisms through which these signals converge on common nodes to support metaflammation. This effort led to the discovery of c-Jun N-terminal kinase (JNK) as a very critical signaling pathway that is downstream of many inflammatory signals in obesity and type 2 diabetes (Hirosumi et al., 2002). JNK activity is elevated in adipose tissue, liver and muscle of obese mice, and $Jnk1^{-/-}$ and $Jnk1^{+/-}Jnk2^{-/-}$ mice are protected from diet-induced insulin resistance (Hirosumi et al., 2002; Tuncman et al., 2006). Perhaps most critically, a mutation in the MAPK81P1 locus which leads to constitutive JNK activation is linked to a Mendelian form of diabetes in humans (Waeber et al., 2000). It is reported that TNF activates JNK via the TNF Receptor II-associated protein TRAF2 (Reinhard et al., 1997), and in turn JNK promotes serine phosphorylation of IRS-1 and inhibits insulin signaling (Aguirre et al., 2002). Interestingly, TRAF2 can also interact with the endoplasmic reticulum (ER)-resident protein IRE1, indicating a link between the unfolded protein response and JNK activation (Urano et al., 2000) and demonstrating that in addition to stress signals JNK can potentially serve to integrate a diverse array of pathways converging on metabolic control (Hotamisligil, 2010). Subsequent studies from the laboratories of Roger Davis and Jens Bruning have been highly instructive in identifying the most relevant cell types in which JNK activation affects systemic metabolism (Sabio et al., 2008; Tsaousidou et al., 2014). Highlighting the translational relevance of this work, increased JNK phosphorylation has been demonstrated in the adipose tissue of obese humans (Boden et al., 2008) and peptide or small molecule inhibitors of JNK generate metabolic benefits (Kaneto et al., 2004; Yan et al., 2017). In summary, pathological JNK activation is a benchmark event in immunometabolic signaling in obesity.

Many cytokines such as TNF also activate nuclear factor kappa B (NF-κB) (Lowenthal et al., 1989; Osborn et al., 1989), which is a central modulator of inflammatory responses, regulating the expression of proinflammatory cytokines including TNF itself and other genes that are part of the immune response (reviewed in (Barnes and Karin, 1997). The upstream activator kinase of NF-κB is IKK, which is also reported to phosphorylate IRS-1 at serine residues to block insulin signaling (Gao et al., 2002). It is possible that alternative mechanisms, such as production of molecules that regulate inflammatory resolution, also couple this signaling pathway to metabolic deterioration, and studies on these mechanisms in further detail are warranted. High doses of salicylates block NF-κB signaling (Kopp and Ghosh, 1994) and improve insulin signaling and glucose homeostasis in rodent models of obesity (Yuan et al., 2001). In the mid-2000s, work from Michael Karin's and Steve Shoelson's groups provided further evidence for the role of these metaflammatory pathways using genetic models, and demonstrated improved glucose homeostasis in mice heterozygous for IKK (Yuan et al., 2001) as well as in mice with myeloid-specific or liver-specific deletion of IKK (Arkan et al., 2005). Reciprocally, expression of a constitutively active IKK in liver induces expression of inflammatory cytokines and the development of insulin resistance (Cai et al., 2005). There is also evidence that inflammation of the central nervous system contributes to dysregulated metabolism in obesity, as hypothalamic-specific

deletion of IKK also improves glucose tolerance and insulin sensitivity in high fat-fed mice (Zhang et al., 2008). Interestingly, adipocyte-specific loss of IKKβ impairs glucose metabolism, leading to the suggestion that adipose tissue inflammation may not be uniformly related to impaired insulin action and glucose intolerance (Park et al., 2016). However, careful examination of this model revealed that complete blockade of IKK-NFκB activity results in an unexpected and massive adipose tissue inflammation, due to the role of this pathway in resolution of inflammation, in part through production of anti-inflammatory cytokine IL-13 (Kwon et al., 2014). Finally, recent studies also demonstrated a critical role for the atypical IκB kinases in insulin sensitivity and glucose metabolism with important translational implications for human disease (Reilly et al., 2013). The balance between inflammatory promotion versus resolution can yield unexpected results due to hormetic effects of cytokine treatments or even in models of individual genetic deletion of inflammatory molecules themselves (Campbell et al., 2001). These studies also underscore the critical importance of balanced inflammatory signaling in adipose tissue and the fact that prodigious manipulation of signaling nodes or mediators may not always yield the predicted, canonical inflammatory, and consequently metabolic, outcomes in the whole body.

Beyond JNK and IKK, multiple other intermediate signaling kinases are also involved in linking inflammatory pathways to insulin action, including PKC, PKR, CAMK, AMPK, mTOR, JAK, PKA, ERK, p38 and other MAP kinases (Copps and White, 2012; Fullerton et al., 2013; Gonzalez-Teran et al., 2016; Hotamisligil, 2006). These kinases can be activated by insulin, in response to lipid mediators, cytokines, or by sympathetic stimulation, and the resultant phosphorylation of the insulin signaling pathway components can be either activating or inhibitory. These pathways are also critical in integrating lipid mediators and abnormal lipid metabolism with insulin action, with or without engaging immune pathways (Petersen et al., 2016). Although all of these signaling pathways are not covered in detail here, it is important to point out that their redundant and overlapping nature highlight the complexity of insulin signaling regulation and its critical importance to organismal homeostasis. One of the most critical integrating mechanisms for immunometabolic integration resides in the ER, and dysfunction of this organelle plays a critical role in metabolic homeostasis as well as disease (Ozcan et al., 2004). Interestingly, a chronic inflammatory environment also impairs the function of the ER (Yang et al., 2015), thus presenting a vicious cycle that prevents resolution of these pathological chronic responses (Cao et al., 2016; Hotamisligil, 2010; Zhang and Kaufman, 2008).

Innate immune cellular mediators of inflammation

Although a role for proinflammatory cytokines in mediating insulin resistance in obesity had been established since the 1990s, and indeed the presence of macrophages in obese adipose tissue was initially reported in the 1960s (Hausberger, 1966; Hellman, 1965), it was not until 2003 that these observations captured the full attention of the research community. At that time, Anthony Ferrante's and Hong Chen's groups independently observed a marked upregulation of inflammatory gene expression in the adipose tissue of obese mice, and associated these changes with an influx of macrophages that supported the inflammatory milieu (Weisberg et al., 2003; Xu et al., 2003). Further analysis revealed that adipose tissue macrophages from lean mice have high levels of arginase 1 and IL-10 expression, whereas

diet-induced obesity results in increased expression of iNOS and TNF by adipose tissue macrophages (Lumeng et al., 2007a), which contributes to the reduction in adipose tissue insulin sensitivity (Lumeng et al., 2007b). Macrophage accumulation in adipose tissue is the result of recruitment, retention, and proliferation of these cells at this site (Hill et al., 2014). The abundant presence of tissue resident macrophages that are polarized towards repair and maintenance functions in lean adipose tissue suggests a physiological role for these cells in homeostasis, and indicates that they are reprogrammed into an inflammatory phenotype in the setting of metabolic stress and during obesity, leading to functional deterioration.

More recent research has provided detailed insight into the activation and functional impact of adipose tissue macrophages (ATMs). For example, proteomic profiling revealed that although metabolic stress and classical macrophage activation by LPS and IFNγ both induce the expression of inflammatory cytokines such as TNF, this seems to occur via separate pathways (Kratz et al., 2014). In this study, Kratz *et al.* showed that classical macrophage markers of inflammation such as CD38 and CD274 are not induced in response to metabolic stimuli, which indicates that alternative activation pathways, including fatty acid-driven PPARγ signaling, may underlie metaflammatory phenotypes (Kratz et al., 2014). Interestingly, recent studies also support the concept that chronic ER stress in obesity may lead to inflammatory polarization in adipose tissue macrophages (Shan et al., 2017). It was also demonstrated that GPS2, a component of the co-repressor complex, restrains expression of pro-inflammatory mediators in ATMs. Expression of GPS2 is decreased in the ATMs of obese humans, and accordingly the ATMs are more sensitive to activation. In agreement with this model, GPS2-deficient mice display exaggerated systemic inflammation and worsened glucose and insulin intolerance in response to high fat diet challenge (Fan et al., 2016). Recently, Galectin-3, a lectin produced by macrophages, was also demonstrated to promote adipose tissue inflammation and glucose intolerance. Furthermore, both genetic deletion and pharmacological inhibition of this molecule resulted in resolution of adipose tissue inflammation and marked improvements in insulin sensitivity and glucose tolerance (Li et al., 2016). These studies, along with related findings from many other groups, indicate the potential that specific metaflammatory pathways may exist that will offer novel therapeutic strategies for metabolic disease.

There has also been a growing recognition that in addition to macrophages, other innate immune cell lineages also contribute to the regulation of metabolism. For example, Carey Lumeng's group recently interrogated the role of adipose tissue dendritic cells (ATDCs), which in previous studies may have been indistinguishable from macrophages because of their expression of F4/80 and CD45, but which can be defined as CD64−, CD11c+ (Cho et al., 2016). This group showed that ATDCs accumulate in adipose tissue of HFD-fed mice and in the subcutaneous adipose tissue of obese humans, and blocking their accumulation improves insulin sensitivity in obese mice (Cho et al., 2016). In further support of this action, Jay Heinekcke's group has produced evidence that dendritic cells constrain healthy expansion of adipose tissue, and depletion of these cells improves glucose homeostasis in lean mice (Pamir et al., 2015). Jerry Olefsky's laboratory has also demonstrated an important role for neutrophils in obesity-related insulin resistance, showing that genetic deletion of neutrophil elastase reduces macrophage influx into the adipose tissue of obese mice and results in improved insulin sensitivity (Talukdar et al., 2012).

It is important to note that innate immune cells also play important roles in healthy tissue physiology, and indeed adipose tissue also naturally harbors immune cells which may contribute to tissue homeostasis. Adipose tissue resident immune cells play a critical role in the healthy expansion and remodeling of the tissue during weight gain (Lee et al., 2013; Wernstedt Asterholm et al., 2014), and have recently been shown to modulate brown adipose tissue innervation (Wolf et al., 2017). Immune cells in adipose tissue may also regulate energy expenditure: cold exposure is reported to result in alternative activation of adipose tissue macrophages (Nguyen et al., 2011) and recruitment of eosinophils (Qiu et al., 2014). Relatedly, type 2 innate lymphoid cells (ILC2s) promote the differentiation of beige adipocytes from adipocyte precursors (Brestoff et al., 2015; Lee et al., 2015) to protect against diet-induced insulin resistance (Molofsky et al., 2013). Alternatively activated macrophages have been proposed to promote adaptive thermogenesis directly via their production of catecholamines (Nguyen et al., 2011), although independent studies found that adipose tissue macrophages from cold-exposed mice do not express the key catecholamine synthesis enzyme tyrosine hydroxylase (TH) (Chang et al., 2016; Fischer et al., 2017; Spadaro et al., 2017), and TH deletion in hematopoietic cells neither affected adipose tissue browning nor energy expenditure in response to cold (Fischer et al., 2017). In contrast, polarization towards a more proinflammatory activation directly inhibits adipose tissue browning (Chung et al., 2017) and in turn, browning has been described to limit adipose tissue inflammation (Cohen et al., 2014). However, regardless of whether macrophages directly promote thermogenesis, all of these studies confirm the presence of immune cells resident in adipose tissue in homeostatic and adaptive settings. As further indication that the number of immune cells in the tissue does not always directly correlate with adverse phenotypes, immune cells have been shown to acutely accumulate in adipose tissue during weight loss in response to lipolysis (Kosteli et al., 2010).

Although we focus here on adipose tissue inflammation in obesity as the origin of this concept, similar phenomena occur in other tissues and have been demonstrated to contribute to alterations in systemic glucose homeostasis. For example, type 2 diabetes has been associated with an increase in the number of islet-associated macrophages which impair the function of beta cells (Ehses et al., 2007). Natural Killer T (NKT) cells are depleted in the livers of mice with diet-induced obesity, which may promote hepatic production of inflammatory cytokines and liver inflammation (Li et al., 2005). Obesity is associated with an influx of macrophages to muscle tissue (Hong et al., 2009), and TNF levels in muscle are higher in diabetic subjects compared with insulin-sensitive individuals (Saghizadeh et al., 1996). As mentioned earlier, high fat feeding is associated with the activation of JNK and IKK signaling in the hypothalamus (De Souza et al., 2005). Taken together, these studies demonstrate that obesity is associated with changes in many immune cell types at multiple sites of critical metabolic function, with a cumulative detrimental effect on systemic insulin action as well as glucose and lipid homeostasis. It is also important to recognize that stromal components (adipocytes, beta cells, hepatocytes, etc.) also produce immune mediators often attributed to immune cells, and thus our measurement of metaflammation reflects a cumulative output of both the immune effector cells and the stroma.

Adaptive immune cellular mediators of inflammation

Over the past decade, evidence has accumulated that the adaptive immune system also participates in the inflammatory response to obesity. Beginning in 2008, multiple groups observed the infiltration of T cells- both T-helper and cytotoxic- into the adipose tissue of obese mice and humans (Nishimura et al., 2009; Rausch et al., 2008; Yang et al., 2010). $CD4^+FOXP3^+$ T regulatory (Treg) cells were also documented in the adipose tissue of lean mice, and suggested to promote insulin sensitivity (Feuerer et al., 2009; Kolodin et al., 2015; Winer et al., 2009). B cells have been implicated in modulating insulin resistance: B cells accumulate in the adipose tissue of obese mice (Winer et al., 2009), the B cells from obese mice produce a more inflammatory repertoire of cytokines, and obese mice with B cell deficiency have reduced insulin resistance (DeFuria et al., 2013). Importantly, transfer of B cells from obese donor mice results in impaired insulin action and glucose homeostasis in the recipients (Winer et al., 2011). By contrast, tolerance-promoting B regulatory cells have also been identified in adipose tissue, and their numbers are decreased in models of obesity (Nishimura et al., 2013). These cells limit adipose tissue inflammation and their adoptive transfer is metabolically beneficial. Similarly, type 1 NKT cells (Ji et al., 2012) and invariant natural killer T (iNKT) cells (Lynch, 2014), which are both thought to have anti-inflammatory roles, decrease in abundance in adipose tissue in the setting of obesity. These topics are covered in recent excellent reviews (Chawla et al., 2011; Sell et al., 2012; Sonnenberg and Artis, 2015) and will not be covered here in detail (Figure 3).

The extent to which adaptive immunity contributes to insulin sensitivity in a context dependent manner may require further studies. In a careful time course analysis, Strissel et al. showed that the influx of $CD3^+$ T cells into adipose tissue is a late event, occurring after more than 20 weeks of high fat feeding in mice and well after the onset of insulin resistance (Strissel et al., 2010), and Vishwa Dixit's group demonstrated that specific depletion of $CD3^+$ T cells from epididymal adipose tissue did not alter insulin sensitivity in adult obese mice (Yang et al., 2010). Similarly, although NKT cells have also been observed to accumulate in the adipose of obese mice, NKT cell deficiency does not protect from diet-induced insulin resistance (Ji et al., 2012). Finally, mice lacking both B and T cells (SCID mice) are not protected against obesity-induced glucose intolerance (Ballak et al., 2013), indicating the complex role of these immune cells in both controlling and promoting inflammatory responses. It is interesting to note that within the adipose tissue environment the T cell receptor repertoire shows significant bias in $CD4^+$ T cells, which supports the possibility that specific antigens presented only in the adipose environment may lead to clonal expansion (Morris et al., 2013). Interestingly, $CD8^+$ T cells have been shown to accumulate in the livers of obese mice and contribute to the development of metabolic dysfunction, but their accumulation and activation is believed to occur in response to interferon signaling, rather the presence of a specific antigen (Ghazarian, 2017). Identification of the tissue-specific differences in inflammatory activation may allow better dissection of functional programming of immune effectors associated with metabolic tissue inflammatory state. Finally, it should be noted that both stromal cells and immune effectors contribute to the inflammatory output within metabolic tissues.

Effects of nutrients and metabolites on inflammation

In the 1960s, work from Eric Newsholme's laboratory began to reveal the important role of circulating lipids in modulating insulin sensitivity, demonstrating that lipids and fatty acids reduced insulin-induced glucose uptake in isolated heart muscle (Randle et al., 1963; Randle et al., 1964). This phenomenon was later shown in experiments in rats and humans (Jenkins et al., 1988; Johnson et al., 1992). However, the mechanism remained unclear for decades, until the innate immune component toll like receptor 4 (TLR4) was identified as a receptor for saturated and polyunsaturated fatty acids (Lee et al., 2003), suggesting that lipids themselves may act as immunomodulatory molecules. Later, it was shown that TLR4 deficiency selectively protected mice from diets high in saturated fat (Davis et al., 2008), and furthermore TLR signaling may play a role in the central control of metabolism, as deletion of the TLR adaptor molecule MyD88 in the central nervous system protects mice from diet induced insulin resistance (Kleinridders et al., 2009).

A further example of the crosstalk between nutrients and inflammation began to become clear in the last several years based on the study of the inflammasome, which produced compelling evidence linking abnormal inflammasome activation to metabolic deterioration (Henao-Mejia et al., 2014). In 2010, Jürg Tschopp's laboratory demonstrated that mice deficient in the inflammasome scaffold protein Nlrp3 displayed enhanced insulin sensitivity (Zhou et al., 2010), and other groups demonstrated similar results in mice with genetic deletions of other inflammasome components shortly thereafter (Stienstra et al., 2010; Stienstra et al., 2011; Vandanmagsar et al., 2011). Concurrently, Jenny PY Ting's group demonstrated that palmitate, a saturated fatty acid that is known to be present at an increased level in the circulation of high fat diet-fed mice, activates the inflammasome and induces IL-1β and IL-18 secretion from macrophages (Wen et al., 2011). This study also illustrated that blocking inflammasome (IL1β) and non-inflammasome (TNF) pathways simultaneously had an additive effect, yielding greater metabolic benefit then single inhibition of either. Emerging evidence suggests that activation of the inflammasome may also be integrated with TLR signaling, as palmitate-induced induction of IL-1β expression can be inhibited by blocking TLRs (Snodgrass et al., 2013). Other molecules such as Protein Kinase R (PKR) which can sense pathogens as well as nutrient signals to alter inflammatory and metabolic responses have also been shown to serve as an important regulator of inflammasome activation (Boriushkin et al., 2016; Hett et al., 2013; Xie et al., 2016).

Notably, other critical mechanisms also clearly contribute to the role of lipid-induced modulation of insulin resistance, possibly through mechanisms independent of cytokine or TLR signaling. For example, Gerald Shulman's group has demonstrated that lipid infusion leads to the accumulation of fatty acyl-CoA and diacylglycerol (DAG) in skeletal muscle, which activates Protein Kinase C θ (PKCθ), resulting in inhibition of IRS-1 through serine phosphorylation (Griffin et al., 1999; Szendroedi et al., 2014; Yu et al., 2002). Both of these signals are also clearly linked to inflammatory outcomes. However, neither the sufficiency of this pathway to mediate diet-induced insulin resistance, nor the precise identity of the mechanism are fully understood. Animal models investigating the role of PKCθ in the development of insulin resistance have had complex results (Kim et al., 2004b; Serra et al., 2003), and IRS1 serine phosphorylation sites are too numerous to reduce to single sites for

definitive experimentation. In recent elegant work, the Shulman group has also characterized the role of additional PKC isoforms and recently used mass spectrometry to demonstrate that the insulin receptor is a target of PKCε in the liver (Petersen et al., 2016). Supporting the metabolic relevance of this biology, mutation of the target threonine on the insulin receptor protects mice from diet-induced insulin resistance (Petersen et al., 2016). Hence, accumulation of these and possibly other detrimental lipid species are of key importance in metabolic deterioration in obesity.

We now also know that some lipids can exert anti-inflammatory effects locally and systemically and regulate metabolism. For instance, the de novo lipogenesis product palmitoleate (C16:1n7) can block lipid-induced inflammatory activation of macrophages, leading to beneficial metabolic outcomes in mouse models of obesity or metabolic disease (Cao et al., 2008; Cimen et al., 2016; Erbay et al., 2009; Talbot et al., 2014). Importantly, palmitoleate administration in humans also generates significant metabolic benefits (Bernstein et al., 2014). Barbara Kahn's laboratory identified fatty acid hydroxy fatty acids (FAHFAs) also regulated during lipogenesis, and demonstrated that treatment with FAHFAs was sufficient to reduce adipose tissue inflammation and improve glucose homeostasis in obese mice (Yore et al., 2014). In addition, extensive work has highlighted the potent anti-inflammatory actions of omega-3 fatty acids and their metabolites resolvins (Oh et al., 2010; Serhan, 2014). Interestingly, the Olefsky group has demonstrated that omega-3 fatty acids exert their immunomodulatory effects through cell surface receptors, specifically the G-coupled protein receptor GPR120. This research demonstrated omega-3 fatty acids inhibit inflammation and improve glucose homeostasis in mice with diet-induced obesity, in a GPR120-dependent manner (Oh et al., 2010). Expanding on this finding, Olefsky's group demonstrated that a small molecule agonist of GPR120 improved insulin sensitivity and reduced steatosis in obese mice (Oh et al., 2010). Finally, there is strong evidence that this pathway of nutrient sensing and metaflammatory response is conserved in humans, as a loss of function mutation in GPR120 has been linked to increased risk of obesity (Ichimura et al., 2012). Hence, anti-inflammatory lipids offer great promise for translational opportunities.

Besides circulating lipids, new research demonstrates that other nutrient and metabolite changes can contribute to insulin resistance. Perhaps most notably, comprehensive analysis of serum from lean and obese subjects has revealed that the metabolites that correlated most closely with insulin resistance were derived not from lipids but branched chain amino acids (BCAAs) (Newgard et al., 2009). Furthermore, supplementing high fat diet with BCAAs induced insulin resistance despite reduced food intake and weight gain, and was associated with increased activity of JNK in muscle (Newgard et al., 2009). Interestingly, a recent report showed that exposure to inflammatory cytokines blocked the uptake and metabolism of BCAAs in adipocytes, which could underlie the elevated levels observed in obese patients (Burrill et al., 2015). In addition, exposure to the macromolecules synthesized by pathogenic and commensal species can also have marked immunomodulatory and metabolic consequences. For example, a glycan found on parasitic helminths has been shown to induce anti-inflammatory cytokine production, which reduces adipose tissue inflammation and improves systemic insulin sensitivity and glucose metabolism (Bhargava et al., 2012).

Furthermore, adipocytes produce numerous peptide hormones with the capacity to alter immune responses. A prime example is leptin; leptin-deficient *ob/ob* mice demonstrate enhanced sensitivity to LPS-induced lethality, and delivery of exogenous leptin extends survival in mice dosed with LPS (Faggioni et al., 1999). *In vitro* it has been shown that leptin treatment of macrophages enhances LPS-induced expression of TNFα and IL-6 (Loffreda et al., 1998). Similarly, RBP4 is an adipocyte product that binds to vitamin A (retinol) that appears to regulate both inflammation and glucose metabolism (Yang et al., 2005) and elevated levels of RBP4 have been demonstrated in both obese mouse models and humans (Graham et al., 2006; Yang et al., 2005). The adipocyte hormone resistin induces secretion TNFα and IL-12 from macrophages (Silswal et al., 2005), and neutralizing resistin improves insulin sensitivity in obese mice (Steppan et al., 2001). Other adipocyte products function to protect against inflammation; for example adiponectin blocks leptin-induced TNFα expression in macrophages (Zhao et al., 2005). Our group showed that adipocyte-produced aP2 (FABP4) plays an important hormonal role in glucose homeostasis (Cao et al., 2013) and its genetic or antibody-mediated blockade results in improved glucose homeostasis and metabolic outcomes. Earlier studies have demonstrated a significant role for aP2 in modulating macrophage inflammatory responses and cardiometabolic pathologies (Erbay et al., 2009; Furuhashi et al., 2008). While it is not yet known whether the hormonal form of aP2 also exerts immunomodulatory activity, the biology and function of this lipid binding protein offers a compelling mode of immunometabolic integration between metabolic and immune cells which may be targeted for therapeutic purposes.

Metabolism as a determinant of immune cell phenotype

Just as it has been clearly demonstrated that energy and nutrient excess and the resulting metabolic stress can trigger metaflammation and alter immune response to promote disease, it has also long been recognized that other alterations that occur during energy and nutrient deficiency can impair immunity. Similarly, specialized metabolic conditions, such as pregnancy, cold adaptation, migration or hibernation can also present challenges for the immune system. There is much to learn about immunometabolic regulation in future studies on these conditions. In addition to systemic changes in metabolism, the mounting of an immune response and functional programming within a cell is associated with innate metabolic changes (O'Neill and Hardie, 2013). One of the most well recognized of these changes is the activation of anaerobic glycolysis, which is a common feature of inflammatory activation of T cells (Chang et al., 2013; Wang and Green, 2012), dendritic cells (Everts et al., 2014), and macrophages (Tannahill et al., 2013). In macrophages, the glycolytic phenotype offers many advantages in the setting of obesity, including enhanced nitric oxide production and reduced reliance on oxygen, a survival advantage in hypoxic environments such as obese adipose tissue (Ghesquiere et al., 2014). In addition, metabolite profiling of activated macrophages has shown that the accumulation of Kreb’s cycle intermediates is important for the production of inflammatory cytokines (Jha et al., 2015). This arm of immunometabolism is rapidly expanding, and has the potential to lead to many exciting therapeutic intervention strategies.

The overlap between metabolic and immune signaling pathways means that altered metabolic states can have an important impact on immune function. For example, obesity is

associated with altered immune responses including reduced T cell responsiveness (Tanaka et al., 1993), and morbidly obese patients have abnormal bactericidal activity of polymorphonuclear (PMN) granulocytes, which improves following weight loss surgery (Palmblad et al., 1980). This is in part related to alterations in circulating nutrient and metabolite signals in the setting of obesity, as macrophage polarization is influenced by nutrient sensing pathways such as AMPK and mTORc1. Macrophages lacking the catalytic AMPK subunit AMPKα1 were shown to have defective M2 polarization (Mounier et al., 2013), and AMPKβ1 deficient macrophages are protected from palmitate induced inflammation (Galic et al., 2011). The nutrient and growth factor sensor mTORc1 regulates multiple metabolic pathways through SREBP (Duvel et al., 2010), and constitutive mTORc1 activation results in defective M2 polarization and enhanced proinflammatory response to LPS (Byles et al., 2013). Relatedly, it was also recently shown that mTOR activity is suppressed by the anti-inflammatory cytokine IL-10, resulting in an increase in mitophagy and suppressed inflammasome activation (Ip et al., 2017). Finally, short chain fatty acids, byproducts of microbial fermentation, can drive the differentiation of T cell subsets, and multiple groups have demonstrated the potential for butyrate and propionate produced by commensal bacteria in the gut to promote Treg cell differentiation (Arpaia et al., 2013; Furusawa et al., 2013; Smith et al., 2013).

Translational strategies and therapeutic implications

The complexity of the immunometabolic networks in chronic disease creates challenges to therapeutic translation, and the small number of studies with classical single molecule immune-targeted therapies for metabolic disease have so far yielded some success in the limited human trials conducted (Donath, 2014). Despite these caveats, the results strongly support the clinical value of targeting immunometabolism, highly promising new areas are in development, and the links to human disease as well as mechanisms for intervention have greatly expanded in the recent years (Hotamisligil, 2017). Furthermore, the connections between these systems are being continuously elaborated: robust genomic studies are highlighting novel associations between variations in inflammatory genes and pathways and metabolic phenotypes (Locke et al., 2015; Shungin et al., 2015), and previously well-characterized developmental and homeostatic signaling pathways such as non-cannonical erythropoietin action are being recognized for their ability to alter inflammation and improve systemic metabolism in model systems as well as in humans (Cerami, 2012; Fuster et al., 2014; Ouchi et al., 2010). The status of human research in this area and emerging therapeutic possibilities are further discussed in recent publications (Donath, 2014; Hotamisligil, 2017). Evidence of the importance of inflammation in metabolic disease may also be deduced from the fact that the current anti-diabetic strategies currently in clinical use, including metformin, thiazolidinediones, DPP4 inhibitors, incretins, and lifestyle interventions, have all been shown to reduce inflammation (Kothari et al., 2016; Lancaster and Febbraio, 2014; Scheen et al., 2015). While our main focus in this discussion has been the negative impact of pro-inflammatory mediators on metabolism, in recent years numerous anti-inflammatory cytokines, such as IL-4, (Chang et al., 2012; Ricardo-Gonzalez et al., 2010) IL-10, (Cintra et al., 2008; Kim et al., 2004a) IL-13, (Darkhal et al., 2015; Stanya et al., 2013) and Hemoxigenase-1 (Huang et al., 2012b; Li et al., 2008), have all been

demonstrated to positively regulate metabolism. We are also now recognizing that some endogenously synthesized lipids and metabolites exert potent immunomodulatory effects with exciting and immediate translational possibilities (Cao et al., 2008; Serhan, 2014; Spite et al., 2014; Yore et al., 2014). For example, a recent clinical trial demonstrated that treating obese diabetic patients with an inhibitor of IKKε improved glucose control and, in a subgroup of patients, the treatment resulted in reduced inflammatory gene expression and improved insulin sensitivity (Oral et al., 2017). Another recent study utilized a novel immunomodulatory technique utilizing immunological stem cells to improve beta cell function in type 1 and type 2 diabetic patients (Zhao et al., 2017). These emerging targets, and the development of strategies that incorporate multi-pronged approaches, offer exciting and highly promising avenues for therapeutic opportunities for metabolic diseases. Having said that, it is also clear that inflammatory mediators are not the sole drivers of metabolic disorders, and questions and pathways remain to be explored and exploited for the benefit of patients in a safe and effective manner and in continued support of healthy lifestyle recommendations.

Conclusions

As we have discussed here, careful observations and experiments in animal models and cellular systems have revealed that metabolism and immunity are inextricably interwoven. Research in this field has accelerated over the last two decades (Figure 2), and it has become increasingly clear that overlapping and redundant inflammatory pathways play pleiotropic and important roles in metabolism, and that the metabolic state is a critical determinant of immune function. We have learned that components of both the innate and adaptive immune system modulate metabolism, and we have identified key molecules that drive the cellular and systemic responses to nutrients. Most relevant to the current global obesity epidemic, we are now learning how these networks are re-wired in response to the stress imposed by chronic nutrient excess. This excellent progress should allow us to overcome the challenges of designing effective therapeutic and disease preventative strategies at the immune:metabolic interface to improve human health.

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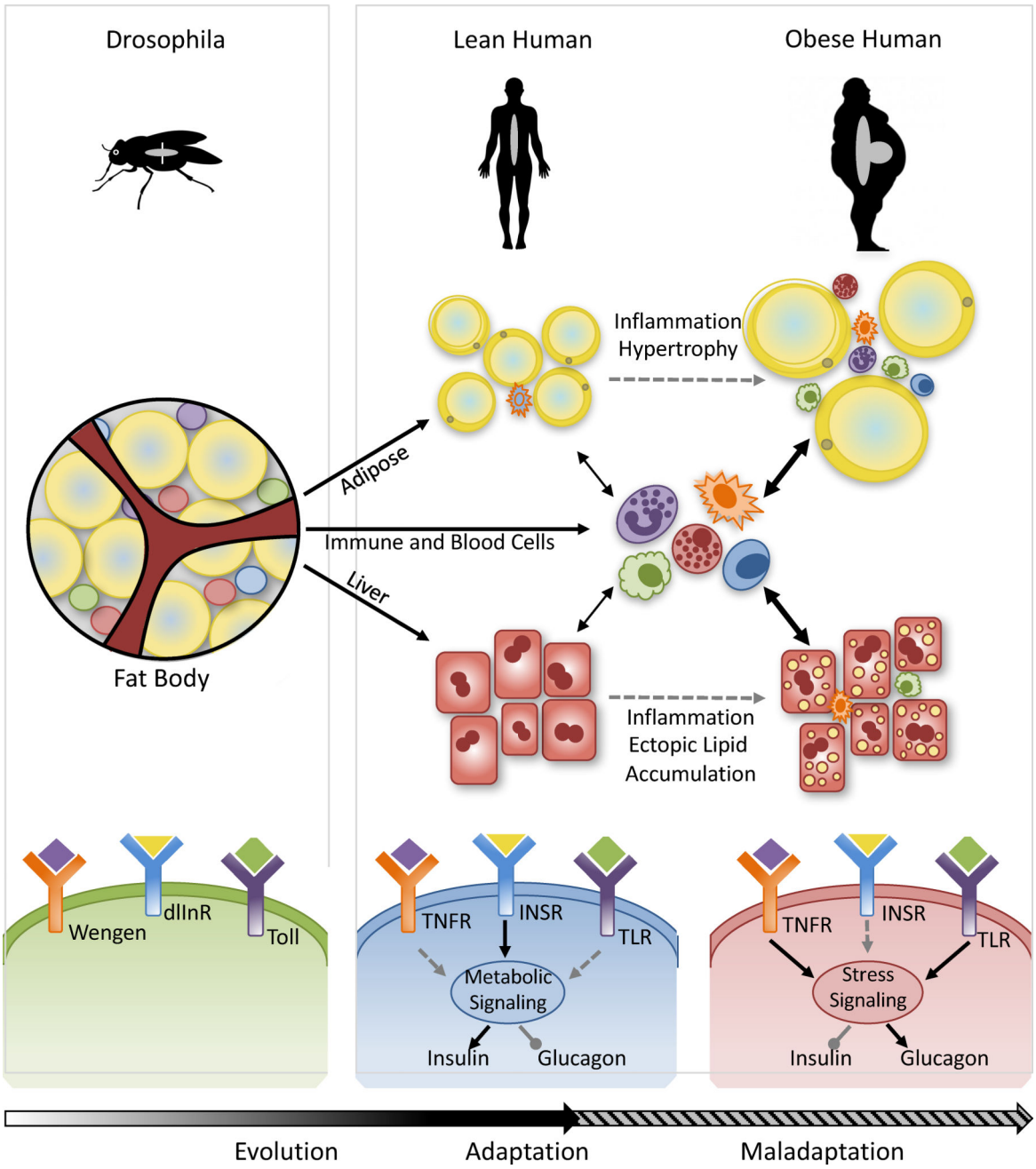

Figure 1. The evolution of immunometabolism

Over the course of evolution, the *Drosophila* fat body, where liver, adipose tissue and the principle immune organ is situated in a single structure, has given rise to the distinct metabolic and immune organs observed in modern mammals. However, despite this seeming delegation of tasks, highly regulated interactions and crosstalk that are required to maintain immune and metabolic homeostasis remain as part of this evolutionary history. In the setting of obesity, this gives rise to activation and infiltration of immune cells into metabolic tissues and chronic activation of inflammatory pathways in both stromal and immune components, triggering stress kinase activation which impinges on the signaling of metabolic hormones

such as insulin, and leading to impaired glucose and lipid homeostasis. The fundamental principles of this transition from an "immunometabolic" adaptive to maladaptive state could be depicted in a simple framework wherein the pathogen sensing, immune signaling and metabolic responses are signaled through Toll-like, TNF (tumor necrosis factor), and, insulin receptors. Each one of the highly conserved signaling components that construct this principle framework of metaflammation could be enriched and expanded with many more molecules and signaling networks in higher organisms and humans. Wengen (Drosophila TNF receptor), dlInR (Drosophila insulin receptor), Toll (Toll receptor), TNFR (TNF receptor), INSR (Insulin receptor), TLR (Toll like receptor).

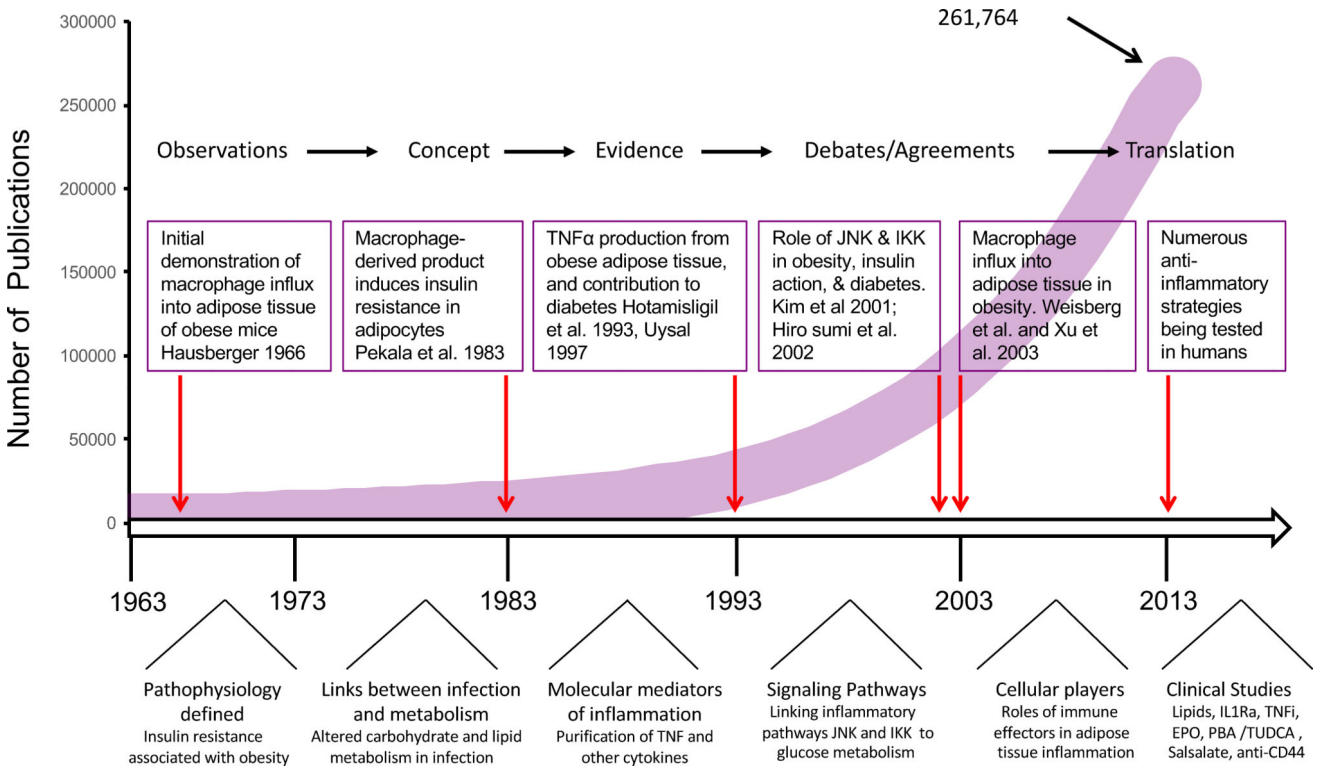

Figure 2. Timeline of immunometabolism

Summary of the major findings that have given rise to the field of immunometabolism. The line graph reflects the total number of publications (261,764) describing links between immunity and metabolism over the last several decades, found with the search terms “metabolism and inflammation” in PubMed. The major findings that laid the ground work for this field are highlighted. At the bottom of the figure processes that marked each decade are illustrated. The arrows point to the critical discoveries that have initiated and stimulated the expansion of the field of immune-metabolism. Publications in this field have proliferated rapidly in the last decades, as the field has recognized the impact of innate and adaptive immunity in metabolism, identified signaling networks and molecular mediators as well as immunomodulatory effects of lipid species and progressed towards new translational avenues with exciting proof of principle studies. These issues are covered in more detail in the manuscript.

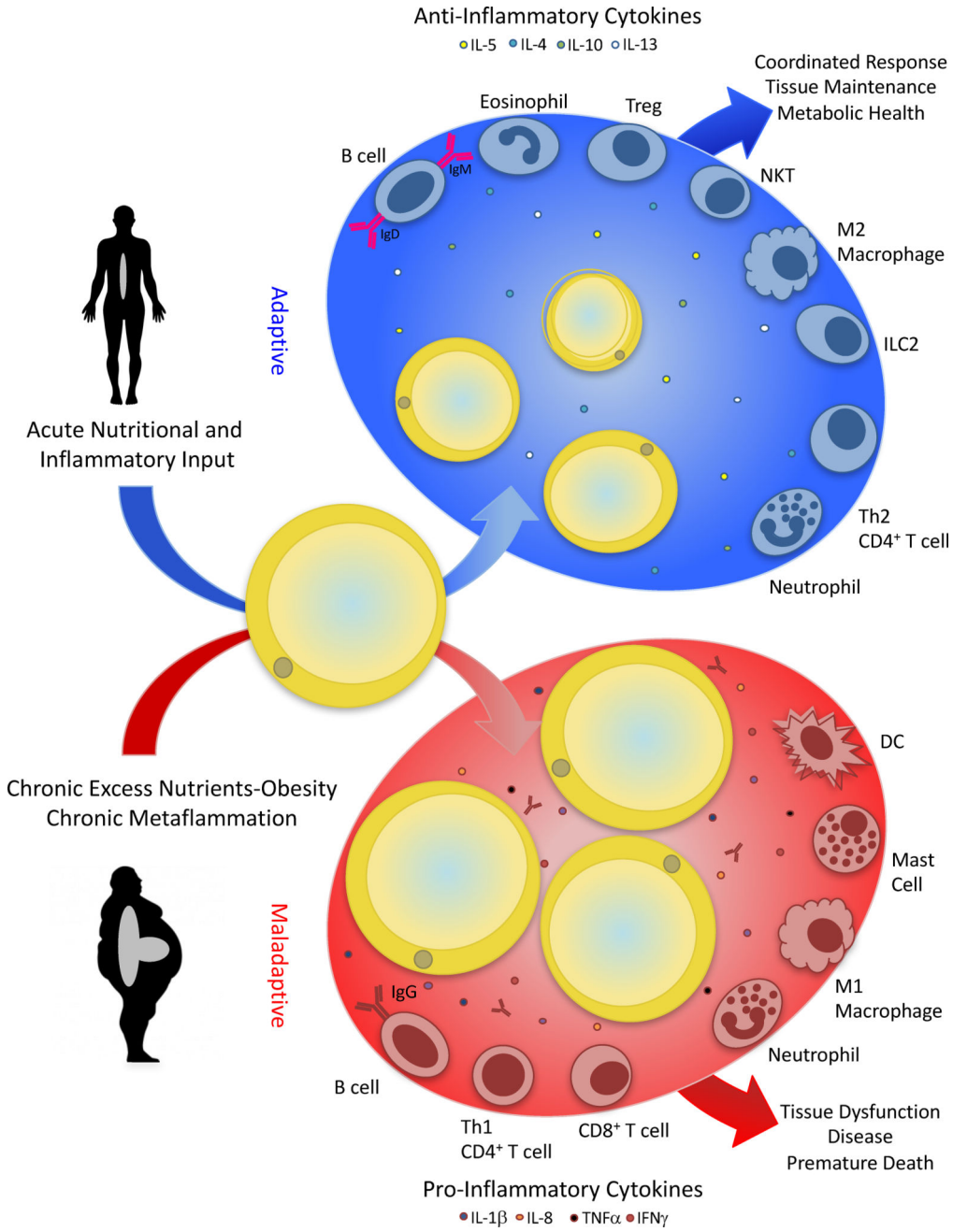

Figure 3. Adipose tissue-immune cell interactions

Interactions with immune effectors and stromal components are critical for tissue maintenance and health. Immune cells and their interactions with adipocytes, for example, are critical for adipose tissue homeostasis and response to acute inflammatory signals. The expression of multiple anti-inflammatory cytokines, and the presence of alternatively activated macrophages, immunomodulatory Tregs, and other cell types in the adipose tissue in the lean state has been well documented and may have adaptive roles in tissue health and maintenance. In the setting of obesity, chronic overnutrition and metabolic stresses trigger an inflamed state in the adipose tissue, characterized by enhanced immune infiltration, skewing

of macrophage polarization towards the inflammatory phenotype, altered B cell antigen production, and expression of pro-inflammatory cytokines. In this case, the maladaptive chronic, non-resolving metabolic inflammation (metaflammation) contributes to tissue dysfunction, disease, and premature death, as best exemplified in obesity and associated metabolic complications. Although adipose tissue is depicted in this scheme as the first discovered and most studied site, similar interactions and transitions are observed in other key metabolic organs, including liver, pancreas, and brain.