Review

Innate-like T Cells in the Context of Metabolic Disease and Novel Therapeutic Targets

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ABSTRACT

Metabolic diseases continue to rise in global prevalence. Although there is evidence that current methods of treatment are effective, the continued rise in prevalence indicates that alternative, more efficient treatment options are needed. Over the last several years, immune cells have been increasingly studied as important players in the development of a range of diseases, including metabolic diseases such as obesity and obesity-induced type 2 diabetes. This review explores how understanding the intrinsic metabolism of innate-like T cells could provide potential targets for treating metabolic disease, and highlights research areas needed to advance this promising therapeutic approach.

KEYWORDS: innate-like T cells; iNKT; MAIT; Vγ9$^+$Vδ2$^+$; metabolic disease; diabetes; immunometabolism

ABBREVIATIONS

α-GalCer, alpha-galactosylceramide; AT, adipose tissue; CD, cluster of differentiation; IL, interleukin; ILT, innate-like T; iNKT, invariant natural killer T; MAIT, mucosal associated invariant T; MHC, major histocompatibility complex; PZLF, promyelocytic leukemia zinc finger; TCR, T cell receptor; T2DM, type 2 diabetes mellitus; Vγ9$^+$Vδ2$^+$, V gamma 9 positive V delta 2 positive

INTRODUCTION

Type 2 Diabetes mellitus (T2DM) and obesity are intrinsically linked metabolic diseases, both of which are rising in global prevalence [1–3]. Immunometabolism represents a promising novel option to better understand and treat metabolic disorders.

The amalgamation of immunity and metabolism has gained traction in the literature over the last decade [4] but it has been argued that the two

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processes have been co-evolving over billions of years due to the need for efficient protection from external pathogens [5]. The idea of immunometabolism has two central concepts. The first concept is that cellular metabolism, as applied to immune cells, dictates cell function; and the second is the theory that immune cells play an integral role in the development and exacerbation of metabolic disease [4]. To date, immune cells have largely only been studied in the context of either the first or second concept, and due to the lack of integration of these, the impact of immunometabolism on metabolic disorders remains to be elucidated. Many studies delve into the second concept of extrinsic immune cell regulation of metabolic disorders through cytokine release; for example, how tumour necrosis factor (TNF) release can induce insulin resistance in adipocytes [6]. This, and immune cell migration during metabolic disease have been reviewed elsewhere [7–9]. However, a knowledge gap remains relating the effect of intrinsic immune cell metabolism—how the different substrates that immune cells are exposed to influences their development and function – and metabolic disease.

This review explores the current literature on a specific subset of T cells, innate-like T (ILT) cells, and highlights gaps in scientific knowledge relating to the intrinsic metabolism of these cells, specifically in metabolic disease research, with the goal to advance our understanding in this area and the identification of immunotherapeutic targets.

OBESITY-INDUCED METABOLIC DISEASE

The pathogenesis of T2DM involves a combination of insulin resistance and relative insulin deficiency. Typically, obesity is the driver of insulin resistance and precedes the onset of T2DM, with individuals progressing through an intermediate phase of prediabetes where pancreatic insulin production and release becomes impaired and blood glucose concentrations begin to rise, before eventually being classified as having T2DM. Lifestyle interventions including dietary modification to promote weight loss, reducing refined carbohydrate and saturated fat, as well as increased physical activity are the cornerstones of T2DM management [10]. A range of pharmacological interventions with diverse mechanisms are used progressively and additively, as required, to control hyperglycaemia. Metformin, which predominantly reduces hepatic insulin resistance, is the first line agent. Newer classes of agents such as the sodium-glucose cotransporter (SGLT-2) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists have become increasingly used as evidence mounts for cardiovascular and renal benefits, and finally, insulin supplementation may be added [11,12]. Bariatric surgery may be considered and can result in remission of T2DM if implemented early enough in the course of the disease [13]. Although the diagnosis of T2DM is based on the development of hyperglycaemia, the underlying mechanisms and relative contribution of insulin resistance and insulin deficiency are highly variable between individuals. Current treatments are broadly effective on an individual

level [14–16], but the rates of obesity and T2DM continue to increase, indicating a need for more effective treatments in the early stages of both.

Obesity contributes to a chronic, low-grade inflammatory state occurring in adipose tissue (AT), due to the secretion of pro-inflammatory cytokines [17]. This inflammation leads to impaired insulin sensitivity, and development of T2DM by interfering with metabolic homeostasis [17–22]. Balance is critical. One murine study has found that low grade inflammation in AT is essential for normal adipogenesis and the accumulation of fat tissue, preventing ectopic fat deposition [23]. This study posits that acute inflammation is requisite for maintaining homeostasis. However, if chronic inflammation develops, it is likely to be detrimental. Together with other factors independently associated with insulin resistance, such as an abundance of free fatty acids (FFA), the chronic inflammatory response observed in obesity becomes pathological [18,24]. Overall, it would seem that a multitude of factors contribute to the inflammatory state of individuals suffering from obesity and obesity-induced T2DM. While it is plausible that some degree of acute inflammation is necessary to maintain homeostasis, it is not yet known to what degree this is, and at what point it begins to become detrimental. Inflammation is controlled by various cells in the immune system; therefore further research into immune cells could provide insight for potential immunometabolic therapeutic targets.

METABOLIC PROFILE OF T CELLS

A previous review article explains the intricately interlaced and diverse metabolic pathways influencing lymphocyte fate [25]. Briefly, naïve T cells are quiescent for extended periods, utilising fatty acid β-oxidation, oxidative phosphorylation and pyruvate oxidation to support their basal functions [26]. Once activated, bioenergetic demand increases as they undergo clonal expansion, and metabolic reprogramming stimulates glycolysis, the pentose phosphate pathway and glutaminolysis to dominate [27]. Enhanced glycolysis has been found to occur in a number of activated immunological cells including dendritic cells, NK cells, macrophages and T and B lymphocytes [28,29]. This phenomenon of aerobic glycolysis taking place when sufficient oxygen is available to support oxidative phosphorylation is known as the Warburg effect [30] which has been thoroughly reviewed elsewhere [31]. Although the ATP yield of glycolysis is comparatively lower than that of oxidative phosphorylation, it remains an essential pathway to produce a multitude of metabolic intermediates which can be shunted into anabolic systems [32]. Alternatively, increasing oxidative phosphorylation would necessitate generation of mitochondria, which is an energetically expensive and time-consuming process [29]. Enhanced aerobic glycolysis therefore enables cells to efficiently generate both a sufficient amount of ATP, as well as a number of the required biosynthetic metabolites that enable it to carry out its effector function. However, mitochondria do not lay dormant during aerobic glycolysis, as

was once imagined. Carbon-13 labelling has shown that some pyruvate generated by glycolysis is oxidised by mitochondria in human cancer cells [33]. Similarly, mice lacking a functional mitochondrial complex III display impaired activation [34], indicating that cells utilise both ATP-generating systems during this time.

INNATE-LIKE T CELLS

Innate-like T (ILT) cells bridge the gap between the two arms of immunity through an alteration of the TCR response [35]. These cells are classed as a subset of T lymphocytes but are unconventional, or innate-like in their rapid response upon activation. ILT cells express a semi-invariant TCR and are restricted by conserved, monomorphic MHC-like molecules [36–38]. The predominant ILT cells in humans are invariant natural killer T (iNKT) cells, mucosal associated invariant T (MAIT) cells and γδ T cells expressing the γ9 and δ2 TCR chains ($V\gamma9^{+}V\delta2^{+}$ T cells), which are restricted by CD1d, MHC related molecule (MR)1 and butyrophilin (BTN)3A1 respectively [39–41]. Similar to conventional T cells, ILT cells mature in the thymus from hematopoietic precursor cells and express the pan-T cell marker CD3 [42].

One of the major gaps in ILT cell knowledge is with regard to activation. It is known that ILT cells possess the ability to become activated from either their TCR, through cytokine signalling, or both, an ability afforded by the expression of the ILT-specific transcription factor PLZF [43]. However, the effect each method of activation has on cell function, whether simultaneous stimulation elicits a different response and the relevance of both for AT health and disease, remains to be fully elucidated [38,44].

Invariant Natural Killer T (iNKT) Cells

iNKT cells are so named due to their expression of the natural killer cell marker NK1.1 [45,46], as well as their ability to proliferate exponentially upon activation in the thymus. The iNKT cell TCR is comprised of an α- and a β-chain. The α-chain is invariant (Vα24-Jα18 in humans) and associates with a small repertoire of β-chains, predominantly Vβ11 in humans, which recognise lipid antigens presented by CD1d [47]. Not to be confused with non-invariant NKT cells which possess a comparably more diverse TCR repertoire. α-Galactosylceramide (α-GalCer) is the prototypical antigen of iNKT cells. Along with iNKT cells exhibiting memory cell characteristics, activation induces the rapid release of cytokines, and cytotoxic capabilities [48].

In murine models of disease, enhanced activity and/or frequency of iNKT cells has been associated with allergic asthma [48], alcoholic and nonalcoholic liver disease [49,50], and ischemia-reperfusion injury resulting from sickle cell disease [51]. Increased frequency of activated iNKT cells was observed in the circulation of human participants with sickle cell disease [52] and nonalcoholic steatohepatitis [50]. Conversely,

decreased frequencies of circulating and splenic iNKT cells was correlated with human herpesvirus 8 and multicentric Castleman disease [53]. These somewhat contradictory observations suggest that solely analysing the frequency of iNKT cells in patients should not be used to predict their influence on disease. Instead, a better understanding of their metabolic demands may provide valuable insights for their therapeutic targeting.

NKT cells differ from their conventional $CD4^+$ T cell counterparts in that NKT cells metabolise glucose through the pentose phosphate pathway (PPP) and tricarboxylic acid (TCA) cycle, as opposed to being converted to lactate via glycolysis [54]. In keeping with this, a recent study on the metabolic profile of T cells in PBMCs demonstrated that key metabolites for the TCA cycle and fatty acid oxidation were higher in NKT cells than conventional $CD4^+$ T cells [55]. Activation in iNKT cells is associated with enhanced glycolysis. However, activated iNKT cells are also characterized by increased mitochondrial capacity, further confirming that aerobic glycolysis and oxidative phosphorylation are not mutually exclusive processes [56]. Aerobic glycolysis is required for optimal iNKT cell IFNγ production through increased TCR recycling [56] but it is not essential for T cell proliferation and survival in general [57]. The finding of a positive feedback loop via aerobic glycolysis generates a mechanistic link between TCR engagement and IFNγ secretion. Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) is the key glycolytic enzyme influencing this mechanism. When GAPDH is not involved in glycolysis it acts as a translational inhibitor for IFNγ mRNA. During glycolysis, it carries out its classical enzymatic function and is therefore not available to inhibit IFNγ production [57].

Mucosal Associated Invariant T (MAIT) Cells

Monomorphic MHC class-I related molecule, MR1, presents riboflavin precursors and metabolites to a semi-invariant αβ TCR found on MAIT cells. As such, these cells are primarily activated by bacteria and fungi, but have also shown activation in response to viral infections [37,58]. Interestingly, activation in response to viral infection is a TCR independent process and has been shown to occur through IL-18 signalling, in combination with IL-12, IL-15 or IFN-α/β [59], indicating that this ILT cell subset has the capacity to respond to inflammatory signals. MAIT cells tend to reside in mucosal tissues, hence their name, but are also found in abundance in human blood and liver under standard physiological conditions [60,61]. Combinations of MAIT cell TCR in humans are Vα7.2 joined to Jα33, Jα20 or Jα12, and paired with a limited β-chain repertoire [62]. MAIT cells were once difficult to target due to their partial phenotypic overlap with other T cell subtypes. For example, historically, MAIT cells were identified on the basis of being $CD3^+$, $Vα7.2^+$ and $CD161^{hi}$ [62], however germline-encoded, mycolyl lipid-reactive TCRs share the Vα7.2 TCR [63]. Additionally, CD161 has been known to downregulate upon MAIT cell activation, which led to the erroneous assumption of MAIT cell loss

associated with HIV infection [64,65]. Reantragoon et al. solved this issue by developing a tetramer which, when bound to a MAIT cell agonist such as 5-(2-oxopropylideneamino)-6-D-ribitylaminouracil (5-OP-RU), was able to distinguish MAIT cells ex vivo [62]. 5-OP-RU is a potent agonist inducing MAIT cell activation and is therefore a valuable antigen in MAIT cell research [66]. Upon activation in humans, MAIT cells migrate to infected tissues, secrete pro-inflammatory cytokines, including IL-17 [36], and exert cytotoxic functions [61]. They are also characterized by a tissue resident and memory T cell phenotype [67].

Microbial colonization controls MAIT cell development [68]. Environmental bacteria are thought to shape the TCR repertoire of MAIT cells and thereby increase their ability to identify cells with bacterial infections [39]. MAIT cell frequency in blood was found to increase from birth, peak between ages 20–29, and progressively decline with further ageing [56,69]. The cause-effect relationship of reduced MAIT cell numbers in blood is currently unclear but could lead to an increased risk of microbial infection, since MAIT cells function as microbial sentinels.

MAIT cells have been implicated in immune diseases such as multiple sclerosis (MS) and inflammatory bowel disease (IBD), with the frequency of MAIT cells in blood decreasing during MS disease progression and increasing during remission [70]. Similarly, in IBD, the frequency of MAIT cells in blood decreases, and activated MAIT cells accumulate in inflamed mucosa [71,72]. Additionally, blood-derived MAIT cells from IBD patients activated in vitro secreted significantly more IL-17 compared to healthy controls. These findings may suggest that MAIT cell dysfunction in blood and tissues may have pathogenic effects.

The intrinsic immunometabolic regulation of MAIT cell activity has almost exclusively been studied in the context of metabolic disease and is therefore discussed in the dedicated section below.

Vγ9^{+}Vδ2^{+} T Cells

Human γδ T cells are typically categorized according to their TCR Vδ chain. Of the eight functional human Vδ gene segments, the first three, i.e., Vδ1, Vδ2 and Vδ3, are the most commonly used in the human γδ T cell repertoire [73]. Importantly, Vδ2 is almost exclusively paired with Vγ9 and the resulting Vγ9^{+}Vδ2^{+} T cell population represents the largest γδ T cell subset in human blood, and the only one commonly referred to as innate-like [73–77]. In mice and humans, γδ T cells are particularly enriched in tissue such as AT, as compared to the circulation and lymphoid organs [78]. Of particular relevance, and in contrast to the compositional bias of blood, Vδ1^{+}, Vδ2^{+} and Vδ3^{+} T cells are found enriched and reach comparable frequencies in human AT [79].

While the antigen specificity of Vδ2^{-} T cells remains an area of intense investigation, Vγ9^{+}Vδ2^{+} T cells are specifically and exquisitely sensitive to the presentation of phosphoantigens, including endogenous prenyl-pyrophosphates, through the MHC-unrelated molecules BTN3A1 and

BTN2A1 [80]. An increase in host cell intracellular phosphoantigen levels is associated with a conformational change in BTN3A1, followed by $V\gamma9^{+}V\delta2^{+}$ T cell activation and associated cytolytic and effector functions [81].

The clinical relevance of $V\gamma9^{+}V\delta2^{+}$ T cells has for the most part been studied in the context of cancer immunology, consistent with $V\gamma9^{+}V\delta2^{+}$ T cells' potent ability to recognize and kill tumour cells [82,83]. However, $V\gamma9^{+}V\delta2^{+}$ T cells may also play a protective role against malaria and other infectious disease [73,84], due to their ability to recognize microbial-derived phosphoantigens [85].

The intrinsic immunometabolic pathways governing $V\gamma9^{+}V\delta2^{+}$ T cell function have not been studied in any detail.

INNATE-LIKE T CELLS IN METABOLIC DISEASE RESEARCH

In the context of metabolic disease, ILT cells have largely been studied in isolation, with few research studies analysing more than one subtype at a time. One review article links MAIT cells to metabolic disease [86]. A low proportion of circulating MAIT cells, for example, has been implicated in obesity and T2DM, with obese individuals harbouring more MAIT cells in their AT compared to healthy controls, implying that they have been recruited by a stimulus from the excess AT. Moreover, the MAIT cells in AT have an IL-17 profile, and therefore probable inflammatory phenotype [87,88]. Further research confirmed these findings, concluding that AT resident MAIT cells are enriched in people who are obese or have T2DM. The production of IL-17 was positively correlated with insulin resistance, while the production of the anti-inflammatory cytokine, IL-10 appeared to be down-regulated [89]. It has been reported that the adoption of an IL-17 phenotype by MAIT cells in obesity is due in part to dysfunctional mitochondria, stemming from an increase in mitochondrial reactive oxygen species in obese individuals compared to healthy controls [90]. Metabolic disease generally appears to correlate with reduced circulating MAIT cells, which adopt a pro-inflammatory phenotype. This occurs in patients with alcoholic and non-alcoholic fatty liver disease, and a number of cardiometabolic disorders [91,92]. It is still uncertain whether these cells accumulate in the affected tissue, or whether they simply undergo apoptosis, although increasing glucose concentration did induce MAIT cell apoptosis in vitro [92]. Furthermore, MAIT cell reduction in peripheral blood has been correlated with increased glycated haemoglobin, a symptom of T2DM pathogenesis. Finally, MAIT cells from obese individuals fail to substantially increase their rate of aerobic glycolysis upon activation [93], which could interfere with a number of intrinsic metabolic pathways, from deficient cytokine release, to mitotic impairment. Indeed, stimulatory cytokine, IFNγ production is impeded as a direct result of insufficient aerobic glycolysis during activation [57,93].

Complementing aspects of ILT cell biology relevant for metabolic homeostasis and disease have been addressed in humans and mice, but a

unifying picture is lacking due to incomplete understanding of functional overlap or redundancy between ILT cells. There is some evidence to suggest that iNKT cells play a protective role in metabolic disease [94]. In particular, the activation of iNKT cells with their prototypical agonist, α-GalCer, has been shown to support weight loss and glycemic control in mice [95,96]. The mechanism of action for this appears to be due in part to iNKT cell activation of fibroblast growth factor 21 (FGF21), which led to increased thermogenesis and browning of white adipose tissue in mice [97]. But whether iNKT cell frequency in humans is sufficient to promote similar health outcomes, provided their functional role in human disease is similar, is currently unknown. Interestingly, FGF21 expression can also be induced by GLP-1, a pharmacological agent mentioned previously to treat T2DM pathogenesis [97]. In lean AT, iNKT cells are generally thought to contribute to inflammatory homeostasis. In mice, AT residing iNKT cells secrete IL-2 and IL-10 [98], and splenic iNKT cells secrete IL-10 [99]. Both promote the accumulation of regulatory T cells, which implies that iNKT cells contribute to the maintenance of immune homeostasis. These cells are depleted in the omental AT of obese individuals [100] which could contribute to the inflamed AT environment. However, there remains conflicting data on whether NKT cells in general play a protective or pathogenic role in metabolic disease, as mice lacking the iNKT cell TCR unit Jα18 displayed reduced weight gain and a better metabolic profile compared to wild type [101,102].

Jα18$^{-/-}$ mice were used since their development in 1997 [103] as models for iNKT deficiency. However, Bedel et al. discovered in 2012 that the particular methodology used for the genetic deletion caused loss of an estimated 60% of Jα-chain diversity, which consequently also led to an indirect MAIT cell deficiency in these mice [104]. Following this surprising finding, the original authors generated novel *Traj*18 deficient mice [105]. Thus, conclusions drawn from experiments using the original strain of Jα18$^{-/-}$ mice should be attributed to a lack of both iNKT and MAIT cells.

Murine AT-resident γδ T cells are described as important mediators of thermogenesis and AT homeostasis in mice through their secretion of IL-17 [79], but whether human Vγ9^{+}Vδ2^{+} T cells equally contribute to metabolic homeostasis remains to be established. Arguably, this function may be carried out by MAIT cells which, as stated previously, have been shown to adopt an IL-17-producing phenotype in people with obesity and T2DM. The effect of Vγ9^{+}Vδ2^{+} T cells was studied in the context of metabolic bone disease, osteoporosis, with data showing increased activity of Vγ9^{+}Vδ2^{+} T cells after the use of bisphosphonates, namely zoledronic acid, both in vitro and in vivo [106,107]. Authors indicate Vγ9^{+}Vδ2^{+} differentiation towards an effector-memory like phenotype, reducing bone loss. To complement this, a randomized control trial involving 60 post-menopausal women with prediabetes and osteopenia who received 12 weeks of either 70 mg/week bisphosphonate or a placebo, found a positive correlation between the group receiving bisphosphonates and

their fasting plasma glucose and HbA1c concentration. These clinical data suggest that Vγ9$^+$Vδ2$^+$ T cell activation by bisphosphonates may be beneficial for metabolic disease [108]. In the context of obesity, one study found that when Vγ9$^+$Vδ2$^+$ T cells are activated, they take up LDL, which can be toxic to the cell. As the intracellular concentration of LDL increased, Vγ9$^+$Vδ2$^+$ T cells downregulated their metabolism, measured by decreased mitochondrial mass, decreased cellular ATP, and lower production rates of secreted effector cytokines [109]. Therefore, obese individuals with a higher proportion of circulating LDL may have impeded functionality of Vγ9$^+$Vδ2$^+$ T cells, leading to increased risk of cancer, and potentially other diseases yet to be linked to the dysfunction of this ILT cell subtype.

The predominantly protective effect described so far for iNKT and Vγ9$^+$Vδ2$^+$ T cells in obesity and T2DM, which contrasts with the proposed pathogenic role attributed to MAIT cells, is reflected in a pilot study recently conducted by Li et al. [110]. The results from this study, the first side-by-side analysis of phenotype and function of human blood-derived iNKT, MAIT and Vγ9$^+$Vδ2$^+$ T cells, indicated that iNKT cells and Vγ9$^+$Vδ2$^+$ T cells concomitantly ceased to produce the regulatory cytokines IL-2 and IL-4, while MAIT cells secreted larger amounts of IL-17. It is interesting to note, although perhaps unrelated, that both iNKT and Vγ9$^+$Vδ2$^+$ T cells may encounter their cognate antigens in AT, during homeostasis. Endogenous glucosylceramides and prenyl-pyrophosphates can indeed be presented by adipocytes to iNKT cells and Vγ9$^+$Vδ2$^+$ T cells through the glucosylceramide biosynthesis and mevalonate pathways, respectively [111,112]. The higher rates of T2DM associated with the use of statins [113], which block the mevalonate pathway upstream of phosphoantigen-formation, suggests that homeostatic adipocyte-ILT cell crosstalk may have a significant role for metabolic health. Since MAIT cell development is entirely dependent on exogenous bacterial metabolites, MAIT cell activation in AT can only occur upon translocation of microbes and/or associated metabolites into AT [114], or TCR-independent activation. It will be important to establish, in future studies, if and how the hypertrophy and altered metabolism of adipocytes, as well as obesity-associated microbial translocation, are mechanistically linked to the collective ILT-specific dysfunction observed in obese and T2DM patients.

Although the AT microenvironment may provide unique tissue-specific cues and stimuli, careful consideration needs to be given to the potentially intrinsic difference between circulating and AT resident ILT cells. It is well documented that ILT cell development relies on the expression of the transcription factor PLZF, as ILT cells are virtually absent in promyelocytic leukemia zinc finger (PLZF)-deficient mice and humans [115–119]. While ILT cells largely retain the expression of PLZF in the periphery, AT-resident iNKT cells have been shown to express the basic leucine zipper transcription factor E4BP4 instead [98], a phenomenon which may be at least partly due to distinct TCR signalling events [120]. Whether similar discrepancies exist between circulating and AT-resident MAIT and

Vγ9$^+$Vδ2$^+$ T cells is currently unknown, but of high interest. In terms of the frequencies of the three ILT subsets and their contribution to disease, Magalhaes et al. find that in the AT of obese participants, there was no significant difference between groups [87].

Immunometabolic discovery platforms have recently gained significant commercial value. In the context of obesity and metabolic disease important questions remain to be answered before immunometabolic strategies can be therapeutically applied. For example, if MAIT cells are indeed pathogenic, and iNKT and Vγ9$^+$Vδ2$^+$ T cells protective, would it be more effective to immunometabolically target MAIT cells' Th17 phenotype, or attempt to promote IL-10 or IL-4 secretion by iNKT and Vγ9$^+$Vδ2$^+$ T cells, and would either approach influence the other? Alternatively, assuming an altered production and presentation of iNKT/Vγ9$^+$Vδ2$^+$ T cell agonists in inflamed AT is at least partly responsible for their dysfunction, would it be more effective to therapeutically target adipocyte instead of iNKT/Vγ9$^+$Vδ2$^+$ T cell metabolism?

CONCLUSIONS

Metabolic flexibility and substrate selection have been established as a fundamental aspect of immune cell function [25,29]. However, gaps remain in the literature of ILT cell biology in the context of metabolic disease, specifically obesity induced T2DM. Not only have the three ILT cells described in this review been predominantly studied in isolation, much of the research has been conducted in murine models, which poses problems in transferability to humans due to the proportion of these cells varying across species by orders of magnitude [121]. To this end, there is still much debate over whether each of the three subsets of ILT cell play a pathogenic or protective role in metabolic disease, with many reporting iNKT and Vγ9$^+$Vδ2$^+$ cells as protective, and MAIT pathogenic, with no apparent link to their respective frequencies in human AT and peripheral blood [87]. Moreover, the metabolic profile of circulating ILT cells and their comparison to conventional T cells is still being determined. Much of the work completed in this field has been limited to iNKT and MAIT cell metabolism, with virtually no information available regarding Vγ9$^+$Vδ2$^+$ cells. Since ILT cells exhibit traits of resident memory T cells [67] and rely on the expression of PLZF for thymic development [116,122], they are likely to rely on different metabolic programs for homeostatic maintenance as compared to conventional T cells [54,123]. Whether PLZF drives immunmetabolic overlaps between ILT cells remains to be addressed. Altered activity of ILT cells has been associated with diseases outlined in this review but research is lacking in the context of how the intrinsic metabolism of immune cells influences metabolic disease. Because immunometabolism is an area in which ILT cells remain poorly understood, gathering data on the metabolism of these cells under healthy conditions, and comparing between groups in various stages of T2DM pathogenesis will provide a foundation for future research into this

heterogeneous lymphocyte subtype. Additionally, next steps include addressing the major knowledge gap in working with ILT cells currently by providing a framework for transferring data collected in mice to humans for therapeutic purposes. While preclinical models remain a logical approach for the development of novel therapeutics, clinical translation, at least in proof-of-concept form, needs to occur more rapidly than in similar areas of research.

AUTHOR CONTRIBUTIONS

HV wrote the paper with input from all authors.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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