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; Vγ9Vδ2+; 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; Vγ9Vδ2+, 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...
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, monomophic 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 (Vγ9Vδ2 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 Ja33, Ja20 or Ja12, 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 CD161hi [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.

**Vγ9Vδ2+ 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 Vγ9Vδ2+ 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, Vγ9Vδ2+ T cells are specifically and exquisitely sensitive to the presentation of phosphoantigens, including endogenous prenylpyrophosphates, 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 \( \gamma^9\delta^2^+ \) T cell activation and associated cytolytic and effector functions [81].

The clinical relevance of \( \gamma^9\delta^2^+ \) T cells has for the most part been studied in the context of cancer immunology, consistent with \( \gamma^9\delta^2^+ \) T cells’ potent ability to recognize and kill tumour cells [82,83]. However, \( \gamma^9\delta^2^+ \) 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 \( \gamma^9\delta^2^+ \) 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, IFN\( \gamma \) 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 Ja18 displayed reduced weight gain and a better metabolic profile compared to wild type [101,102].

Ja18−/− 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 Ja-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 Traj18 deficient mice [105]. Thus, conclusions drawn from experiments using the original strain of Ja18−/− 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 Vy9‘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 Vy9‘Vδ2‘ T cells was studied in the context of metabolic bone disease, osteoporosis, with data showing increased activity of Vy9‘Vδ2‘ T cells after the use of bisphosphonates, namely zoledronic acid, both in vitro and in vivo [106,107]. Authors indicate Vy9‘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 Vγ9Vδ2+ T cell activation by bisphosphonates may be beneficial for metabolic disease [108]. In the context of obesity, one study found that when Vγ9Vδ2+ T cells are activated, they take up LDL, which can be toxic to the cell. As the intracellular concentration of LDL increased, Vγ9Vδ2+ 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 Vγ9Vδ2+ 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 Vγ9Vδ2+ 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 Vγ9Vδ2+ T cells, indicated that iNKT cells and Vγ9Vδ2+ 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 Vγ9Vδ2+ 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 Vγ9Vδ2+ 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 immunometabolic 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.

REFERENCES

1. Cho NH, Shaw JE, Karuranga S, Huang Y, da Rocha Fernandes JD, Ohlrogge AW, et al. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res Clin Pract. 2018;138:271-81.
2. Kaiser AB, Zhang N, Der Pluijm WV. Global Prevalence of Type 2 Diabetes over the Next Ten Years (2018-2028). Diabetes. 2018;67(Suppl 1):202-LB.
3. Ogurtsova K, da Rocha Fernandes JD, Huang Y, Linnenkamp U, Guariguata L, Cho NH, et al. IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. Diabetes Res Clin Pract. 2017;128:40-50.
4. Mathis D, Shoelson SE. Immunometabolism: an emerging frontier. Nat Rev Immunol. 2011;11(2):81.
5. Hotamisligil GS. Foundations of Immunometabolism and Implications for Metabolic Health and Disease. Immunity. 2017;47(3):406-20.
6. Pekala P, Kawakami M, Vine W, Lane MD, Cerami A. Studies of insulin resistance in adipocytes induced by macrophage mediator. J Exp Med. 1983;157(4):1360-5.
7. Tack CJ, Stienstra R, Joosten LAB, Netea MG. Inflammation links excess fat to insulin resistance: The role of the interleukin-1 family. Immunol Rev. 2012;249(1):239-52.
8. Hotamisligil GS. Inflammation, metaflammation and immunometabolic disorders. Nature. 2017;542(7640):177-85.
9. McNelis Joanne C, Olefsky Jerrold M. Macrophages, Immunity, and Metabolic Disease. Immunity. 2014;41(1):36-48.
10. American Diabetes Association. 3. Prevention or Delay of Type 2 Diabetes: Standards of Medical Care in Diabetes-2020. Diabetes Care. 2020;43(Suppl 1):S32-6.
11. Buse JB, Wexler DJ, Tsapas A, Rossing P, Mingrone G, Mathieu C, et al. 2019 update to: Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2020;63(2):221-8.
12. Khan RMM, Chua ZJY, Tan JC, Yang Y, Liao Z, Zhao Y. From Pre-Diabetes to Diabetes: Diagnosis, Treatments and Translational Research. Medicina. 2019;55(9):546.

13. Cummings DE, Rubino F. Metabolic surgery for the treatment of type 2 diabetes in obese individuals. Diabetologia. 2018;61(2):257-64.

14. O’Brien PE, Hindle A, Brennan L, Skinner S, Burton P, Smith A, et al. Long-Term Outcomes After Bariatric Surgery: a Systematic Review and Meta-analysis of Weight Loss at 10 or More Years for All Bariatric Procedures and a Single-Centre Review of 20-Year Outcomes After Adjustable Gastric Banding. Obes Surg. 2019;29(1):3-14.

15. Schlender L, Martinez YV, Adeniji C, Reeves D, Sommerauer C, et al. Efficacy and safety of metformin in the management of type 2 diabetes mellitus in older adults: a systematic review for the development of recommendations to reduce potentially inappropriate prescribing. BMC Geriatr. 2017;17(Suppl 1):227.

16. Aroda VR, Knowler WC, Crandall JP, Perreault L, Edelstein SL, Jeffries SL, et al. Metformin for diabetes prevention: insights gained from the Diabetes Prevention Program/Diabetes Prevention Program Outcomes Study. Diabetologia. 2017;60(9):1601-11.

17. Ferrante AW Jr. Obesity-induced inflammation: a metabolic dialogue in the language of inflammation. J Intern Med. 2007;262(4):408-14.

18. Boden G. Obesity and free fatty acids. Endocrinol Metab Clin North Am. 2008;37(3):635-46.

19. Tataranni PA, Ortega E. A burning question: does an adipokine-induced activation of the immune system mediate the effect of overnutrition on type 2 diabetes? Diabetes. 2005;54(4):917-27.

20. Izaola O, de Luis D, Sajoux I, Domingo JC, Vidal M. [Inflammation and obesity (lipoinflammation)]. Nutr Hosp. 2015;31(6):2352-8. Spanish.

21. Al-Goblan AS, Al-Alfi MA, Khan MZ. Mechanism linking diabetes mellitus and obesity. Diabetes Metab Syndr Obes. 2014;7:587-91.

22. Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrbach K, et al. Bariatric surgery: a systematic review and meta-analysis. JAMA. 2004;292(14):1724-37.

23. Wernstedt Asterholm I, Tao C, Morley Thomas S, Wang Qiong A, Delgado-Lopez F, Wang Zhao V, et al. Adipocyte Inflammation Is Essential for Healthy Adipose Tissue Expansion and Remodeling. Cell Metab. 2014;20(1):103-18.

24. Shi H, Kokoeva MV, Inouye K, Tzameli I, Yin H, Flier JS. TLR4 links innate immunity and fatty acid-induced insulin resistance. J Clin Invest. 2006;116(11):3015-25.

25. Buck MD, Sowell RT, Kaech SM, Pearce EL. Metabolic Instruction of Immunity. Cell. 2017;169(4):570-86.

26. Patsoukis N, Bardhan K, Chatterjee P, Sari D, Liu B, Bell LN, et al. PD-1 alters T-cell metabolic reprogramming by inhibiting glycolysis and promoting lipolysis and fatty acid oxidation. Nat Commun. 2015;6:6692.
27. Wang R, Dillon CP, Shi LZ, Milasta S, Carter R, Finkelstein D, et al. The transcription factor Myc controls metabolic reprogramming upon T lymphocyte activation. Immunity. 2011;35(6):871-82.

28. Rodríguez-Prados JC, Través PG, Cuenca J, Rico D, Aragonés J, Martín-Sanz P, et al. Substrate fate in activated macrophages: a comparison between innate, classic, and alternative activation. J Immunol. 2010;185(1):605-14.

29. O’Neill LA, Kishton RJ, Rathmell J. A guide to immunometabolism for immunologists. Nat Rev Immunol. 2016;16(9):553-65.

30. Warburg O. On the Origin of Cancer Cells. Science. 1956;123(3191):309-14.

31. Koppenol WH, Bounds PL, Dang CV. Otto Warburg’s contributions to current concepts of cancer metabolism. Nat Rev Cancer. 2011;11(5):325-37.

32. Lunt SY, Heiden MGV. Aerobic Glycolysis: Meeting the Metabolic Requirements of Cell Proliferation. Ann Rev Cell Dev Biol. 2011;27(1):441-64.

33. Fan TWM, Lane AN, Higashi RM, Farag MA, Gao H, Bousamra M, et al. Altered regulation of metabolic pathways in human lung cancer discerned by 13C stable isotope-resolved metabolomics (SIRM). Mol Cancer. 2009;8(1):41.

34. Sena Laura A, Li S, Jairaman A, Prakriya M, Ezponda T, Hildeman David A, et al. Mitochondria Are Required for Antigen-Specific T Cell Activation through Reactive Oxygen Species Signaling. Immunity. 2013;38(2):225-36.

35. Wencker M, Turchinovich G, Di Marco Barros R, Deban L, Jandke A, Cope A, et al. Innate-like T cells straddle innate and adaptive immunity by altering antigen-receptor responsiveness. Nat Immunol. 2014;15(1):80-7.

36. Lantz O, Legoux F. MAIT cells: an historical and evolutionary perspective. Immunol Cell Biol. 2018;96(6):564-72.

37. van Wilgenburg B, Scherwitzl I, Hutchinson EC, Leng T, Kurioka A, Kulicke C, et al. MAIT cells are activated during human viral infections. Nat Commun. 2016;7:11653.

38. Brennan PJ, Brigi M, Brenner MB. Invariant natural killer T cells: an innate activation scheme linked to diverse effector functions. Nat Rev Immunol. 2013;13(2):101-17.

39. Gold MC, Cerri S, Smyk-Pearson S, Cansler ME, Vogt TM, Delepine J, et al. Human mucosal associated invariant T cells detect bacterially infected cells. PLoS Biol. 2010;8(6):e1000407.

40. Vavassori S, Kumar A, Wan GS, Ramanjaneyulu GS, Cavallari M, EL Daker S, et al. Butyrophilin 3A1 binds phosphorylated antigens and stimulates human γδ T cells. Nat Immunol. 2013;14(9):908-16.

41. Crosby CM, Kronenberg M. Tissue-specific functions of invariant natural killer T cells. Nat Rev Immunol. 2018;18(9):559-74.

42. Rothenberg EV, Moore JE, Yui MA. Launching the T-cell-lineage developmental programme. Nat Rev Immunol. 2008;8(1):9-21.

43. Savage AK, Constantinides MG, Bendelac A. Promyelocytic Leukemia Zinc Finger Turns on the Effector T Cell Program without Requirement for Agonist TCR Signaling. J Immunol. 2011;186(10):5801.

44. Slichter CK, McDavid A, Miller HW, Finak G, Seymour BJ, McNevin JP, et al. Distinct activation thresholds of human conventional and innate-like memory T cells. JCI Insight. 2016;1(8):e86292.

Immunometabolism. 2020;2(4):e200031. https://doi.org/10.20900/immunometab20200031
45. Kronenberg M, Kinjo Y. Innate-like recognition of microbes by invariant natural killer T cells. Curr Opin Immunol. 2009;21(4):391-6.
46. Krovi SH, Gapin L. Invariant Natural Killer T Cell Subsets—More Than Just Developmental Intermediates. Front Immunol. 2018;9:1393.
47. Gapin L. Check MAIT. J Immunol. 2014;192(10):4475-80.
48. Deng N, Chen Q, Guo X, Liu L, Chen S, Wang A, et al. Blockade of CD40L inhibits immunogenic maturation of lung dendritic cells: Implications for the role of lung iNKT cells in mouse models of asthma. Mol Immunol. 2020;121:167-85.
49. Lee KC, Chen P, Maricic I, Inamine T, Hu J, Gong S, et al. Intestinal iNKT cells migrate to liver and contribute to hepatocyte apoptosis during alcoholic liver disease. Am J Physiol Gastrointest Liver Physiol. 2019;316(5):G585-97.
50. Maricic I, Marrero I, Eguchi A, Nakamura R, Johnson CD, Dasgupta S, et al. Differential Activation of Hepatic Invariant NKT Cell Subsets Plays a Key Role in Progression of Nonalcoholic Steatohepatitis. J Immunol. 2018;201(10):3017-35.
51. Wallace KL, Linden J. Adenosine A2A receptors induced on iNKT and NK cells reduce pulmonary inflammation and injury in mice with sickle cell disease. Blood. 2010;116(23):5010-20.
52. Wallace KL, Marshall MA, Ramos SI, Lannigan JA, Field JF, Strieter RM, et al. NKT cells mediate pulmonary inflammation and dysfunction in murine sickle cell disease through production of IFN-gamma and CXCR3 chemokines. Blood. 2009;114(3):667-76.
53. Sbihi Z, Dossier A, Boutboul D, Galicier L, Parizot C, Emarre A, et al. iNKT and memory B-cell alterations in HHV-8 multicentric Castleman disease. Blood. 2017;129(7):855-65.
54. Kumar A, Pyaram K, Yarosz EL, Hong H, Lyssiotis CA, Giri S, et al. Enhanced oxidative phosphorylation in NKT cells is essential for their survival and function. Proc Natl Acad Sci U S A. 2019;116(15):7439.
55. Ahl PJ, Hopkins RA, Xiang WW, Au B, Kaliaperumal N, Fairhurst A-M, et al. A novel strategy for single-cell metabolic analysis highlights dynamic changes in immune subpopulations. bioRxiv 914663 [Preprint]. 2013 Jan 23. doi: 10.1101/2020.01.21.914663
56. Fu S, Zhu S, Tian C, Bai S, Zhang J, Zhan C, et al. Immunometabolism regulates TCR recycling and iNKT cell functions. Sci Signal. 2019;12(570):eaau1788.
57. Chang C-H, Curtis Jonathan D, Maggi Leonard B, Faubert B, Villarino Alejandro V, O’Sullivan D, et al. Posttranscriptional Control of T Cell Effector Function by Aerobic Glycolysis. Cell. 2013;153(6):1239-51.
58. van Wilgenburg B, Lob L, Chen Z, Pediongco TJ, Wang H, Shi M, et al. MAIT cells contribute to protection against lethal influenza infection in vivo. Nat Commun. 2018;9(1):4706.
59. Ussher JE, Bilton M, Attwod E, Shadwell J, Richardson R, de Lara C, et al. CD161+CD8- T cells, including the MAIT cell subset, are specifically activated by IL-12’IL-18 in a TCR-independent manner. European J Immunol. 2014;44(1):195-203.
60. Jeffery HC, van Wilgenburg B, Kurioka A, Parekh K, Stirling K, Roberts S, et al. Biliary epithelium and liver B cells exposed to bacteria activate intrahepatic MAIT cells through MR1. J Hepatol. 2016;64(5):1118-27.

61. Toubal A, Nel I, Lotersztajn S, Lehuen A. Mucosal-associated invariant T cells and disease. Nat Rev Immunol. 2019;19(10):643-57.

62. Reantragoon R, Corbett AJ, Sakala IG, Gherardin NA, Furness JB, Chen Z, et al. Antigen-loaded MR1 tetramers define T cell receptor heterogeneity in mucosal-associated invariant T cells. J Exp Med. 2013;210(11):2305-20.

63. Van Rhijn I, Kasmar A, de Jong A, Gras S, Bhati M, Doorenspleet ME, et al. A conserved human T cell population targets mycobacterial antigens presented by CD1b. Nat Immunol. 2013;14(7):706-13.

64. Cosgrove C, Ussher JE, Rauch A, Gärtner K, Kurioka A, Hühn MH, et al. Early and nonreversible decrease of CD161++/MAIT cells in HIV infection. Blood. 2013;121(6):951-61.

65. Leeansyah E, Ganesh A, Quigley MF, Sönnerborg A, Andersson J, Hunt PW, et al. Activation, exhaustion, and persistent decline of the antimicrobial MR1-restricted MAIT-cell population in chronic HIV-1 infection. Blood. 2013;121(7):1124-35.

66. Xiao X, Cai J. Mucosal-Associated Invariant T Cells: New Insights into Antigen Recognition and Activation. Front Immunol. 2017;8:1540.

67. Salou M, Legoux F, Gilet J, Darbois A, du Halgouet A, Alonso R, et al. A common transcriptomic program acquired in the thymus defines tissue residency of MAIT and NKT subsets. J Exp Med. 2019;216(1):133-51.

68. Koay HF, Gherardin NA, Enders A, Loh L, Mackay LK, Almeida CF, et al. A three-stage intrathymic development pathway for the mucosal-associated invariant T cell lineage. Nat Immunol. 2016;17(11):1300-11.

69. Gherardin NA, Souter MN, Koay HF, Mangas KM, Seemann T, Stinear TP, et al. Human blood MAIT cell subsets defined using MR1 tetramers. Immunol Cell Biol. 2018;96(5):507-25.

70. Salou M, Nicol B, García A, Baron D, Michel L, Elong-Ngono A, et al. Neuropathologic, phenotypic and functional analyses of Mucosal Associated Invariant T cells in Multiple Sclerosis. Clin Immunol. 2016;166-7:1-11.

71. Serriari NE, Eoche M, Lamotte L, Lion J, Fumery M, Marcelo P, et al. Innate mucosal-associated invariant T (MAIT) cells are activated in inflammatory bowel diseases. Clin Exp Immunol. 2014;176(2):266-74.

72. Haga K, Chiba A, Shibuya T, Osada T, Ishikawa D, Kodani T, et al. MAIT cells are activated and accumulated in the inflamed mucosa of ulcerative colitis. J Gastroenterol Hepatol. 2016;31(5):965-72.

73. Fichtner AS, Ravens S, Prinz I. Human γδ TCR Repertoires in Health and Disease. Cells. 2020;9(4):800.

74. Triebel F, Faure F, Graziani M, Jitsukawa S, Lefranc MP, Hercend T. A unique V-J-C-rearranged gene encodes a gamma protein expressed on the majority of CD3+ T cell receptor-alpha/beta- circulating lymphocytes. J Exp Med. 1988;167(2):694-9.

75. Triebel F, Faure F, Mami-Chouaib F, Jitsukawa S, Griscelli A, Genevée C, et al. A novel human V delta gene expressed predominantly in the Ti gamma A
fraction of gamma/delta+ peripheral lymphocytes. Eur J Immunol. 1988;18(12):2021-7.

76. Bottino C, Tambussi G, Ferrini S, Ciccone E, Varese P, Mingari MC, et al. Two subsets of human T lymphocytes expressing gamma/delta antigen receptor are identifiable by monoclonal antibodies directed to two distinct molecular forms of the receptor. J Exp Med. 1988;168(2):491-505.

77. Casorati G, De Libero G, Lanzavecchia A, Migone N. Molecular analysis of human gamma/delta+ clones from thymus and peripheral blood. J Exp Med. 1989;170(5):1521-35.

78. Johnson MD, Witherden DA, Havran WL. The Role of Tissue-resident T Cells in Stress Surveillance and Tissue Maintenance. Cells. 2020;9(3):686.

79. Kohlgruber AC, Gal-Oz ST, LaMarche NM, Shimazaki M, Duquette D, Nguyen HN, et al. Gammadelta T cells producing interleukin-17A regulate adipose regulatory T cell homeostasis and thermogenesis. Nat Immunol. 2018;19(5):464-74.

80. Karunakaran MM, Willcox CR, Salim M, Paletta D, Fichtner AS, Noll A, et al. Butyrophilin-2A1 Directly Binds Germline-Encoded Regions of the Vγ9Vδ2 TCR and Is Essential for Phosphoantigen Sensing. Immunity. 2020;52(3):487-98.e6.

81. Sebestyen Z, Scheper W, Vyborova A, Gu S, Rychnavska Z, Schiffler M, et al. RhOB Mediates Phosphoantigen Recognition by Vγ9Vδ2 T Cell Receptor. Cell Rep. 2016;15(9):1973-85.

82. Nussbaumer O, Koslowski M. The emerging role of γδ T cells in cancer immunotherapy. Immuno-Oncol Technol. 2019;1:3-10.

83. Li X, Lu H, Gu Y, Zhang X, Zhang G, Shi T, et al. Tim-3 suppresses the killing effect of Vγ9Vδ2 T cells on colon cancer cells by reducing perforin and granzyme B expression. Exp Cell Res. 2020;386(1):111719.

84. Bertrand L, Lehuen A. Mucosal-Associated Invariant T Cell Alters in Obesity and Type 2 Diabetic Patients. Microbes Infect. 2015;17(4):491-498.

85. Magalhaes I, Pingris K, Poitou C, Bessoles S, Venteclaf N, Kief B, et al. Mucosal-associated invariant T cell alterations in obese and type 2 diabetic patients. J Clin Invest. 2015;125(4):1752-62.

86. Carolan E, Tobin LM, Mangan BA, Corrigan M, Gaoatswe G, Byrne G, et al. Targeting mitochondrial dysfunction in MAIT cells limits IL-17 production in obesity. Cell Mol Immunol. 2020;17(4):414-23. doi: 10.1038/s41423-017-0011-x.
91. Hegde P, Weiss E, Paradis V, Wan J, Mabire M, Sukriti S, et al. Mucosal-associated invariant T cells are a profibrogenic immune cell population in the liver. Nat Commun. 2018;9(1):2146.

92. Touch S, Assmann KE, Aron-Wisnewsky J, Marquet F, Rouault C, Fradet M, et al. Mucosal-associated invariant T (MAIT) cells are depleted and prone to apoptosis in cardiometabolic disorders. FASEB J. 2018;32(9):5078-89.

93. O’Brien A, Loftus RM, Pisarska MM, Tobin LM, Bergin R, Wood NAW, et al. Obesity Reduces mTORC1 Activity in Mucosal-Associated Invariant T Cells, Driving Defective Metabolic and Functional Responses. J Immunol. 2019;202(12):3404-11.

94. Lynch L. Adipose invariant natural killer T cells. Immunology. 2014;142(3):337-46.

95. Lynch L, Nowak M, Varghese B, Clark J, Hogan AE, Toxavidis V, et al. Adipose tissue invariant NKT cells protect against diet-induced obesity and metabolic disorder through regulatory cytokine production. Immunity. 2012;37(3):574-87.

96. Schipper HS, Rakhshandehroo M, van de Graaf SF, Venken K, Koppen A, Stienstra R, et al. Natural killer T cells in adipose tissue prevent insulin resistance. J Clin Invest. 2012;122(9):3343-54.

97. Lynch L, Hogan AE, Duquette D, Lester C, Banks A, LeClair K, et al. iNKT Cells Induce FGF21 for Thermogenesis and Are Required for Maximal Weight Loss in GLP1 Therapy. Cell Metab. 2016;24(3):510-9.

98. Lynch L, Michelet X, Zhang S, Brennan PJ, Moseman A, Lester C, et al. Regulatory iNKT cells lack expression of the transcription factor PLZF and control the homeostasis of T(reg) cells and macrophages in adipose tissue. Nat Immunol. 2015;16(1):85-95.

99. Sag D, Krause P, Hedrick CC, Kronenberg M, Wingender G. IL-10-producing NKT10 cells are a distinct regulatory invariant NKT cell subset. J Clin Invest. 2014;124(9):3725-40.

100. Lynch L, O’Shea D, Winter DC, Geoghegan J, Doherty DG, O’Farrelly C. Invariant NKT cells and CD1d(+) cells amass in human omentum and are depleted in patients with cancer and obesity. Eur J Immunol. 2009;39(7):1893-901.

101. Wu L, Parekh VV, Gabriel CL, Bracy DP, Marks-Shulman PA, Tamboli RA, et al. Activation of invariant natural killer T cells by lipid excess promotes tissue inflammation, insulin resistance, and hepatic steatosis in obese mice. Proc Natl Acad Sci U S A. 2012;109(19):E1143-52.

102. Ren Y, Sekine-Kondo E, Shibata R, Kato-Itoh M, Umino A, Yanagida A, et al. A Novel Mouse Model of iNKT Cell-deficiency Generated by CRISPR/Cas9 Reveals a Pathogenic Role of iNKT Cells in Metabolic Disease. Sci Rep. 2017;7(1):12765.

103. Cui J, Shin T, Kawano T, Sato H, Kondo E, Toura I, et al. Requirement for Valpha14 NKT cells in IL-12-mediated rejection of tumors. Science. 1997;278(5343):1623.

104. Bedel R, Matsuda JL, Brigl M, White J, Kappler J, Marrack P, et al. Lower TCR repertoire diversity in Traj18-deficient mice. Nature Immunology. 2012;13(8):705-6.
105. Dashtsoodol N, Shigeura T, Ozawa R, Harada M, Kojo S, Watanabe T, et al. Generation of Novel Traj18-Deficient Mice Lacking Va14 Natural Killer T Cells with an Undisturbed T Cell Receptor α-Chain Repertoire. PLoS One. 2016;11(4):e0153347.

106. Ferlazzo V, Sferrazza C, Caccamo N, Di Fede G, Di Lorenzo G, D’Asaro M, et al. In vitro effects of aminobisphosphonates on Vgamma9Vdelta2 T cell activation and differentiation. Int J Immunopathol Pharmacol. 2006;19(2):309-17.

107. Sprini D, Di Stefano L, Rini GB, Cianferotti L, Napoli N. Vy9Vδ2 T lymphocytes activation in osteoporotic patients treated with bisphosphonates. Clin Cases Miner Bone Metab. 2014;11(2):126-8.

108. Karimi Fard M, Aminorroaya A, Kachuei A, Salamat MR, Hadi Alijanvand M, Aminorroaya Yamini S, et al. Alendronate improves fasting plasma glucose and insulin sensitivity, and decreases insulin resistance in prediabetic osteopenic postmenopausal women: A randomized triple-blind clinical trial. J Diabetes Investig. 2019;10(3):731-7.

109. Rodrigues NV, Correia DV, Mensurado S, Nóbrega-Pereira S, deBarros A, Kyle-Cezar F, et al. Low-Density Lipoprotein Uptake Inhibits the Activation and Antitumor Functions of Human Vy9Vδ2 T Cells. Cancer Immunol Res. 2018;6(4):448-57.

110. Li Y, Woods K, Parry-Strong A, Anderson RJ, Capistrano C, Gestin A, et al. Distinct Dysfunctional States of Circulating Innate-Like T Cells in Metabolic Disease. Front Immunol. 2020;11:448.

111. Rakhshandehroo M, van Eijkeren RJ, Gabriel TL, de Haar C, Gijzel SMW, Hamers N, et al. Adipocytes harbor a glucosylceramide biosynthesis pathway involved in iNKT cell activation. Biochim Biophys Acta Mol Cell Biol Lipids. 2019;1864(8):1157-67.

112. Balaz M, Becker AS, Balazova L, Straub L, Müller J, Gashi G, et al. Inhibition of Mevalonate Pathway Prevents Adipocyte Browning in Mice and Men by Affecting Protein Prenylation. Cell Metab. 2019;29(4):901-16.e8.

113. Crandall JP, Mather K, Rajpathak SN, Goldberg RB, Watson K, Foo S, et al. Statin use and risk of developing diabetes: results from the Diabetes Prevention Program. BMJ Open Diabetes Res Care. 2017;5(1):e000438.

114. Massier L, Chakaroun R, Tabei S, Crane A, Didt KD, Fallmann J, et al. Adipose tissue derived bacteria are associated with inflammation in obesity and type 2 diabetes. Gut. 2020 Apr 21:gutjnl-2019-320118.

115. Kim EY, Lynch L, Brennan PJ, Cohen NR, Brenner MB. The transcriptional programs of iNKT cells. Semin Immunol. 2015;27(1):26-32.

116. Savage AK, Constantinides MG, Han J, Picard D, Martin E, Li B, et al. The transcription factor PLZF directs the effector program of the NKT cell lineage. Immunity. 2008;29(3):391-403.

117. Kovalovsky D, Uche OU, Eladad S, Hobbs RM, Yi W, Alonzo E, et al. The BTB–zinc finger transcriptional regulator PLZF controls the development of invariant natural killer T cell effector functions. Nat Immunol. 2008;9(9):1055-64.

118. Rahimpour A, Koay HF, Enders A, Clanchy R, Eckle SB, Meehan B, et al. Identification of phenotypically and functionally heterogeneous mouse
mucosal-associated invariant T cells using MR1 tetramers. J Exp Med. 2015;212(7):1095-108.

119. Eidson M, Wahlstrom J, Beaulieu AM, Zaidi B, Carsons SE, Crow PK, et al. Altered development of NKT cells, γδ T cells, CD8 T cells and NK cells in a PLZF deficient patient. PLoS One. 2011;6(9):e24441.

120. Vieth JA, Das J, Ranaivoson FM, Comoletti D, Denzin LK, Sant’Angelo DB. TCRα-TCRβ pairing controls recognition of CD1d and directs the development of adipose NKT cells. Nat Immunol. 2017;18(1):36-44.

121. Cui Y, Franciszkiewicz K, Mburu YK, Mondot S, Le Bourhis L, Premel V, et al. Mucosal-associated invariant T cell-rich congenic mouse strain allows functional evaluation. J Clin Invest. 2015;125(11):4171-85.

122. Dimova T, Brouwer M, Gosselin F, Tassignon J, Leo O, Donner C, et al. Effector Vγ9Vδ2 T cells dominate the human fetal γδ T-cell repertoire. Proc Natl Acad Sci U S A. 2015;112(6):E556-65.

123. Man K, Kutyavin VI, Chawla A. Tissue Immunometabolism: Development, Physiology, and Pathobiology. Cell Metab. 2017;25(1):11-26.

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