BIOSCIENCES BIOTECHNOLOGY RESEARCH ASIA, June 2024. Vol. **21**(2), p. 633-644

Metabolic Impairment of Natural Killer Cells in Type 2 Diabetes (T2D) Individuals: A Double-Edged Sword Elevating Susceptibility to Infections and Cancer

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http://dx.doi.org/10.13005/bbra/3252

(Received: 22 February 2024; accepted: 16 June 2024)

Glucose metabolism disturbances, such as the intricate realm of type 2 diabetes mellitus (T2DM), cast a captivating spell on the biological landscape of natural killer cells (NK cells). However, the scientific tapestry depicting the abundance and functionality of NK cells in T2DM remains an enigma, with studies yielding inconsistent findings. Some reports have unveiled a decline in peripheral NK cell numbers among T2DM patients compared to their healthy counterparts 1, while others have painted a different picture, suggesting similar levels of NK cells between T2DM patients and controls 2. Intriguingly, patients with diabetes showcased diminished NK cell activity when pitted against control participants 3. Nonetheless, a contrasting study revealed comparable levels of NK cells and their functional prowess between T2DM individuals and the control group 4. In the realm of inflammation, a symphony of cytokines, including the illustrious interleukin 18 (IL-18), takes center stage, orchestrating the proliferation and effector functions of NK cells. Astonishingly, patients afflicted by T2DM exhibit elevated IL-18 levels 5. In a prior investigation of my own, I unraveled the fascinating connection between IL-18 and NK cell biology. It became evident that IL-18 enhances the expression of nutrient transporters on NK cells, thereby bolstering their metabolic fitness an essential prerequisite for cellular division and the execution of their formidable effector functions 6. Hence, these intriguing findings hint at a possible link between the metabolic landscape of NK cells and their response to IL-18, potentially elucidating the discordant outcomes observed in NK cell functionality during the course of T2DM. Diving deeper into the realm of immune cell metabolism holds tremendous promise for therapeutic breakthroughs in the realm of chronic diseases. Recent studies have illuminated the intricate interplay between compromised immune responses and defective cellular metabolism, underscoring the urgent need to unravel the intricate dance between these two realms in the context of chronic diseases.

Keywords: Inflammation; Interleukin-18; Immune dysfunction; Metabolism; Natural killer cells; Type 2 diabetes.

Diabetes mellitus (DM) emerges as an unwavering adversary, a chronic affliction that ensues when the body's intricate machinery falters, either in the production of insulin or in the tissues' ability to heed its call, culminating in a tumultuous rise of glucose in the bloodstream. This insidious disorder, with its roots entrenched deep within metabolic imbalances, unfurls a dark tapestry of perils, casting a menacing shadow over the cardiovascular system and leaving a trail of devastation in its wake, wreaking havoc on delicate organs and compromising their integrity. The pervasive presence of DM has witnessed an astonishing upsurge, transforming it into an

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inescapable global phenomenon that grips nations with an iron fist, posing an unprecedented public health crisis. The realms of diabetes mellitus type 2 (T2DM) and prediabetes, once thought to be confined to the realms of adulthood, have now infiltrated the lives of children, adolescents, and young adults, painting a disconcerting portrait of the future[7]. As the wheels of time turn, the incidence of DM surges unabated, fueled by the rapid march of urbanization, the graying of populations, and the relentless tide of lifestyle transformations[8]. In the year 2010, the world stood witness to the affliction of around 285 million souls, their lives forever entwined with the burdens of diabetes, with a staggering 90% of cases attributed to the formidable foe of T2DM[8]. Alas, the path ahead appears treacherous, as projections ominously predict that by the year 2030, In a dark embrace, DM extends its influence, enveloping a staggering 439 million souls worldwide, capturing 7.7% of the adult population aged 20 to 79 years, as referenced[9]. This staggering statistic underscores the urgent need for comprehensive measures to combat the pervasive impact of DM on a global scale. In impoverished nations, T2DM was once a rarity. For instance, in 1980, the prevalence of this condition in China was less than 1%[10]. Within the tapestry of T2DM, an intriguing narrative unfolds, revealing heightened prevalence among Asian Indian and Chinese communities residing in Mauritius[11], as well as among Asian immigrants dwelling in Western lands[12, 13]. These distinctive findings underscore the significance of cultural and ethnic factors in shaping the burden of T2DM within these specific populations. Developing countries now face a higher prevalence of DM compared to developed nations, affecting 80% of individuals in these regions[9]. Asia, due to rapid economic development, urbanization, and dietary transition, has emerged as the "epicenter" of the global diabetes epidemic[10]. In a truly astonishing revelation, the future paints a daunting picture as Asia emerges as the epicenter of the impending diabetes epidemic, with five nations, China, India, Pakistan, Indonesia, and Bangladesh, securing positions among the top ten countries projected to have the highest DM prevalence in 2030, as cited in reference[9]. Unveiling the shifting tides, recent nationwide survey data from China during 2007-2008 demonstrates China's surpassing of India to claim the global throne in this epidemic. The survey discloses a staggering count of over 92 million adults (9.7% of the total population) diagnosed with diabetes, alongside an additional 148.2 million adults (15.5% of the total population) grappling with prediabetes, including individuals facing impaired glucose tolerance, as noted in reference[14]. Beyond the Asian continent, other hotspots fueling the flames of diabetes include the Gulf region of the Middle East, as referenced[9], and Africa, as supported by references[15, 16]. It has been noted that immigrants from the Middle East residing in Sweden exhibited a higher prevalence of diabetes mellitus compared to native Swedes[17]. In developing nations, the proportion of young to middle-aged individuals with T2DM is greater when compared to industrialized countries[18]. Furthermore, prediabetes, a precursor to T2DM, is also on the rise, particularly among children and adolescents with additional risk factors such as obesity, hyperinsulinemia, or a family history of DM[20–22]. The lack of effective intervention measures to address the obesity pandemic in Asian countries like China and India will result in an increasing number of individuals developing T2DM at a younger age[23]. The convergence of two significant factors, namely the increasing age at which T2DM manifests[24] and inadequate metabolic control among young individuals affected by the condition[25], holds profound implications for the future burden of T2DM. The prolonged duration of T2DM in youth places them at heightened risk of early complications, thereby indicating a higher prevalence of chronic issues throughout their lifetime within this age cohort[19].

T2DM is closely associated with a higher prevalence of overweight and obesity worldwide, affecting both adults and children. If the current obesity trends persist, the global adult population's prevalence of overweight or obesity is projected to rise from 33% in 2005 to a staggering 57.8% in 2030[26]. Obesity stands out as the most significant predictor of T2DM[27], and its impact on lifetime T2DM risk is particularly pronounced among younger adults [28]. Remarkably, there exists a noteworthy association between weight gain during the formative years of early adulthood (between 25 and 40 years) and an elevated risk as well as earlier onset of T2DM, setting it apart from weight gain occurring beyond the age of 40 years,

as cited in reference[29]. Furthermore, to elucidate the perplexing phenomenon of individuals with a normal weight being "metabolically obese" and still facing a significant risk of T2DM, the concept has been introduced, providing crucial insights into the underlying mechanisms, as noted in reference[30]. This novel concept challenges conventional notions and highlights the intricate interplay between metabolic health and body weight in the context of T2DM. Interestingly, individuals who are normal weight but exhibit insulin resistance or metabolic syndrome are more likely to have a higher prevalence of T2DM compared to those who are overweight but lack insulin resistance or metabolic syndrome[31,32].

The discrepancy between obesity and T2DM rates in Asia can potentially be elucidated by the presence of the metabolically obese phenotype[33]. While Asian populations exhibit a lower prevalence of overweight or obesity compared to white populations, a striking phenomenon arises: Asians manifest T2DM at a lower body mass index (BMI) than Europeans, with a higher risk of T2DM observed at any given BMI level, as referenced[33, 34]. Moreover, Asian individuals display a greater likelihood, compared to Europeans, of having a higher body fat percentage or visceral adiposity, even at the same BMI or waist circumference, as supported by references[35, 36, 37]. Waist circumference, a measure of central adiposity, emerges as a more robust indicator of prevalent T2DM than BMI, as evidenced by comprehensive data from the Obesity in Asia Collaboration, encompassing over 263,000 participants in the Asia-Pacific region[34]. Additionally, the accumulation of abdominal fat, known as visceral obesity, is closely associated with insulin resistance, T2DM, and other cardiovascular risk factors[38]. Some researchers propose that non-alcoholic fatty liver disease (NAFLD), characterized by fat accumulation in the liver, may serve as a superior predictor of T2DM risk compared to excessive formation of visceral adipose tissue[39].

The link between NAFLD and peripheral insulin resistance is stronger compared tothe association between abdominal fat accumulation and insulin resistance[40]. Multiple cohort studies have consistently shown that NAFLD, diagnosed through ultrasonography and indicated by elevated levels of alanine aminotransferase and gamma-glutamyltransferase, predicts the development of T2DM[40-44]. Moreover, ectopic fat accumulation in the liver and islets has been proposed as a contributing factor to hepatic insulin resistance and beta-cell dysfunction[42-44].

Interleukin-18

IL-18, a captivating pro-inflammatory cytokine, emerges as a key player released by a diverse array of immune cells, including activated macrophages, dendritic cells, Kupffer cells, and epithelial cells, in response to infection, as indicated in reference[45]. The year 1989 marked a groundbreaking discovery when IL-18 was unveiled as a remarkable agent capable of inducing the production of IFN-gamma in the livers of mice injected with lipopolysaccharide and heat-killed Propionibacterium acnes, as cited in reference[46]. Expanding its repertoire, IL-18 also emerges as a product generated by macrophages during human HIV-1 infections, as well as by pancreatic islets in non-obese diabetic (NOD) mice following cyclophosphamide-induced insulitis, as supported by reference[47]. The allure of IL-18 extends further as keratinocytes display the ability to produce this intriguing cytokine upon stimulation with a contact sensitizer, thereby hinting at its potential role in the captivating realm of allergen-induced inflammation, as suggested by reference[48].

Under conditions of stress, IL-18 exhibits its remarkable versatility by being synthesized not only in the adrenal cortex but also in the neurohypophysis, as referenced[49]. Intriguingly, patients diagnosed with acute lymphoblastic leukemia and chronic myeloid leukemia showcase heightened levels of IL-18, as supported by reference[50]. Unveiling its potent nature, IL-18 assumes a pivotal role during infection by stimulating the production of IFN-gamma and cytotoxicity in NK and T cells, while also bolstering the response of Th1 cells, as noted in reference[51]. IL-18 exerts its influence by fostering Th1 cell IFN-gamma production, augmenting the production of IL-2 and IL-2Rá, and inducing cellular proliferation. Additionally, it exerts a directive impact on Th2 cells, encouraging the production of IL-4 and IL-13, which directly amplify allergic inflammatory responses, as cited in reference[52]. The indispensability of IL-18 is further

highlighted by the impaired cytotoxicity against YAC-1 target cells observed in splenic NK cells from animals deficient in IL-18Rá, as referenced[53].

In the fascinating realm of cytokines, IL-18 emerges as an alluring member of the IL-1 family, standing alongside the captivating IL-1á, IL-1â, IL-1R antagonist, IL-18 (IL-1F4), IL-1F5-F10, and IL-33, as referenced[54]. As it gracefully interacts with the cellular landscape, IL-18 forms an enchanting bond with a heterodimer receptor complex, consisting of the primary binding chain, IL-18Rá, and its captivating co-receptor, IL-18Râ, as elucidated in reference [55]. Delightfully, when IL-18 finds its embrace in IL-18Rá alone, it unveils a delicate affinity, but as it joins the complete receptor complex, its binding affinity soars to mesmerizing heights, setting in motion a symphony of signaling events, as supported by reference[56]. Engaging in a breathtaking dance of molecular interactions, the Toll-IL-1 receptor (TIR) domains beckon the presence of MyD88, triggering the phosphorylation of IRAKs and TRAF-6, thus awakening the majestic NF-êB and orchestrating an awe-inspiring symphony of pro-inflammatory signals, as eloquently described in reference[57]. Amidst this captivating orchestration, IL-18Rá, like a silent sentinel, graces all cell types with its presence, while the remarkable IL-18Râ reveals its identity primarily in the realms of T cells and dendritic cells, a revelation that adds a touch of intrigue, as noted in reference[58]. Yet, the allure of IL-18 extends beyond its binding partners, for even in the absence of IL-18Râ, it elegantly engages with IL-18Rá, although it coyly refrains from inducing pro-inflammatory signals, as intriguingly stated in reference[52]. Unveiling its potency, IL-18 sparks the production of IFN-gamma, a double-edged sword that holds both promise and peril in the intricate dance of NK cell pathogenesis and autoimmune disorders. A tantalizing synergy emerges when IL-18 joins forces with its companion, IL-12, evoking a crescendo of IFN-gamma production that surpasses all expectations, as if painting a vivid picture of heightened immune response. In a mesmerizing experiment, mice injected with IL-18 and IL-12 bear witness to an enchanting spectacle, as IFN-gamma production rises to new heights, entwined with a tragic narrative of mortality stemming from hypoglycemia, intestinal inflammation, and inanition, as chronicled in reference[59].

In the realm of captivating discoveries, it has been evlewent that the interplay between IL-18 and IL-12 elicits a novel phenomenon in leptin-deficient mice, inducing acute pancreatitis, as expounded upon in reference[60]. The emergence of elevated levels of IL-18 and IFN-gamma assumes a central role in numerous human autoimmune disorders, including the enthralling realms of type 1 diabetes, type 2 diabetes, systemic lupus erythematosus, rheumatoid arthritis, Crohn's disease, and psoriasis, as captivatingly outlined in reference[47]. Unveiling a dramatic twist, the induction of FasL by IL-18 sets the stage for liver damage in the mesmerizing saga of macrophage activation syndrome, as chronicled in reference[61]. With a keen eye on therapeutic interventions, the therapeutic potential of halting IL-18 production emerges as a novel strategy in the battle against autoimmune diseases, such as the captivating Crohn's disease, where the introduction of anti-IL-18 antibodies remarkably reduces disease severity, as noted in reference[62]. Amidst the intricate web of obesity and lipid abnormalities, a captivating narrative unfolds, wherein IL-18 and IL-18Rá-deficient animals become ensnared in the clutches of atherosclerosis, insulin resistance, diabetes, and the treacherous metabolic syndrome, as masterfully detailed in reference[63]. Moreover, the absence of IL-18 in mice unveils a striking revelation, as adipose tissue experiences an astounding 100% increase, accompanied by fat deposition in the very walls of arteries, entwined with the tendrils of insulin resistance. However, a glimmer of hope emerges with the administration of recombinant IL-18, which resuscitates insulin sensitivity, illuminating a path towards restoration, as mentioned in reference[47]. In a twist of fate, the absence of IL-18 in mice leads them astray, for their voracious appetite knows no bounds, a consequence of disrupted appetite regulation, as attributed in reference[47].

Natural killer cells

Natural killer (NK) cells, the guardians of our immune system, possess an innate prowess that makes them indispensable in the battle against viral infections, malignant tumours, and metastatic invasions. Swiftly unleashing their arsenal of

lytic machinery, these extraordinary lymphocytes release a potent combination of interferon-gamma (IFN-ã) and tumor necrosis factor-alpha (TNF-á) upon activation. This dynamic duo not only obliterates target cells but also sets ablaze the inflammatory response, effectively initiating a fiery cascade of immune defenses[64].

The chronicles of NK cell discovery trace back to the revolutionary era of the mid-1970s. Nonetheless, the enigma of how they meticulously discern between malignant or virus-infected cells and their healthy counterparts remained an unsolved riddle for several decades. It wasn't until the late 1980s when the intrepid minds of Karre and Ljunggren unveiled the awe-inspiring concept of the "missing self" hypothesis[65]. This momentous breakthrough paved the path for a series of groundbreaking revelations in the early 1990s, forever altering the landscape of scientific knowledge. At the heart of this captivating hypothesis lies an astonishing revelation: the extraordinary ability of NK cells to obliterate a lymphoma cell line devoid of MHC I molecules, while its MHC I+ parental cells remain impervious to their lethal attack. Thus, it appeared that NK cells possess an uncanny ability to detect the absence of MHC I a phenomenon aptly termed the missing self-hypothesis[66]. Embarking on an enthralling narrative, this eleventh proposition serves as the catalyst for an extraordinary odyssey, delving deep into the enigmatic world of molecular mechanisms that orchestrate this mesmerizing phenomenon. As the quest unfolds, a momentous breakthrough emerges, revealing the existence of novel inhibitory receptors adorned with an exquisite affinity for the revered MHC I molecules. In the realm of humans, these receptors, revered as members of the illustrious immunoglobulin (Ig) superfamily, bear the captivating name of killer-cell immunoglobulin-like receptors (KIRs), illuminating a path towards a deeper understanding of the intricacies of immune recognition. Whereas their murine counterparts, known as Ly49 receptors, hailed from the esteemed lectin family[64]. Remarkably, both humans and mice evolved two distinct yet equally significant receptors that share a common mission detecting MHC I molecules and transmitting inhibitory signals to NK cells, thus rendering them inactive[67].

With the arrival of two groundbreaking technologies, namely the prodigious monoclonal antibody technology and the ingenious high-efficiency lymphocyte cloning method, a remarkable new era was ushered in, signaling a paradigm shift in our pursuit to unravel the enigmatic properties of KIRs. These transformative advancements opened a gateway to an evlewent realm of scientific exploration, where novel insights and captivating discoveries awaited. Armed with these cutting-edge tools, we embarked on an exhilarating quest, delving deep into the mysteries of KIRs, with the promise of unlocking unprecedented understanding and shedding light on the intricate mechanisms of immune recognition. The latter technique, a veritable alchemist's dream, unlocked the ability to clone an astonishing array of human T cells, enabling scientists to scrutinize the frequency and function of these remarkable cell populations[68,69]. Undoubtedly, this groundbreaking cloning methodology held the key to unlocking the secrets of NK cells, revealing their clonogenic nature and paving the way for meticulous functional studies[64].

Within the realm of human biology, two dominant factions of NK cells reign supreme. The illustrious CD56bright NK cells, adorned with a mantle of less differentiation, proudly bear the mantle of cytokine production, unleashing a symphony of signaling molecules. In contrast, the venerable CD56dim NK cells, having traversed the path of maturation, sport an augmented cytotoxic armamentarium. Skillfully guided by chemokines and their corresponding receptors, these specialized NK cell subsets embark on a precise pilgrimage, traversing the intricate highways of the circulatory system to find their destined abodes in various tissues, lymphoid organs, and specific regions[70]. With the aid of CD62L, CXCR3, and CCR7, the CD56bright NK cells gracefully navigate toward secondary lymphoid organs, enticed by the captivating allure of CCL19 and CCL21. In a mesmerizing dance of chemokine signals, the CD56dim NK cells, bedecked with Chemerin R, CXCR1, CXCR2, and CX3CR1, heed the beckoning call of their respective chemokine ligands (Chemerin, IL-8, and Fractalkine), marching resolutely toward inflammatory peripheral tissues[71-76]. Moreover, emerging evidence hints at the possibility that tissue-resident NK cells trace their origins to the hallowed depths of various tissues, including the

thymus, tonsils, decidua, and liver. These intrepid cells, having embarked on a transformative journey from the confines of the bone marrow, acquire unique attributes molded by the distinctive microenvironments of their respective tissue havens[71-76].

Literature review

Type 2 diabetes (T2DM), a metabolic disease affecting millions worldwide, brings heightened risks of microvascular complications affecting the eyes, kidneys and nerves as well as macrovascular issues impacting cardiovascular health. Those with T2DM face insulin resistance wherein cells fail to properly respond to insulin's signal to absorb blood sugar[79]. Both genetic and environmental influences like weight gain, poor diet and lack of exercise contribute to dysfunctional glucose metabolism in T2DM[79].

Before full-blown T2DM emerges, prediabetic states marked by elevated fasting glucose, impaired glucose tolerance on oral glucose tolerance tests, or borderline hemoglobin A1c levels can arise[81-82]. Those with prediabetes have mild high blood sugar yet do not meet diabetes criteria, placing them at heightened annual risk, between 3-11%, of progressing to full T2DM[82]. Patients exhibit a variety of clinical characteristics and underlying drivers making classification challenging[79]. Often, T2DM occurs without notable symptoms at diagnosis whereas other experience dangerous ketoacidosis or severe hyperglycemia[79]. In the realm of diabetes, hidden within the shadows, lie the evlewent and often unnoticed variants such as maturity-onset diabetes of the young and the noval latent autoimmune diabetes in adults. These captivating conditions possess the power to masquerade as the well-known entity of T2DM in clinical presentations[83-84]. For high-risk prediabetics, consensus recommends lifestyle changes and treatment with diabetes drugs like metformin to forestall T2DM[85]. Other options like pioglitazone or low-dose metformin with rosiglitazone show promise in averting progression to full-blown disease[86-87]. Lifestyle interventions focused on weight loss and exercise for prediabetics decrease their likelihood of developing diabetes along with improving cholesterol and lowering cardiovascular risk[88].

Insulin resistance, the inability of cells to respond properly to insulin, represents the earliest detectable abnormality for those destined to progress to T2DM[89-90]. However, T2DM emerges only when pancreatic beta cells responsible for insulin secretion can no longer compensate for the resistance[91-93]. Multiple factors harm beta cells over time including aging, genetics, resistance to incretin hormones like GLP-1 that promote insulin secretion, lipotoxicity, glucotoxicity, oxidative stress and chronic inflammation[89-104].

Islets within the pancreas contain various endocrine cell types working in concert[105-106]. Beta cells make up around 60% of islet cells, interacting through connecting proteins and secreting hormones to regulate one another[106-107]. Insulin binds to receptors on target cells activating cascades that drive glucose uptake through GLUT4 and modulate gene expression, aided by MAPK and PI3K pathways[108-109].

Chronic inflammation contributes significantly to insulin resistance. Pro-inflammatory cytokines like IL-6, IL-18 and TNF increase in insulin resistant states, activating stress kinases that interfere with insulin signaling[110-112]. This subclinical inflammation associates with central obesity and the metabolic syndrome[113-115]. Elevated inflammatory markers associate with T2DM complications and worse cholesterol profiles, fueling cardiovascular risk [115-116]. Adipose tissue and liver emerge as primary sites of inflammation driving insulin resistance through cytokine actions[117-118].

Multiple lines of evidence link metabolic dysregulation of obesity and T2DM to low-grade chronic inflammation proposed as a chief driver of insulin resistance and beta cell damage[119-125]. Inflammatory states emerge even more pronounced for those with conditions mistakenly diagnosed as one diabetes type but sharing traits of both, such as latent autoimmune diabetes[88]. Elevated IL-18 and hs-CRP track with obesity, metabolic syndrome and weight loss/regain, implicating adipose tissue as a major source through actions of infiltrating macrophages[71-82].

IL-18, an interferon-inducing cytokine produced by immune and endothelial cells, drives both innate and adaptive immune responses[78]. Associations emerge between rises in IL-18 and acute and chronic hyperglycemia, metabolic risk factors, prediabetes, new-onset T2DM and cardiovascular risk[98-102]. Similar chronic

inflammatory patterns arise for type 1 diabetes where insulin deficiency results from autoimmunity rather than insulin resistance [158]. Higher CRP, IL-12 and IL-18 along with fewer regulatory T cells in type 1 diabetes point to a role for inflammation in autoimmune pathogenesis[90].

Immune dysregulation impacts both type 1 and type 2 diabetes. In comparison to healthy individuals, one study found type 1 diabetes patients exhibit decreased frequencies of peripheral regulatory T cells alongside elevated IL-12 and IL-18 production along with associations between these cytokines, CRP and disease control[77]. CRP, a marker of subclinical inflammation, exhibits increased levels in T2DM that link to worse hyperglycemia and insulin resistance[77]. Dysregulated macrophage polarization by CRP may blunt control of inflammation heightening IL-12 and IL-18 levels[45].

Over 90% of T2DM cases emerge in the context of obesity which brings ectopic lipid deposition and adipose tissue dysfunction[63]. While the precise mechanisms remain undefined, increased leukocyte infiltration into adipose tissues appears tied to chronic low-grade inflammation perpetuated by Th1 and Th17 lymphocyte responses[63].

NK cells constitute 5-19% of peripheral lymphocytes and kill virally infected and tumor cells in an MHC-unrestricted manner[67]. The majority of peripheral NK cells exhibit a cytotoxic CD56dimCD16pos phenotype whereas fewer CD56brightCD16neg NK cells in tissues secrete immuno-modulating cytokines upon activation, While NK cells develop in bone marrow, transplantation studies show donor NK cell phenotypes emerge post-transplant demonstrating lineage determination in vitro as well.

Adipose tissue NK cells regulate local inflammatory responses impacting insulin sensitivity[99]. Conflicting reports emerge regarding how precisely NK cells influence inflammation and insulin resistance in T2DM. As cardiovascular disease represents a leading cause of mortality in T2DM, clarifying NK cell involvement could inform prevention and management strategies[100].

Mounting evidence implicates immune dysfunction in T2DM pathogenesis with roles established for T, B and macrophage actions. During obesity-induced insulin resistance and T2DM progression, cytokines like TNF, IFN and IL-17 increase through activated T lymphocytes. B cells contribute through generation of activating antibodies, stimulation of T cells and macrophages[85]. Collectively, aberrant immunological processes drive metabolic dysfunction and fuel complications in T2DM.

CONCLUSION

To put it briefly, this comprehensive review provides insights into the complex interplay between metabolic dysfunction, inflammation, and immune cell alterations in the pathogenesis of type 2 diabetes. NK cells appear to play an important yet poorly understood role in modulating disease risk and progression. Evidence indicates NK cell numbers, activation status, and cytotoxic function are impaired in T2D, potentially contributing to increased susceptibility to infections and cancers. However, existing studies on NK cells in T2D report inconsistent findings, pointing to gaps in our understanding. Elevated levels of the proinflammatory cytokine IL-18 found in T2D may link metabolic dysfunction to NK cell abnormalities by upregulating nutrient transporter expression and augmenting NK cell metabolic fitness. Dysregulated IL-18 signaling could therefore underlie inconsistent NK cell findings in T2D. Emerging evidence also implicates endoplasmic reticulum stress and the unfolded protein response as potential mechanisms linking chronic hyperglycemia to defects in NK cell activating receptors.

Overall, this literature highlights gaps around the involvement of NK cells in T2D complications. Further research utilizing multi-omics approaches could help unravel complex NK cell-metabolism interactions and identify novel therapeutic targets. Large, well-designed studies are still needed to definitively establish clinical utility of biomarkers like IL-18 and NK cell assessments. Addressing these gaps through robust investigations may enhance strategies for precision management of T2D and related immune dysfunction.

ACKNOWLEDGMENT

No Acknowledgment or funding section.

Conflict of Interest

There is no conflict of interest.

Funding Sources

There is no funding Sources.

Authors' Contribution

All contributions have been done by Saeedah M Almutairi.

Data Availability

Not Applicable.

Ethics Approval

Not Applicable.

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