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Immune System Should be the Target of Type 2 Diabetes Therapy

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ABSTRACT

Diabetes is one of the popular disease of the 21st century. The prevalence of diabetes increased worldwide and created a significant burden on health systems, promoting the need for the development of innovative therapeutic approaches. Type 2 diabetes (T2DM) is historically considered a metabolic ,non-immune condition. But more and more research indicated it is a immune related disease. Infection of virus and some bacteria, unhealthy food and nutrient load, high blood glucose lead to T2DM through immune dysfunction. Obese is combined with T2DM on immune dysfunction. Insulin itself may disturb the function of immune system. In addition, therapy through adjusting immune function in patients with T2DM shows good effect. All these suggest that immune dysfunction is the most critical factor for the presentation, development and its progression of T2DM,and that therapeutic strategies targeted at attenuating the progression of chronic low-grade inflammation and immune dysfunction are urgently required to prevent or slow the development and progression of type 2 diabetes.

KEYWORDS: Type 2 diabetes, infection, diet, inflammation, immune dysfunction, immune therapy

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INTRODUCTION

Diabetes is one of the major health threats facing humans. The World Health Organization(WHO) has called diabetes the epidemic of the 21st century. More than 200 million people affected by diabetes worldwide. Approximately 439 million people will be suffering from diabetes and its complications by 2030 [1, 2]. Type 2 diabetes mellitus (T2DM) was historically considered a non-immune condition[3]. But more and more research has challenged the stereotypical view that T2DM is solely a metabolic disease by identifying autoimmunity as an overlapping feature of type 1 diabetes (T1DM) and T2DM, which leads to impaired insulin secretion in β cells and promotes hyperglycaemia. Recent work highlighting adiposity-associated chronic inflammation in T2DM implicates immune mediators in metabolic dysregulation. In conjunction with adipocytes, the innate and adaptive immune system drives systemic inflammation, promoting both insulin resistance and associated complications such as diabetic nephropathy [4, 5].

Immune cells and cytokines contribute directly and significantly to the metabolic dysfunction seen in insulin target organs, such as adipose tissue (AT), or in the liver in the course of obesity. The chronic low-grade inflammation seen in AT and the liver is unequivocally linked to the development of insulin resistance and T2DM, and their cardiovascular complications. On the other hand, the inflammation in the pancreatic islets, as the presence of macrophages and IL-1beta-dependent reactions, contributes directly to the islet dysfunction in the course of T2DM pathogenesis. Pancreatic islet inflammation is thought to be directly associated with apoptosis in the islets. The combine of immunologic and inflammatory mechanisms play a pivotal role in the presentation, development and its progression of T2DM[6-8].

Infection and the Development of type 2 Diabetes

The development of type 2 diabetes is thought to involve both environmental, and genetic factors,which led to the insufficient production of insulin (either absolutely or relative to the body's needs), production of defective insulin, or the inability of cells to use insulin properly and efficiently[9].Infection can led to T2DM through dysfunction of immune system. Nehal N. Mehta et al[10] demonstrated that acute

inflammation induces systemic insulin resistance(IR) following modulation of specific adipose inflammatory and insulin signaling pathways. This provides a rationale for focused mechanistic studies and a model for human proof-of-concept trials of novel therapeutics targeting adipose inflammation in IR and related consequences in humans.

High prevalence of human herpesvirus 8 (HHV8) infection was observed in type 2 diabetes patients, and specific killer cell immunoglobulin-like receptors (KIR) allotypes were associated to both increased susceptibility to herpesvirus infection and risk to develop diabetes. These findings provide evidence that HHV8 infection might be a cofactor for type 2 diabetes in a specific subset of genetically susceptible individuals, and suggest the possibility that such patients might have an impaired immune-mediated component contributing to the development of type 2 diabetes[11].Chronic Hepatitis C virus, mainly genotype 1, has the potential of inducing insulin resistance and T2DM in vitro and in vivo . Structural and non-structural proteins of HCV modulate cellular gene expression through hamper the insulin signaling.The mechanisms of HCV induced insulin resistance involving the upregulation of Inflammatory cytokine TNFa, hypophosphorylation of insulin receptor substrate(IRS-1 and IRS-2), phosphorylation of Akt, up-regulation of gluconeogenic genes,accumulation of lipids and targeting lipid storage organelles.IRS proteins are key players in insulin signal transduction and are the major substrates of the insulin receptor. HCV core protein impairs the insulin signalling cascade which could be attributed to a significant proteasomal degradation of IRS-1 protein, in a dose-dependent way. In addition, datas show that liver cells transfected by HCV core protein show a marked attenuation of the regulatory inhibitory role of insulin on insulin growth factor binding protein-1 (IGFBP-1) expression. Since IGFBP-1 may have a role in glucose regulation and hepatic insulin sensitivity, this effect of HCV core protein can contribute to insulin resistance in chronic HCV infection. These results suggest that the degradation of IRS-1 by HCV core protein translates to impaired ability of insulin to inhibit the expression of the target gene IGFBP-1 in the liver and may serve as a novel mechanism for insulin resistance and hyperglycaemia[12].Hyeong-Kyu Park and co-worker[13] demonstrated that human resistin modulates glucose homeostasis under inflammation using a humanized resistin mouse model. Resistin

attenuates endotoxemia induced hypoglycemia by inducing insulin resistance in liver and promotes hepatic insulin resistance by exacerbating inflammatory responses in chronic endotoxemia. Increased inflammation is accompanied by increased infiltration of macrophages, which can augment resistin induction. Thus, induction of resistin is thought to be a component of the pathophysiology of inflammation-induced insulin resistance in humans. Therefore, we can say that the development of T2DM related to the dysfunction from infection.

Food and type 2 Diabetes

One of the most important cause of T2DM is the excess calories due to overeating and/or lack of physical activity. Diet remains the cornerstone of effective T2DM management and encouraging the adoption of a lifelong healthy diet, which optimises metabolic control as the ultimate aim of dietary interventions. Maintaining energy balance is one of the most important and effective therapeutic challenges in obese individuals. When a negative energy balance is achieved, glycaemic control, lipid levels, blood pressure and mortality risk all improve[14]. The optimal dietary macronutrient composition for achieving energy balance in T2DM remains controversial. But we must emphasise and reinforce the importance of higher fibre, fruit, vegetable and wholegrain intake and the substitution of monounsaturated for saturated-fat sources, in energy balanced conditions[15].The isotope ratios δ13C andδ15N may both serve as potential biomarkers of fish protein intake, whereas only d15N may reflect broader animal-source protein intake in a European population.The inverse association ofδ13C but a positive association ofδ15N with incident diabetes should be interpreted in the light of knowledge of dietary intake and may assist in identifying dietary components that are associated with health risks and benefits[16]. High fat diet increased blood glucose, glycosylated hemoglobin, fasting plasma insulin, and reduced oral glucose tolerance, indicating the manifestation of insulin resistance. High fat diet fed mice rapidly develop insulin resistance[17].Body mass index, fasting plasma glucose, HbA1c, triglyceride and high-sensitivity C-reactive protein negatively associated with dietary fiber intake after adjusting for age, sex, duration of diabetes, current smoking,current drinking, total energy intake, fat intake, saturated fatty acid intake, leisure-time physical activity and use of oral hypoglycemic agents or insulin. Increased

dietary fiber intake was associated with better glycemic control and more favorable cardiovascular disease risk factors including chronic kidney disease in type 2 diabetic patients[18,19].

The gastrointestinal (GI) microbiota is the collection of microbes which reside in the GI tract and represents the largest source of non-self antigens in the human body.The GI tract functions as a major immunological organ as it must maintain tolerance to commensal and dietary antigens while remaining responsive to pathogenic stimuli. If this balance is disrupted, inappropriate inflammatory processes can result, leading to host cell damage and/or autoimmunity[20].Diet can cause dysbiosis, an alteration in the composition of the microbiota, which could lead to aberrant immune responses. The intestinal microbiota plays a crucial role in the development of local and systemic immunity, as well as in maintaining colonic homeostasis. The complex consortium of microbes that we harbor within our gastrointestinal tract are not just passive bystanders, rather these organisms seem to actively shape our immune system responses both inside and outside the intestine. Many diseases have been suggested to be associated with a disruption in the commensal microbiota, which highlight the importance of understanding the individual species that make up a healthy microbiota[21,22]. The microbiota influences disease progression and/or prevention. There is an intimate communication between host and microbe that involves bacterial molecules and host derived sensors. While much of the data to date has explored TLRs and NOD-like receptors as the bacterial communication devices. There is evidence that alternative means, such as presentation of enteric bacterial derived molecules by DCs, can influence immune responses that affect autoimmunity. The focus of future endeavors is to identify these molecules as well as the host receptors that recognize them, as beneficial microbial products could offer new therapeutics to enhance human health. The alteration of the nutrient load induced rapid changes in the gut microbiota. These changes were directly correlated with stool energy loss in lean individuals such that a 20% increase in Firmicutes and a corresponding decrease in Bacteroidetes were associated with an increased energy harvest of 150 kcal. A high degree of overfeeding in lean individuals was accompanied by a greater fractional decrease in stool energy loss. These results show that the nutrient load is a key variable that can influence the gut bacterial community structure over short time scales[23,24].Gut microbiota characterizations were determined with 16S rDNA-based high-throughput sequencing. Observation of

T2DM-related dysbiosis, including the separation of microbial communities and a change of alpha diversity between the different glucose intolerance statuses. There is significant association between metabolic parameters and gut microbiota. Butyrate-producing bacteria (Akkermansia muciniphila ATCCBAA-835, and Faecalibacterium prausnitzii L2-6) had a higher abundance in the non-diabetes(NGT) group than in the pre-DM group. The abundance of Bacteroides in the T2DM group was only half that of the NGT and Pre-DM groups. Verrucomicrobiae may be a potential marker of T2DM as it had a significantly lower abundance in both the pre-DM and T2DM groups. This research provides further evidence of the structural modulation of gut microbiota in the pathogenesis of diabetes[25].Gut microbiota is one of the key factors regulating early events triggering inflammation associated with obesity and metabolic dysfunction. This effect seems to be related to diet- and obesity-associated changes in gut microbiota composition and to increased translocation of immunogenic bacterial products, which activate innate and adaptive immunity in the gut and contributing to an increase in inflammatory tone. Innate immune receptors, like Toll-like receptors (TLRs), are known to be up-regulated in the tissue affected by most inflammatory disorders and activated by both specific microbial components and dietary lipids. This triggers several signaling transduction pathways (e.g. JNK and IKKβ/NF-κB), leading to inflammatory cytokine and chemokine (TNF-α, IL-1, MCP1) production and to inflammatory cell recruitment, causing insulin resistance. T-cell differentiation into effector inflammatory or regulatory T cells also depends on the type of TLR activated and on cytokine production, which in turn depends upon gut microbiota-diet interactions[26,27].

In a word, we may say that diet and nutrient load induced changes in the gut microbiota, which led to immune dysfunction, and then promote T2DM.

Blood Glucose and Immune

Hyperglucose is not only the result of diabetes, but also the cause of diabetes. High blood glucose play a critical role in the presentation, development and its progression of T2DM.Increased circulating glucose concentrations activate the NOD-like receptor P3 inflammasome while increased free fatty acid concentration activate TLR2 and TLR4, which leads to recruitment of macrophages and eventually

β-cell stress. Glucolipotoxicity-induced β-cell apoptosis could favour the autoantibody production, and activation of T cells reactive to β-cell antigens, culminating in further autoimmune destruction of β cells[28].Neutrophils serve as an active constituent of innate immunity and are endowed with distinct ability for producing neutrophil extracellular traps (NETs) to eliminate pathogens. Study has demonstrated a dysfunction of the innate immune system in diabetic subjects leading to increased susceptibility to infections. NETs are influenced by glucose homeostasis.IL-6 is a potent inducer of energy dependent NET formation. Hyperglycemia mimics a state of constitutively active pro-inflammatory condition in neutrophils leading to reduced response to external stimuli making diabetic subjects susceptible to infections[29].

Advanced glycation endproducts (AGEs) contribute to the development of vascular complications of diabetes and have been recently implicated in the pathogenesis of diabetes. AGEs are generated within foodstuffs upon food processing. It is increasingly recognised that the modern diet is replete with AGEs. AGEs are thought to stimulate chronic low-grade inflammation and promote oxidative stress and have been linked to the development of insulin resistance. Prebiotics which selectively stimulate the growth of beneficial bacteria in the human colon might offer protection against AGE-related pathology in people at risk of developing type 2 diabetes. AGEs and its receptor, RAGE, was involved in inducing chronic immune imbalance of diabetic patients. Such interaction attract immune cell into diffused glycated tissue and activate these cells to induce inflammatory damage, whereas disturb the normal immune rhythm in diabetic wound[30].

Obese Led to type 2 Diabetes through Immune Dysfunction

Adipose tissue lies at the crossroad of nutrition, metabolism and immunity. Adipose tissue inflammation was proposed as a central mechanism connecting obesity with its metabolic and vascular complications. Resident immune cells constitute the second largest adipose tissue cellular component after adipocytes and play important roles in maintaining adipose tissue homeostasis. Obesity induced changes in their number and activity result in activation of local and later systemic inflammatory response marking the transition from simple adiposity to diseases like type 2 diabetes mellitus, arterial hypertension

and ischemic heart disease[31].Interactions between metabolism and immunity play a pivotal role in the development of obesity-associated chronic co-morbidities. Obesity involves impairment of immune function affecting both the innate and adaptive immune system. This leads to increased risk of infections as well as chronic low-grade inflammation, which in turn causes metabolic dysfunction ,such as insulin resistance and chronic disease type-2 diabetes[32]. Metabolic inflammation may contribute to the pathogenesis of obesity and its comorbidities, including type 2 diabetes and cardiovascular disease. The actin-binding protein profilin-1 (pfn) plays a role in atherogenesis because pfn heterozygote mice (PfnHet) exhibited a significant reduction in atherosclerotic lesion burden and vascular inflammation. pfn haplo insufficiency protects against diet-induced IR and inflammation by modulating white adipose tissue immune homeostasis[33]

CD4+ T-lymphocytes in visceral adipose tissue (VAT) control insulin resistance in diet-induced obese (DIO) mice and humans. DIO VAT-associated T cells display biased TCR-Vα repertoires suggesting antigen-specific expansion. CD4+ T-lymphocyte control of glucose homeostasis is compromised in DIO when VAT accumulates pathogenic IFNγ-secreting Th1 cells, overwhelming static numbers of Th2 (CD4+GATA-3+) and regulatory Foxp3+ T cells. CD4+ T cell transfer into DIO, lymphocyte-free RAGnull mice reversed weight gain and insulin resistance predominately through Th2 cells. Brief systemic treatment with αCD3antibody or its F(ab′)2 fragment, restores the Th1/Foxp3+ balance and reverses insulin resistance for months, despite continuing high-fat diet. The progression of obesity-associated metabolic abnormalities is physiologically under CD4+ T cell control, with expansion of adipose tissueresident T cells that can be manipulated by immunotherapy[34].

Obese patients with insulin resistance displayed significantly decreased natural Tregs compared with lean control subjects. Treg depletion using an anti-CD25 monoclonal antibody enhanced insulin resistance as shown by increased fasting blood glucose levels as well as an impaired insulin sensitivity. Treg-depleted db/db mice developed increased signs of diabetic nephropathy, such as albuminuria and glomerular hyperfiltration. This was paralleled by a pro-inflammatory milieu in both murine visceral adipose tissue and the kidney. Conversely, adoptive transfer of CD4+FoxP3+ Tregs significantly improved insulin sensitivity and diabetic nephropathy. There was increased mRNA expression of FoxP3

as well as less abundant pro-inflammatory CD8+CD69+ T cells in visceral adipose tissue and kidneys of Treg-treated animals. This suggest a potential therapeutic value of Tregs to improve insulin resistance and end organ damage in type 2 diabetes by limiting the pro-inflammatory milieu[35,36].

Insulin and Immune Dysfunction

Type 2 diabetes, obesity, and metabolic syndrome are pathologies that insulin resistance plays a central role, and that affect a large population worldwide. T2DM is the result of insulin resistance combined with relatively reduced insulin secretion.These pathologies are usually associated with a dysregulation of insulin secretion leading to a chronic exposure of the tissues to high insulin levels and hyper-insulinemia, which diminishes the concentration of key downstream elements, causing insulin resistance.

Insulin plays an important role in the nutrient-induced insulin resistance. Chronic exposure to excess long-acting insulin can cause typical T2DM in normal mice fed on a chow diet. C57BL/6 mice treated with glargine once a day for 8 weeks showed that chronic exposure to glargine caused insulin resistance, hyper-insulinemia, and relative insulin deficiency (T2DM). Treatment with excess glargine led to loss of pancreatic islets, ectopic fat accumulation in liver, oxidative stress in liver and pancreas, and increased cholesterol content in mitochondria of liver and pancreas. Prolonged exposure of cultured primary hepatocytes and HIT-TI5 b-cells to insulin induced oxidative stress in a cholesterol synthesis-dependent manner[37, 38].

Zebrafish larvae appeared to be sensitive to human recombinant insulin, becoming insulin-resistant when exposed to a high dose of the insulin. RNA-seq-based transcriptomic profiling of these larvae revealed a strong downregulation of a number of immune-relevant genes as a consequence of the exposure to hyper-insulinemia.The negative immune modulator protein tyrosine phosphatase nonreceptor type 6 (ptpn6) appeared to be upregulated in insulin-resistant larvae. Knockdown of ptpn6 was found to counteract the down regulation of the immune system and insulin signaling pathway caused by hyper-insulinemia. These results indicate that ptpn6 is a mediator of the metabolic switch between insulin-sensitive and insulin-resistant states[39].

Study shows that Tregs express the insulin receptor, and that high levels of insulin impair the ability of Tregs to suppress inflammatory responses via effects on the AKT/mTOR signaling pathway. Insulin activated AKT signaling in Tregs, leading to inhibition of both IL-10 production and the ability of Tregs to suppress the production of TNF-α by macrophages in a contact-independent manner. Tregs from the visceral adipose tissue of hyperinsulinemic, obese mice showed a similar specific decrease in IL-10 production, as well as a parallel increase in production of IFN-γ. These data suggest that hyperinsulinemia may contribute to the development of obesity-associated inflammation via a previously unknown effect of insulin on the IL-10-mediated function of Tregs[40].

The data above suggests that insulin itself can led to immune dysfunction, which has negative effect on diabetes and that exogenous insulin is not the best choice of T2DM.

Immune System Change in type 2 Diabetes

More and more evidence points to a close crosstalk between metabolic organs and innate immunity in the course of metabolic disorders. Cellular and humoral factors of innate immunity are thought to contribute to metabolic dysregulation of the adipose tissue or the liver, as well as to dysfunction of the pancreas. All these conditions are linked to the development of insulin resistance and diabetes mellitus[41].Type 2 diabetes mellitus has been gradually considered as a micro- inflammatory disease. β-Cell failure is crucial for the onset and progression of human type 2 diabetes.Studies have suggested that inflammation may play a role. Immune cell infiltration has been reported in subpopulations of islets in some cases of human type 2 diabetes, and altered gene expression of a few cytokines and chemokines has been observed in isolated islets and laser captured β-cells from diabetic subjects. Modulating the autophagic processes could protect the β-cells from cytotoxicity induced by inflammatory mediators[42].

Patients with type 2 diabetes had higher WBC counts than control subjects along with a higher percentage of T cells and activated T helper (Th) and cytotoxic T (Tc) cells but lower proportions of natural killer (NK) cells. Parameters of glycemic control related positively to Treg cells in type 2 diabetes[43]. T cells have been demonstrated to exert central roles in the development of T2DM. Study shows that serum CRP, C3, IgA and plasma sIL-2 R were all significantly higher in T2DM than those in

healthy control (HC) .Compared with HC, the percentage of peripheral CD3(+)CD4(+)T cells and ratio of CD3(+)CD4(+)T cells to CD3(+)CD8(+)T cells in T2DM were both significantly increased .Tthe percentage of peripheral CD4(+)CD25(+)T cells, Teff cells increased .Treg cells strikingly decreased in T2DM. A positive correlation between sIL-2R levels and peripheral CD4(+)CD25(+)T cells or Teff cell percentages, as well as a negative correlation between plasma sIL-2 R levels and serum HDL, LDL or CHOL levels in T2DM were shown[44]. Th1/Th2/Th17/Treg paradigm skewed to Th1 and Th17 in T2DN patients. Urine albumin: creatinine ratio (UACR) was positively related to the proportions of Th1 and Th17 cells, as well as the ratio of Th17:Treg cells, and negatively related to the proportions of Treg cells. Furthermore, serum levels of IL-6, IL-17, IFN-γ, TNF-α, IL-2 and IL-10 were increased in T2DM patients, and positively related to UACR. These data indicate that the alteration of Th1/Th2/Th17/Treg paradigm exists in T2DN patients, which may contribute to the enhanced immune activation and inflammation, and subsequent development and progression of T2DM[45]. Foxp3(+) CD4(+) regulatory T (Treg) cells, recognized to be one of the most important defences of the human body against an inappropriate immune response.Adipose tissue derived Treg cells are distinct from their counterparts in lymphoid organs based on their transcriptional profile, T-cell receptor repertoire, and cytokine and chemokine receptor expression pattern. These cells are abundant in visceral adipose tissue of lean mice but their number is greatly reduced in insulin-resistant animal models of obesity[46].A research demonstrate that initiation but not effector function of autoreactive T cells was defective in NOD–B7-2–/– mice.Moreover, the residual proliferation of the autoreactive cells was effectively controlled by CD28-dependent CD4+CD25+ regulatory T cells, while depletion of Tregs partially restored proliferation of autoreactive T cells and resulted in diabetes in an adoptive-transfer model. Similarly, disruption of the CD28-B7 pathway and subsequent Treg deletion restored autoimmunity in NOD-CD40L–/– mice. These results demonstrate that development of diabetes is dependent on a balance of pathogenic and regulatory T cells that is controlled by costimulatory signals. Elimination of Tregs results in diabetes even in the absence of costimulation, which suggests a need for alternative strategies for immunotherapeutic approaches[47].Chronic inflammation and decreased frequency of regulatory T cells in visceral adipose tissue contribute to the propagation of insulin resistance to diabetes mellitus[48].Pancreatic beta cell failure

dictates the clinical onset of type 2 diabetes. Islet inflammation causes beta cell failure. IL-1 is central to this insult, impairing insulin secretion in preclinical and clinical studies. Islet-infiltrating macrophages are a major source of IL-1 and other cytokines in response to elevated levels of nutrients (glucose, saturated fatty acids), endocannabinoids and islet amyloid polypeptide. Immune cell subsets present in islets from individuals with type 2 diabetes. Increased numbers of CD45(+) leucocytes were found in these islets compared with islets from healthy controls, with an elevated proportion of CD20(+) B cells within the CD45(+) population. Absolute numbers of CD3(+) T cells and CD11b(+)CD11c(+) myeloid cells increased in islets from individuals with type 2 diabetes[49]. T2DM islets, especially those without first-phase insulin secretion, displayed higher CCL2 and TNFa expression than healthy islets. CD45(+) leucocytes were elevated in type 2 diabetic islets, to a greater extent in moderately functional type 2 diabetic islets compared with poorly functional ones, and corresponded with elevated ALOX12[8].

Study shows that the mechanism by which Intrauterine growth restriction leads to the development of T2D in adulthood is via transient recruitment of T-helper 2 (Th) lymphocytes and macrophages in fetal islets resulting in localized inflammation. Although this immune response is short-lived, it results in a permanent reduction in islet vascularity and impaired insulin secretion. Neutralizing interleukin-4 antibody therapy given only in the newborn period ameliorates inflammation and restores vascularity and β-cell function into adulthood, demonstrating a novel role for Th2 immune responses in the induction and progression of T2D. In the neonatal stage, inflammation and vascular changes are reversible and may define an important developmental window for therapeutic intervention to prevent adult-onset diabetes[50].

A cross-sectional study conducted in Peking University Aerospace Center Hospital showed that the percentage of circulating CD8+ T cells is associated with albuminuria in type 2 diabetes mellitus, which may support the rationality of systemic inhibition of T lymphocytes in treating albuminuria in these patients[51].

A central component of innate immunity is the complement system. Complement proteins are a component of innate immunity and kill non-self cells by perforating the plasma membrane, a reaction prevented by CD59. Human pancreatic islets express CD59 at very high levels. CD59 is primarily known

as a plasma membrane protein in membrane rafts, but most CD59 protein in pancreatic β cells is intracellular. Removing extracellular CD59 disrupts membrane rafts and moderately stimulates insulin secretion, whereas silencing intracellular CD59 markedly suppresses regulated secretion by exocytosis, as demonstrated by TIRF imaging. CD59 interacts with the exocytotic proteins VAMP2 and Syntaxin-1. CD59 expression is reduced by glucose and in rodent diabetes models but upregulated in human diabetic islets, potentially reflecting compensatory reactions. This unconventional action of CD59 broadens the established view of innate immunity in type 2 diabetes[52].C3 levels were longitudinally associated with higher homeostasis model assessment of IR. Changes in C3 were associated with changes in several measures of IR and may reflect progression of metabolic dysregulation, which eventually leads to abnormalities in glucose tolerance and T2DM[53].

Obesity is associated with chronic inflammation of various tissues ,which contributes to insulin resistance. B cells are important contributors to this process. Some B cells and the antibodies they produced can promote obesity associated and systemic inflammation, leading to insulin resistance[54]. The rate of lymphocyte apoptosis was significantly higher in type 2 diabetic patients than that in normal population. Mitochondrial apoptosis pathway may play a very important role in decreasing function of lymphocyte in diabetes[55].

Lymphocyte homeostasis in T2DM is associated with increased susceptibility to infections. Mitochondrial oxidative stress is implicated primarily in the immune pathophysiology of diabetes. An inverse correlation between mitochondrial DNA content in lymphocytes and hemoglobin A1 (HbA1c) levels were observed in both early diagnosed patients and patients with late complications[56]. Compared with controls, nuclear DNA damage response was higher in diabetic subjects with increased accumulation of phospho-ataxia-telangiectasia γ-H2AX, along with active recruitment of repair proteins (Mre11, Rad50, and Nbs1). A higher frequency of stable chromosomal anomalies with loss of telomere integrity was observed in cases with late complications. A significant decrease in enzyme activity of complex II, III, and IV of mitochondrial respiratory chain was evident in both diabetic groups in comparison with healthy controls. Activation in the cascade of nuclear factor kappa-beta (NF-κβ)-mediated feed-forward proinflammatory cytokine response was noted among T2DM subjects. Increased oxidative stress,

mitochondrial membrane depolarization, activation of caspase-3, and PARP observed in diabetic groups indicated bax triggered mitochondrial mediated cellular apoptosis. These results provide sugest lymphocyte mitochondrial dysfunction that might be helpful in explaining the clinical significance of immunologic perturbation observed in type 2 diabetic conditions.The increased cardiovascular risk in type 2 diabetes mellitus is the result of disorders of the immune system,including the enhanced reactivity of monocytes and impaired secretion of inflammatory cytokines.Monocytes and macrophages, as effector cells of innate immunity, not only participate in nearly all stages of development of atherosclerotic plaque, but also acquire a functional derangement in the diabetic milieu, which promotes atherosclerotic disease[57].

Therapy of type 2 Diabetes

The prevalence of T2DM is increasing worldwide and creating a significant burden on health systems, highlighting the need for the development of innovative therapeutic approaches.The therapy of T2DM nowadays includes prevention and early treatment of overweight and obesity, consuming a nutritious diet(including low-fat content, especially saturated fat, low sugar) , active lifestyle ,medicine for promote insulin secretion and insulin sensitivity, and many kinds of insulin. Much progress has been made in recent years towards finding ways to prevent the reduction of β-cell mass, preserve function of remaining β cells and develop approaches to regenerate them. But we still can not control T2DM as expected, especially its complications[58].While exogenous insulin therapy has dramatically improved the quality of life, chronic diabetic complications develop in a substantial proportion of subjects with diabetes and generally show a progressive worsening over time. Intensive insulin therapy has proven effective to delay and sometimes prevent the progression of complications such as nephropathy, neuropathy or retinopathy. However, it is difficult to achieve and maintain long term in most subjects, either for compliance issues or for the increased risk of severe hypoglycemic episodes, which is generally associated with intensification of exogenous insulin therapy. Some cases of T2DM patients who lost their ability to feel hypoglycemic prodromic symptoms such as sweating, tremor, tachycardia and anxiety.Since it is very challenging and potentially dangerous to treat these subjects with intensive

insulin therapy, transplantation of insulin-producing cells could be of assistance in restoring proper glucose regulation[39].

Insulin secretion from pancreatic β cells is integral to the regulation of blood glucose levels, and the loss of functional β cells is seminal in the development of both T1DM and T2DM. While T2DM results from a combined loss of β-cell mass and β-cell function, where the loss of β-cell mass could result from β-cell dysfunction[4].

Considering the fact that autoimmune reactions contribute to the pathogenesis of T2DM , which is likely a key factor in the development of insulin resistance and islet failure in T2DM ,anti-inflammatory and immunomodulatory therapeutic approaches may be beneficial in improving metabolic regulation in T2DM.Clinical data from phase 1/phase 2 study demonstrate that Stem Cell Educator therapy is a safe approach that produces lasting improvement in metabolic control for individuals with moderate or severe T2D who receive a single treatment. Stem Cell Educator therapy reverses immune dysfunctions through immune modulation on monocytes and balancing Th1/Th2/Th3 cytokine production.In addition, this approach does not appear to have the safety and ethical concerns associated with conventional stem cell-based approaches[59].Neutralizing interleukin-4 antibody therapy given only in the newborn period ameliorates inflammation and restores vascularity and β-cell function into adulthood, demonstrating a novel role for Th2 immune responses in the induction and progression of T2D. In the neonatal stage, inflammation and vascular changes are reversible and may define an important developmental window for therapeutic intervention to prevent adult-onset diabetes[60]. Some reports demonstrated the efficacy of regulatory T cell therapy in the prevention of diabetes. Systemic immunocompromise and Treg instability remain key safety concerns. Protective transfers of iTregs maintained IL-10 expression, expanded in vivo and controlled diabetes, despite losing FoxP3 expression. Following acute viral clearance, iTregs transferred early suppressed both CD4 and CD8 T cell responses, which resulted in the reversion of diabetes. The observation indicates that iTregs suppress local autoimmune processes while preserving the immunocompetent host's ability to combat acute viral infection[61]. Anti-CD3 treatment induced immediate reduction of blood glucose after administration. A single dose of anti-CD3 treatment corrected hyperglycemia in all nonobese diabetic mice with recently diagnosed diabetes. This

glucose-lowering effect was not attributable to major T cell produced cytokines. When tested in a normal strain of mice, the serum levels of C-peptide in anti-CD3 treated animals were significantly lower than control mice. Paradoxically, anti-CD3 treated animals were highly tolerant to exogenous glucose challenge. Anti-CD3 treatment significantly induced activation of T and B cells in vitro and in vivo. Further studies demonstrated that anti-CD3 treatment lowered the glucose levels in T cell culture media and increased the intracellular transportation of 2-(N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)amino)-2 deoxyglucose (2-NBDG) particularly in activated T and B cells. In addition, injection of anti-CD3 antibodies induced enhanced levels of Glut1 expression in spleen cells. T cell islet autoimmunity has been demonstrated to be common in patients with phenotypic T2DM and islet-specific T cells (T+) to be correlated positively with more severe beta cell dysfunction. Down-regulation of islet-specific T cell autoimmunity through anti-inflammatory can improve beta cell function in autoimmune phenotypic T2DM patients[62].Compared with control subjects, peripheral blood mononuclear cells (PBMC) from type 2 diabetes patients showed activated MAPK (P38, c-Jun NH2-terminal protein kinase and extracellular signal-regulated kinase) signaling pathway, elevated superoxide anion, increased pro-inflammatory cytokines (tumor necrosis factor-α, interleukin-1β, interleukin-6) and chemokines (CCL5/regulated on activation normal T-cell expressed and secreted and CXCL10/interferon-γ-induced protein 10). Glucagon-like peptide (GLP-1) receptor agonist, exendin-4 can attenuate these changes ,possibly through the suppression of p38 MAPK[63].GLP-1 analogue therapy reduced levels of the inflammatory macrophage activation molecule sCD163 .This occurred independent of changes in body weight, fructosamine and HbA1c. GLP-1 analogue therapy was associated with a decrease in levels of the inflammatory cytokines TNF-α , IL-1β and IL-6 and an increase in levels of the anti-inflammatory adipokine adiponectin. Dipeptidyl peptidase (DPP) inhibitors and GLP-1 analogues alter the inflammatory profile and reduce inflammatory cytokine secretion, while improving glucose metabolism. The DPP-4 inhibitor sitagliplin reduces autoimmunity by decreasing the homing of CD4+ cells into pancreatic β cells in NOD mice and helps preserve islet cell mass.The clinical efficacy of peroxisome proliferator-activated receptor gamma (PPAR-g) agonists in cell-mediated autoimmune diseases results from downregulation of inflammatory cytokines and autoimmune effector cells[64].

CONCLUTION AND FUTURE PROSPECTS

The therapy of T2DM nowadays can not control the development and progression of T2DM and its complications as we expected,highlighting the need for the development of innovative therapeutic approaches.Virus infection, diet and nutrient load, hyperglucose and obese can led to diabetes through disturbance of immune system.Immune dysfunction play a critical roll in the presentation, development and finally its progression of T2DM.We should not pay attention only on how to reduce blood glucose. Reducing blood glucose should not be the last aim of T2DM therapy, but one of the basic ways for T2DM.On the contrary,we must care much about the immune system. The immune dysfunction is the most critical factor for the presentation, development and its progression of T2DM.How to prevent the islet β-cells from damage and protect its function depend on adjusting the function of immune system.In the same way, maybe we can delete the insulin resistence. Simple therapeutic strategies targeted at attenuating the progression of chronic low-grade inflammation and immune dysfunction are urgently required to prevent or slow the development and progression of type 2 diabetes.

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