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Polyvaccine: joining the links in the cascade of type 1 diabetes

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The incidence of type 1 diabetes mellitus (T1DM), an autoimmune disorder, has ascended considerably with around 98,200 and 15,900 incidents in children below 15 years of age, globally and in India, respectively. This is typically due to environmental changes leading to genetic modifications. Also, T1DM encompasses the presence of autoantigens and many other etiologies which can be targeted by proper immunization. In this paper, we consciously discuss and collate various candidate triggers of islet autoimmunity and other factors expected to promote progression of T1DM. This paper bridges all the mechanisms caused by these factors and linking them with each other. We have also highlighted on the novel corona virus as a trigger for T1DM. Finally, we suggest that an amalgamated model of polyvaccine can batter the condition by inducing protection against various triggers of T1DM.

Keywords: Type 1 diabetes mellitus, Viruses, Coronavirus, Cow's milk, Hybrid insulin peptides, Vaccines

Introduction

Diabetes mellitus is caused either by insulin deficiency or insulin resistance, and sometimes a combination of both. Insulin deficiency may be caused due to pancreatitis, pancreatectomy, alcoholic chronic pancreatitis, cystic fibrosis, hemochromatosis, mitochondrial DNA mutations, leprechaunism, lipoatrophy, autoimmune diseases, glucagonoma, acromegaly, pheochromocytoma, thyroid disease, Cushing's syndrome, and/or by drugs and toxins. This is the cause for type 1 diabetes mellitus (T1DM) which by nature may be autoimmune or idiopathic. The combination of insulin deficiency and insulin resistance may cause type 2 diabetes mellitus (T2DM) or gestational diabetes. In contrast to T2DM, T1DM shows acute presentation with prediabetes as the phase before its onset which provides a window for early intervention [1].

Globally, a total of 600,900 children and adolescents below 15 years of age are estimated to suffer from T1DM and 98,200 children and adolescents of the same age group are diagnosed with T1DM every year. Among these, India witnesses 95,000 children and adolescents below 15 years with T1DM, with an incidence of 15,900. The complications caused due to T1DM, affects the quality of life in patients and even after a proper diagnosis it may cause mortalities in the countries with insufficient health service provisions [2]. The expenses for the medical treatment of T1DM are high [3]. In this

paper, we converse about the aspirant triggers of islet autoimmunity and the factors thought to encourage progression to explicit T1DM. The specific cause of T1DM is unidentified [4] but we have reviewed data for predictive environmental factors that are not yet confirmed to cause T1DM.

Genetic factors

The human leukocyte antigen (HLA) class II DRB1-DQA1-DQB1 genotypes are broadly documented as the robust genetic risk factors for T1DM; however, more than a few other genes also contribute its risk [5] which are grouped into the categories of insulin expression, immune function, and β cell function [6]. In addition to HLA class II alleles, HLA class I alleles are associated with T1DM [7].

Extracellular matrix (ECM) plays a significant role in T1DM. There are anomalies in ECM in the extended vascular ductal pole adjacent the actual islet. The vascular-ductal pole is also involved in generation of islets during the phase of fetal development phase and also during postnatal periods. Myeloid cells which accumulate in insulitis causes damage of EMC. Macrophages and myeloid cells are involved in the development of normal islets [8]. Hence, the abnormalities in ECM causes abnormal islets which further leads to T1DM.

Viral infections and toxins

T1DM is associated with coxsackievirus B [9], enteroviruses, mumps, rubella, and cytomegalovirus [4,10]. Along with these viruses, the current pandemic is also assumed to be involved in the development of T1DM. A letter published in the New England Journal of Medicine advocates coronavirus disease 2019 (COVID-19) as the prospect for the onset of T1DM. COVID-19 and T1DM show a bidirectional relationship as diabetic patients are at an increased risk of COVID-19 infection and vice-versa. The scientists mentioned that due to the virus, the body's immune system may destroy beta cells, and hence leading to T1DM [11]. This relationship between these viruses and T1DM have created a new opportunity to prevent T1DM due to viral infections and hence decreasing the associated risk of complications and fatality.

Environmental factors

Studies have shown the increasing incidence of T1DM in countries with oceanic climates and with lower sunshine durations [12]. Also, the population with low-pigment skin type are at a higher risk for T1DM [13,14].

Nutrition and dietary factors

Nutritional and dietary factors also play a role in T1DM. These factors include undissolved gluten, lack of breastfeeding, early introduction of cow's milk, foods and water containing nitrates, nitrites or nitrosamines [4], and lack of vitamin D [8].

Due to albumin, cow's milk promotes autoimmunity of islet cells because of the cross-reactivity between the surface protein (ICA-1) β-cell and serum antibodies to albumin [8]. Wheat proteins, specifically gluten, have also been associated with T1DM. Similar to cow's milk proteins, immune reaction against wheat proteins in T1DM could be the general result of an abnormal mucosal response rather than the specific driver of islet autoimmunity [8]. Studies have shown a reverse correlation between T1DM and the contact with the sunshine. The plasma from T1DM patients showed low levels of vitamin D metabolite. Also, a study in mice and humans has shown reduced incidence of T1DM with increased intake of vitamin D. Hence, it can be reasonably proposed that vitamin D deficiency in early childhood may lead to T1DM development [8].

Autoantigens and autoantibodies

Several autoantibodies have been recognized in T1DM patients, which includes, 65 kDa form of glutamic acid decarboxylase, insulin autoantibodies, insulinoma antigen 2, and zinc transporter 8 [4]. The CD4+ T cells are involved in the pathogenesis of T1DM and respond to the self-peptides, chromogranin A [15] and islet amyloid polypeptide [16]. A study showed that diabetes inducing CD4 T cell clones which were isolated from non-obese diabetic mice recognized the epitopes formed by covalent cross-linking of proinsulin peptides to the other peptides present in β cell secretory granules. These hybrid insulin peptides (HIPs) exhibit to be antigenic for CD4T cells. The CD4 T cells from the pancreatic islets of two organ donors with T1DM also recognized HIPs [17].

Theoretical Co-relation of Etiological Cascade to Control T1DM

Various etiological factors, as described in the previous section, are defined individually in preclinical and clinical studies. But there is a disconnect between these factors and also there is lack of bridging these mechanisms. Hence, in the paper, we have tried to co-relate the mechanism of pathogenesis and the hypothetical mechanism of T1DM linking all the etiologies. Fig. 1 explains the cascade links the various etiological factors causing T1DM and the hypothetical mecha-

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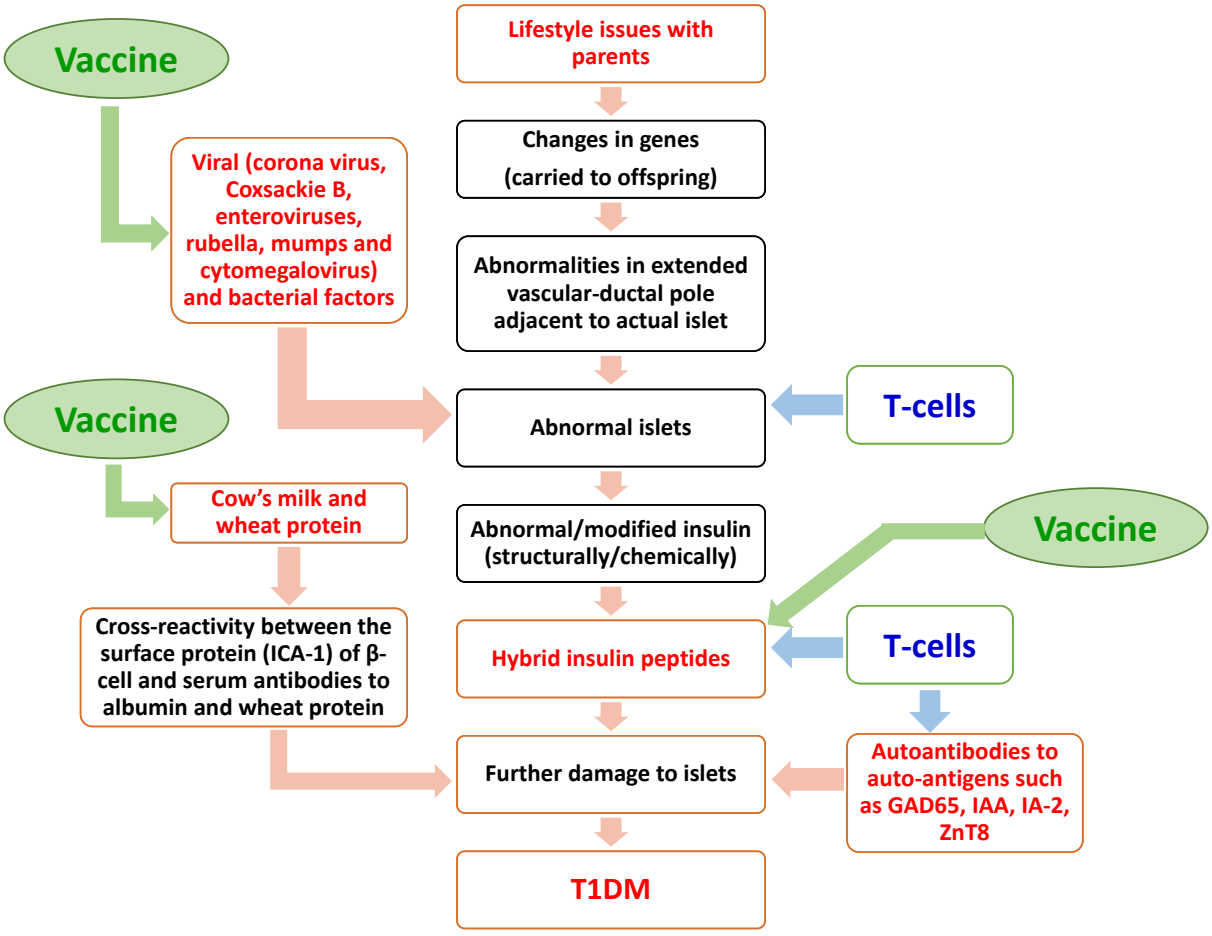

Fig. 1. Etiological cascade for type 1 diabetes mellitus (T1DM) and targets for vaccines. This cascade links the various etiological factors causing T1DM and the hypothetical mechanism behind the occurrence of T1DM due to these factors. The words in red represents the causative factors, black text represents the intermediate mechanisms, blue words represent the T cells which attack at various targets in the mechanism of causing T1DM, and green words represent the hypothesized vaccines which may be tested at various targets. GAD65, 65 kDa form of glutamic acid decarboxylase; IAA, insulin autoantibodies; IA-2, insulinoma antigen 2; ZnT8, zinc transporter 8.

nism behind the occurrence of T1DM due to these factors along with the targets which can be battered by the vaccines.

Hitting the Targets

Prevention of T1DM will be more achievable if modifiable frontiers are clearly understood and the cascade is well connected. If we transparently understand the etiology, intervention at those points might be further feasible to eradicate T1DM. The invention of vaccines has led to one of the greatest advancements in the history of managing various diseases. As T1DM is an autoimmune disease with various trigger targets, we can control it by the virtue of vaccination. Connecting different pointers in this cascade will help in better understanding of the whole process of causing T1DM, and hence, we can target various pointers at different stages.

Prenatal and perinatal care

We assume that there are a few factors involving parental habits which may cause genetic modifications over time and these modifications are carried to the next generations. This may lead to abnormal insulin or formation of HIPs causing T1DM. Hence, refraining from such habits can prevent T1DM in the next generations.

Target vaccines

If viral infection is one of the pathways, then vaccination against viruses might confer benefit. But in addition to these vaccines, other vaccines are also essential because of the evidence of other etiological trigger antigens.

Anti-viral vaccines

As T1DM is expected to be caused by corona virus, coxsackievirus B, enteroviruses, mumps, rubella, and cytomegalovirus [4,9-11], vaccinating the potential candidates with these vaccines may prevent the development of T1DM. The antiviral vaccines are assumed to educate the immune system and prevent the onset of T1DM due to these viruses.

Bovine serum albumin vaccine

Bovine serum albumin is a serum albumin protein which is derived from cow's milk. Consumption of cow's milk promote the cross-reactivity between the surface protein (ICA-1) β-cell and serum antibodies to albumin. This leads to destruction of β-cell and finally causes T1DM. Thus, we can hypothesize that introducing a milder form of this protein in the form of vaccine can modulate the immune responses which is expected to occur later due to albumin from cow's milk.

Vaccines to autoantigens including hybrid insulin peptides

Similar to bovine serum albumin vaccine, the candidates at the risk of T1DM can be vaccinated with milder forms of the autoantigens after recognizing the causative targets.

How Would a Polyvaccine Work?

A single target vaccine may help to control individual factor. But there are various targets identified for T1DM. Hence, combining all possible vaccines against targets mentioned above, along with modern devices of advanced therapies, would lessen the heavy burden associated with T1DM. These vaccines can be tested in animal models as per the guidelines for vaccine development. This approach can definitely bring an end to T1DM.

Conclusion

T1DM is an autoimmune disease where many distinguished factors contribute to its initiation and worsening. The worldwide upsurge in the incidence and prevalence of T1DM with no permanent remedy necessitates the identification of the etiological factors and develop approaches for preventing it. Many etiological targets are identified and hence now it is assumed that immunization against some viruses and bacteria may prevent it. Also, there is a possibility to control T1DM with the development of vaccine against various other targets, such as bovine serum albumin, and autoantigens. Modulation of the immune system and vaccination against T1DM autoantigens can be of great help to reduce its incidence and eventually to eradicate it successfully. A combination of vaccines against all possible targets, after performing preclinical and clinical studies, can diminish the heavy burden of T1DM and can definitely bring an end to it.

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