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Editorial

Attempting Getting Insulin Independent Immunotherapies in Type 1 Diabetes Mellitus (T1D) in the Pre Stage 1 (Before Islet Autoantibodies)

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Type 1 diabetes mellitus (T1D) represents roughly 5 - 10% of all diabetic patients. Prevalence of this pathology points that > 500,000 children suffer from T1D globally, that are located mostly in North America as well as Europe [1]. But the epidemiology points that the incidence of T1D has escalated rapidly in recent years [2]. In 2017, the International Diabetes Federation (IDF) declared 132,600 newly diagnosed T1D cases all over the world. It is predicted that incidence of T1D in ≤ 5yr age will increase 2 fold in less than 20yrs [3]. But a total preservation of β cells mass along with insulin independency is not getting achieved despite massive exploration. Due to that right now no existing targeted immunotherapies are incapable of replacing the standard insulin delivery [4], it is important to understand pathophysiology of T1D deeply to be able to prevent development of T1D. Type 1 diabetes mellitus (T1D) forms via elimination of the immune system against theβ-cell antigen along with provocation of proinflammatory responses. Following presentation of beta-cell antigens to the immune system via antigen presenting cells (APC), chronic immunological responses start secondary to improper control of immunological reactions that result in the β-cell destruction. β-cell death through virus directed/physiological modes stimulates liberation of antigens as well as onset of immune responses against other β-cells. Mostly dendritic cells (DC's) take up these Antigens, presenting them to T-cells. Possibility of any autoimmune process can be there only if autoreactive T-cells have escaped thymic negative selection. Autoreactive T-cells, that get activated via DC's stimulate Autoreactive T as well as B-cells. Ultimately effector mechanisms of the β-cell destruction need the collective action of DC's, macrophages, T as well as B cells and natural killer (NK) cells [5]. Of the environmental factors decrease in gut microbiota (GM), obesity, early fruit introduction or cow milk in childhood, gluten, toxins, absence of vitamins as well as viruses [6-8]. Moreover, pancreas take part in etiopathogenesis of T1D (Figure 1-upper right t quadrant have lymph nodes as well as associated mechanisms). Immune cell confrontation with GM occurs early in childhood, that activates immunocontrolling modes that control autoimmune reactions-a phenomenon called ''hygiene-hypothesis''. Toll like receptor 4 (TLR4), stimulating lipopolysaccharides (LPS), as well as other bacterial products which have contact with immune system are documented as suppressors of immunity [9]. Thus, decrease in GM loss of control of immune system followed by immune cell actions against cells of self, ultimately T1D [10]. Correlation of early fruit introduction relates to increase in autoimmunity to β-cells. Possibly abnormal immune response to solid food antigens in immature gut immune system in children that possess HLA susceptibility to DM. Moreover, overload hypothesis points that environmental food exposures might over stimulate β-cell increased autoimmune mediated damage. Similarly, increased amounts of bovine milk products increased risk of autoimmunity in children that possess HLA susceptibility. This might be due to insulin autoantibody, in view of cross reactivity between bovine as well as human insulin [6]. Gluten foods (cereals) in children < 3yrs significant increase in islet autoantibody synthesis. DM patients with HLA-DR allele have increased T-cell reactivity to gluten derived polypeptides. This is secondary to interferon ɣ (IFNɣ) as well as IL-17 liberation. Intestinal inflammation as well as T-cell activation induced by gluten β-cell autoimmunity [11]. Vit D can modify T as well as B-cells function. VDR agonists Treg cell induction. By stimulation of tolerance [12] as well as stop differentiation as well as maturation of DC's, downregulate expression of costimulatory molecules like CD40, CD80 and CD 86 and decrease IL-10 production, Viruses might T1D by 2 modes i) a direct cytolytic action on β-cells (like dsRNA virus-figure 1) or ii) Indirect triggering of a DM-related autoimmune process against β-cells that β-cells destruction. This is due to structural similarity of some viral structures as well as β-cells antigen. Persistent virus infection may cause β-cell autoimmunity. Enterovirus, rotavirus, cytomegalovirus (CMV), mumps, rubella virus, retrovirus etc [13]. 60 Genes identified by gene wide association system (GWAS). Genetic factors-HLA and non-HLA. Genetic factors of genomic locus of HLA-50% of genetic risk of T1D-Most correlations with HLA-class II genes, that get expressed in APC's like DC, macrophages &thymus epithelium. In thymus epithelium they cause presentation of self-antigen that cause self-tolerance. Inefficient HLA-class alleles in interacting and presenting insulin in thymic epithelium are relatively related to T1D [14]. This may insulin negative T cells to escape negative

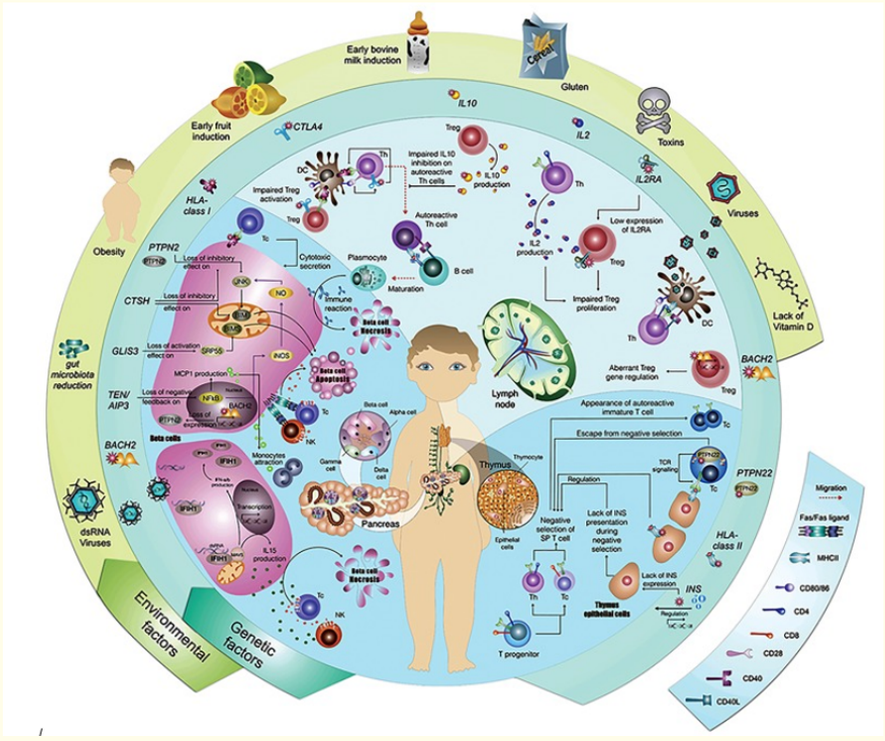

Figure 1: Courtesy ref no- 23-Genetic, immunologic, and environmental etiologies of type 1 diabetes mellitus (T1DM). The outer circle shows some of the most important environmental etiologies of T1DM and the inner circle presents some of the most important genetic etiologies. The central circle demonstrates each genetic or environmental factor's known mechanisms of action. The left lower part of the circle shows the dsRNA virus, TEN/AIPS, GLIS3, CTSH, PTPN2 and HLA class 1 mechanism of action at the cellular level in the pancreas microenvironment, which leads to either necrosis or apoptosis of islet beta-cells. The upper part of the circle shows CTLA4, IL10, IL2, IL2RA, BACH2, and viral mechanisms of action in the lymph node. The right lower part of the circle shows PTPN22, HLA class2, and insulin mechanisms of actions which take place in the thymus.

AIP3: Actin Interacting Protein 3; CTLA4: Cytotoxic T-Lymphocyte Associated Protein 4; CTSH: Cathepsin H; GLIS3: GLIS Family Zinc Finger 3; HLA: Human Leukocyte Antigen; IFIH1: Interferon Induced with Helicase C Domain 1; IL: Interleukin; IL2RA: Interleukin 2 Receptor Subunit Alpha; INS: Insulin; JNK: c-Jun N-Terminal Kinase; MAVS: Mitochondrial Antiviral-Signaling; PTPN2: Protein Tyrosine Phosphatase Non-Receptor Type 2; PTPN22: Protein Tyrosine Phosphatase Non-Receptor Type 22; BACH2: BTB Domain and CNC Homolog 2; Tc: Cytotoxic T Cell; Th: Helper T Cell; NK: Natural Killer Cell; Treg: Regulatory T Cell; DC: Dendritic Cell; SP T cell: Single Positive T Cell; TCR: T Cell Receptor; NF-.B: Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells.

selection. Absence of insulin expression in thymus might hamper negative selection. Polymorphisms of in protein tyrosine phosphatase non-receptor22 (PTPN22) gene encodes lymphocyte specific tyrosine phosphatase (LYK) might alter immune self-tolerance. LYP-negative controller of T-cell receptor (TCR) signaling hyperactive LYP encoded via PTPN22-risk variant-can inhibit TCR signaling in negative selection. Polymorphisms of cytotoxic lymphocyte associated protein 4 gene (CTLA4) related to T1D. CTLA4-has immunoregulatory role in effector T cells by suppression of T cells response [15]. CTLA4-key for regressive function of Treg in mice-CTLA4 dampens immune response via both effector and Treg. BTB and CNC homology 1 gene (BACH2) expresses transcription factor that controls Treg action. T1D risk related variant of BACH2 abnormal Treg can stimulate autoimmunity-secondary to improper control on inflammatory responses [16]. Various IL and ILR genes like IL10, IL12 and IL2RA (codes-α subunit of IL2R) are genetic risk factors for T1D. Polymorphisms of interferon induced with the helicase C domain 1 gene (IF1H1) might explain interaction bet genetic and environmental factors of T1D. IF1H1-evokes immune response against RNA viruses. IF1H1 variants-decreased expression –protective against T1D [17]. Immune β-cell destruction mediated by extrinsic apoptotic pathway involves FAS mediated T cell interaction and proinflammatory cytokines like IL-1β and IFNγ [18]. BACH2 also inhibits BIM activation and JNK1 phosphorylation via β-cell response to proapoptotic signals. It cross talks with PTPN22 an inhibitor of proapoptotic protein JNK1 [19]. This pathway targeted by other T1D genes like CTSH and GLIS3 [20]. TN-

FAIP3 another T1D gene gives negative feedback loop for proapoptotic action of NFκB [21]. Hence efforts are further being made to deeply explore in this though some partial positive effects obtained by earlier studies [22], use of formula of Orban., *et al.* [22] T1DM metabolic recovery index (DMMRI) using 3 studies using studies on abatacept, rituximab and glutamic acid decarboxylase (GAD) vaccine (since these 3 studies they used C peptide, and Hb A1c and decrease in insulin and placebo controlled trial [1]). Thus, sustenance or enhancement of the positive index (DMMRI > 5) maximum seen in abatacept, rituximab, while in GAD vaccine DMMRI < 5 observed. Further studies using controls needed to ultimately achieve the final immunotherapy that we get insulin independent

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