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PD1 gene polymorphisms in pediatric autoimmune disease

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Abstract:Background: Programmed cell death protein 1, also known as PD-1 or CD279 is a protein expressed on T cells and pro-B cells. It is a cell surface receptor that belongs to the immunoglobulin superfamily. PD-1 is known to be the major inhibitory receptor that functions as an immune checkpoint, playing an important role in down regulating the immune system. Autoimmunity is an odd reaction of immune system to human antigens (autoantigens). The triggers leading to recognition of own determinants, receptors, surface molecular cellular antigens as 'foreign', followed by activation of T and B lymphocytes, are unknown. The genetic background seems to play a limited role. This autoimmune process include tissue infiltration with immunocompetent cells, overproduction of pro-inflammatory cytokines, and production of autoantibodies by plasmocytes. The increased prevalence of diabetes mellitus is considered one of the greatest public health diseases nowadays. Type 1 diabetes mellitus (T1DM), a polygenic autoimmune disease, is resulted from both genetic and environmental factors.

Keywords:*PD1 gene polymorphisms, pediatric autoimmune disease*

Introduction

Programmed cell death protein 1, also known as PD-1 or CD279 is a protein expressed on T cells and pro-B cells. It is a cell surface receptor that belongs to the immunoglobulin superfamily. PD-1 is known to be the major inhibitory receptor that functions as an immune checkpoint, playing an important role in down regulating the immune system**(Grywalska*et al.*, 2018)** .

Programmed cell death protein 1 is a 55-kDa transmembrane protein containing 288 amino acids with an extracellular N-terminal domain (IgV-Like) **Figure (1).** PD1 protein that belongs to CD28 family is encoded by PDCD1 gene located in chromosome 2q37 **(Guan *et al.*, 2017)**.

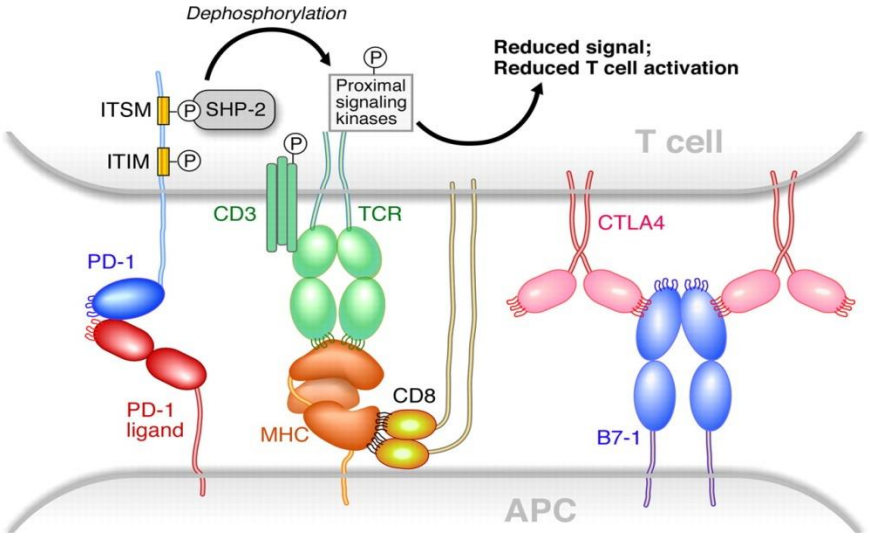

Figure (1): structure of PD1 with its ligands **(Freeman, 2008)**.

Programmed cell death protein 1 has 2 major ligands: PD-L1/CD274 (encoded by PDCD1LG1 in chromosome 9) and PD-L2/CD273 (encoded by PDCD1LG2 in chromosome 9). Binding of PD-1 to either PD-L1 or PD-L2 results in the activation of inhibitory kinases involved in T-cell proliferation, adhesion, and cytokine production/secretion via phosphatase SHP2. PD-1/PD-L interaction has been shown to play an important role in limiting the initial response of T cells upon antigen exposure and inducing T cell tolerance **(Pardoll, 2012)**.

Transcription factors such as nuclear factor of activated T cells (NFAT), NOTCH, Forkhead box protein (FOX) O1 and interferon (IFN) regulatory factor 9 (IRF9) may trigger the transcription of PD-1 **(Staron *et al.*, 2014)**.

Programmed cell death protein 1 is an inhibitor of both adaptive and innate immune responses, **(Ahmadzadeh *et al.*, 2009)**. PD-L1 is usually expressed by macrophages, some activated T cells and B cells, dendritic cells as well as some non–immune cell types, such as vascular endothelial cells, pancreatic cells and some epithelial cells, particularly under inflammatory conditions. In addition, PD-L1 is expressed by tumor cells as an "adaptive immune mechanism" to escape anti-tumor responses **(Ohaegbulam*et al.*, 2015)**. There are differences between PD-L1 and PD-L2; PD-L2 is largely limited to antigen-presenting cells, such as macrophages and dendritic cells **(Guan *et al.*, 2017).**

Programmed cell death protein 1 plays two opposing roles, as it can be both beneficial and harmful. As regards to its beneficial effects, it plays a key role in the regulation of ineffective or harmful immune responses and maintaining immune tolerance. However, PD-1 causes the dilation of malignant cells by interfering with the protective immune response **(Salmaninejad*et al.*, 2018)**.

Pediatric autoimmune diseases

Autoimmunity is an odd reaction of immune system to human antigens (autoantigens). The triggers leading to recognition of own determinants, receptors, surface molecular cellular antigens as 'foreign', followed by activation of T and B lymphocytes, are unknown. The genetic background seems to play a limited role. This autoimmune process include tissue infiltration with immunocompetent cells, overproduction of pro-inflammatory cytokines, and production of autoantibodies by plasmocytes *(Pituch-Noworolska Aet al .,2017)*

As well as increased susceptibility to infections, autoimmune and inflammatory manifestations also eventuate due to dysregulation of immune system in a substantial proportion of patients with primary immunodeficiency (PID). Autoimmune and inflammatory manifestations can occur prior or after diagnosis of PID*(M. Yildirim Kaplan et al .,2020)*

PD1 gene polymorphisms in different autoimmune diseases in children

Type1 diabetes mellitus (T1DM)

The increased prevalence of diabetes mellitus is considered one of the greatest public health diseases nowadays. Type 1 diabetes mellitus (T1DM), a polygenic autoimmune disease,
is resulted from both genetic and environmental factors *(J. Tian* ***et al.,2017)***. Although T1DM has a lower prevalence compared with type 2 diabetes mellitus (T2DM), it is the most common form of diabetes in childhood and has a greater impact on the quality of living life. Programmed cell death 1 (PD-1) is an immunoinhibitory factor belonging to the CD28/B7 family. It plays a vital role in regulating T cell activation and maintaining peripheral tolerance as a core costimulatory molecule *(R. Fujisawa* ***et al.,2015)*** . Recently, PD-1 has been widely studied as an immune checkpoint that is applied to the treatment of numerous advanced cancers *(E. Nolan* ***et al.,2017)*** . Programmed death ligand-1 (PD-L1) has been shown to be overexpressed in many cancers, including gastric cancer *(C. Wu* ***et al.,2006)*** , esophageal cancer, pancreatic cancer, and other human gastrointestinal tumors*(W. Zou* ***et al.,2006)*** . Accumulated studies showed that blockage of the interaction between PD-1 and PD-L1 can help with better prognosis in various malignant tumors *(Q. Li* ***et al****.,2017)* . However, autoimmune diabetes has been reported after receiving anti-PD-1 therapy for tumor in both mouse models and human cases *(J. Hughes* ***et al****.,2015)*. Increasing studies had been committed to the association with PD-1/PD-L1 and autoimmune disease, including systemic lupus erythematosus, ankylosing spondylitis, allergic bronchial asthma, and autoimmune diabetes . Studies had shown that low PD-1 might increase T cell proliferation and activation which lead to the destruction of beta cells, providing a possible mechanism for T1DM. PD-L1 recently had been found expressed in the islets of people with type 1 diabetes *(M. L. Colli* ***et al****.,2018)*, and we also found that PD-L1 was significantly reduced in the serum of T1DM patients***(C. Pizarro et al****.,2014)*. Since single nucleotide polymorphisms (SNPs) play vital roles in the transcription and translation of genes and have associations with the occurrence and development of diseases, studies had been devoted to the associations between gene polymorphismswith T1DM susceptibility.

Inflammatory bowel disease

Inflammatory bowel disease (IBD) is inflammation of the colon and small intestine. Chronic autoimmune situations typically affect the gastrointestinal tract and colon leading to Crohn's disease (CD) and ulcerative colitis (UC), respectively ***(E.V. Loftus Jret al****.,2004)*. Major symptoms of both types of IBD include mucosal inflammation, abdominal pain, diarrhea, and weight loss. Aberrant and dysregulated immune response toward commensal bacteria of gut may elicit chronic inflammation of the intestinal mucosa. In normal conditions, microbial microenvironment of the intestine is rigidly controlled alongside with meticulous immune response, resulting in tolerance towards intestinal flora as well as undesirable responses and also protection against invasive pathogen***s*** *(J.A. Katz* ***et al****.,2007).*

Intestinal epithelial cells from IBD patients were realized to express PD-L1 in higher amount relative to healthy subjects, implying to an potentially important role of PD-1:PD-L1 interaction
to establish mucosal tolerance in the gut*(Nakazawa* ***et al****.,2004)*. The PD-1 expressing non-colitogenic T cells obtained from spleens of naive mice are potentially capable of recognition of PD-L1, culminating in the generation of a subpopulation of Tregs. In CD4+ CD45RBhigh effector T cells received mice with severe combined immunodeficiency(SCID), the colitis was suppressed when CD4+CD25_PD-1+ T cells were transferred to mice *(T. Totsuka et al.,2005)* .

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is known as a systemic autoimmune disease characterized by the production of an autoantibodies. T cells are found to be abnormal based on their alterations in the phenotype, receptor and signaling physiology, gene transcription, and perturbed suppressor activities of regulatory lymphocytes in SLE. It seems that aberrant function of T cells may result in dysregulated B cell activity and antibody production *[H. Moutsopoulos et al ., 1994]*. In an in vitro experiment, cross-linking of PD-1 with soluble PDL1 (sPD-L1) demonstrated a suppressive role in proliferation of normal T cells and cytokine production . However, adding serum from patients with active lupus significantly diminished the suppression

of T cell proliferation. It seemed that the serum from lupus patients might contain high levels of inflammatory cytokines, immune complexes consist of self DNA with autoantibodies, and soluble costimulators, and that the inflammatory environment might dominate the suppressive effect of sPD-L1 in vitro *[G.K. Bertsias et al., 2009]*. Nonetheless, another report by Her et al. does not show a suppressive role for sPD-L1 in SLE activity. Even though the sPD-L1 was detectable in the plasma from SLE patients, there
was an insignificant difference in sPD-L1 plasma levels between active and inactive SLE patients *[M. Her et al., 2009].*
The decreased expression of PD-1, PD-L, or both seems to causes disturbance of immune tolerance in SLE *[N. Mozaffarian et ai .,2008].* the level of PD-1 expression on the CD25high Tregs was significantly reduced in SLE patients in comparison to healthy individuals *[H. Kristjansdottir et al., 2010].*

Autoimmune hepatitis

autoimmune hepatitis (AIH) develop worldwide in children and adults of both sexes in various ethnic groups.clinical manifestations ranging from asymptomatic mild chronic hepatitis to fulminant hepatic failure. Developing towards cirrhosis and end-stage liver disease may occur in 10–20% of the cases *[E.L. Krawitt et al.,2006].*Naturally CD4+CD25+ Tregs are vital in maintaining immunologic self-tolerance and regulation of pathologic immune responses *[S. Sakaguchi et al.,2004].* The concurrent loss of Tregs and PD-1-mediated signaling can induce the development of fatal AIH. Autoreactive CD4+ T cells are essential for induction of AIH, whereas CD8+ T cells play an important role in progression toward fatal hepatic damage *[M. Kido et al.,2008].* On the other side, ligation of PD-1 on T cells with both B7-H1 and B7-DC on kupffer cells and liver sinusoidal endothelial cells (LSEC) might lead to suppression of autoreactive lymphocytes and, therefore, regulation of AIH pathogenesis *[T. Oikawa et al., 2007].* Moreover, PDL1 expression on hepatocytes has been depicted to induce apoptosis in T cells *[M. Mühlbauer et al .,2006]*. Additionally, it has been shown that serum anti-PD-1 antibody, which reflects the clinical features of type 1 AIH, is useful for the diagnosis of type 1 AIH as an auxiliary diagnostic marker *[Y. Miyake et al.,2014].* In the human liver, PD-L1 has expressed on LSEC, kupffer cells, hepatocytes and stellate cells. Accordingly, impaired PD-1/PD-L1 pathway might be associated with hepatic immune modulation *[C.-L. Chen et al.,2016]*.Both nonparenchymal liver cells and hepatocytes constitutively express PD-L1 in low levels. Activated T cells and viral infection can significantly stimulate the PD-L1expression on hepatocytes.Interaction between hepatocytes and PD-L1 expressing lymphocytes in hepatocytes may characterize the unique immunological properties of the liver *[M. Mühlbauer et al .,2006]*. PD-L1 and PD-L2 expressions have been correlated with the level of IFN-c *[N. Mataki et al.,2007]*. Therefore, modulation of PD-1/PD-L1 and PD-L2 systems may be involved in development of autoimmune liver diseases. The PD-1/PD-L1 interaction pathway has been demonstrated to be contributing factor for CD8+ T cell exhaustion in viral infection including LCMV, HCV, HBV and HIV *[M.E. Keir et al.,2008].*

Therapeutic value of PD1

Immunotherapy is becoming the fourth pillar in cancer treatment next to surgery, chemotherapy and radiotherapy. Its aim is to activate a tumor-specific cytotoxic T lymphocyte (CTL) response that eradicates all tumor mass, regardless of metastatic spread. CTL responses generally are polyclonal, harboring T cells with different antigenic specificities. Therefore, immunotherapy can be effective against genetically heterogeneous, disseminated tumors, where targeted chemotherapies fail **(Sharma *et al*., 2017)**.
Immunotherapy targeting the Programmed Death (PD-1) receptor/ligand (L) “checkpoint” rapidly gains ground in the treatment of many cancer types. This therapy proved to evoke durable responses in a proportion of patients with stage IV melanoma, non-small cell lung cancer and cancer colon. PD-L1 blockade transiently activates CD8+ T cells by enabling T cell receptor signaling and CD28 co-stimulation, either in the tumor or in the tumor-draining lymph nodes **(Borst et al., 2021).**
When anti-PD-1 or anti-PD-L1 antibodies are allowed to react to a specified antigen, PD-1 is unable to bind to PD-L1, and an anti-tumour effect is exerted by disabling their immunotolerance **(Malas et al., 2014).** Two reports have analysed a study population of over 3000 patients. Although the reported effect of anti-PD-1 and

anti-PD-L1 antibodies were equivalent in a 2017 study **(Pillai et al.,2018),** a 2018 study showed that the response rate of anti-PD-1 was superior to that of anti-PD-L1 antibody **(You et al ., 2018).** These results indicate that different mechanisms of action may exist as the anti-PD-1 antibody suppresses tumours**(Yoshida et al., 2020).**

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