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New concepts in pathogenesis of primary immune thrombocytopenia

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Abstract:

Primary immune thrombocytopenia (ITP) is a common condition characterized by a low peripheral platelet count (100000/L) caused by cell-mediated and humoral-mediated destruction of the platelet. Immunological tolerance to platelet antigens is lost in these patients. The main step in the pathogenesis includes the overactivation of T-cells, particularly T-helper cells, the release of various cytokines, and the interaction of autoantibodies with platelet surface antigens, which results in platelet destruction by the immune system in the spleen. The most common PLT antigens against which autoantibodies are directed are CD41 and CD61. These antigens are occupied by autoantibodies so there is decreased detection of these antigens on the surface of platelets. PD1 is an important negative stimulatory molecule of the immune system a member of the CD28/B7 family. ITP patients have considerably increased levels of PD-1 on CD4+T-cells in their peripheral blood than healthy people., indicating that the PD1 molecule plays an important role in illness etiology.

Keywords: Primary immune thrombocytopenia, PD1, Pathogenesis.

Abbreviations: ITP: Primary immune thrombocytopenia, PD1: programmed death 1.

Introduction:

ITP is frequent autoimmune thrombocytopenia that causes various degrees and types of bleeding, ranging from minor bruising in the skin and mucosa to more serious, life-threatening bleeding in the gastrointestinal or cerebral areas. Several types of immune disturbance are included in the pathogenesis of this disease. Understanding new concepts in ITP pathogenesis is a standard step that helps in the emergence of new treatments for the disease [(1)].

Epidemiology:

In adults, the annual incidence of ITP is between 0.2 and 0.4 new cases per 10,000. The annual incidence of ITP in children and adolescents is 0.2–0.7 new cases per 10,000. Adult ITP patients are 50–55 years old on average. In pediatric ITP, boys are more likely than girls to be affected, but in middle age, females are more likely than males to develop ITP. After 60 years, men reclaim their dominance. In Egypt, over 1800 new cases of ITP are detected each year [(3)].

Pathogenesis:

The immune system's ability to distinguish what is'self' and not respond or attack it is known as self-tolerance. When the body's immunological self-tolerance

is lost, it develops autoimmunity towards its own tissues and cells, which becomes the basis of autoimmune illness. Several pathways contribute to the loss of self-tolerance in ITP. [2]

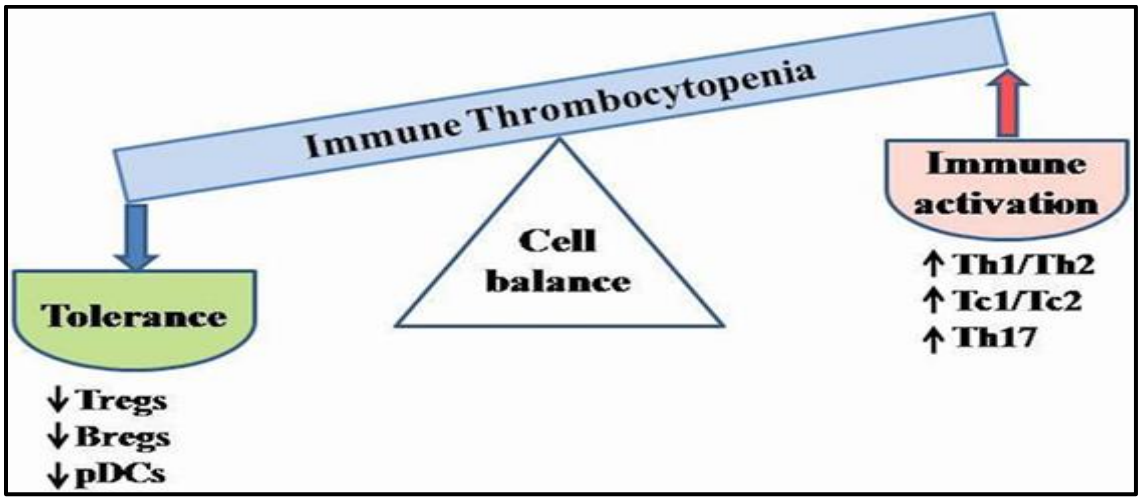

Figure (1): Imbalance in ITP (9).

1-T-cell role:

ITP patients have an increase in Th1 and Th17 cell activation, as well as cytokine release by Th1 and Th17 cells. Th1 cells can release interferon (IFN)-, which promotes the stimulation and multiplication of cytotoxic T-lymphocytes, killer cells, and macrophages, and hence causes cytotoxicity responses. Th17 cells primarily release interleukin (IL)-17, which increases the production of inflammatory mediators and chemokines by a variety of cells, collects neutrophils, and mediates inflammatory reactions. Psoriasis, rheumatoid arthritis, and multiple sclerosis all have Th17 cells that play a role in the initiation and progression of autoimmune diseases [4].

2-B-cell role:

Platelet-reactive immunoglobulin gamma (IgG) antibodies are thought to be the cause of ITP, as they speed up platelet clearance and, to a lesser extent, sabotage platelet formation [5]. Patients with ITP create anti-platelet IgG antibodies (and, less frequently, IgM or IgA antibodies), which bind to platelets and mark them for a phagocytic breakdown in the spleen and liver. These antibodies frequently attach to platelet glycoproteins, particularly GPIIb3 (GPIIbIIIA) and GPIb-IX-V molecules, which are prevalent on the platelet surface [6]. Fc receptors on macrophages in the spleen and elsewhere recognize the antibodies, which cause them to be removed more quickly. Platelet clearance could be more essential than decreased marrow platelet generation, which could potentially be a factor. CD8+ T cells' cytotoxic activities have been shown to produce thrombocytopenia in some ITP patients, possibly via affecting megakaryocytopoiesis [7].

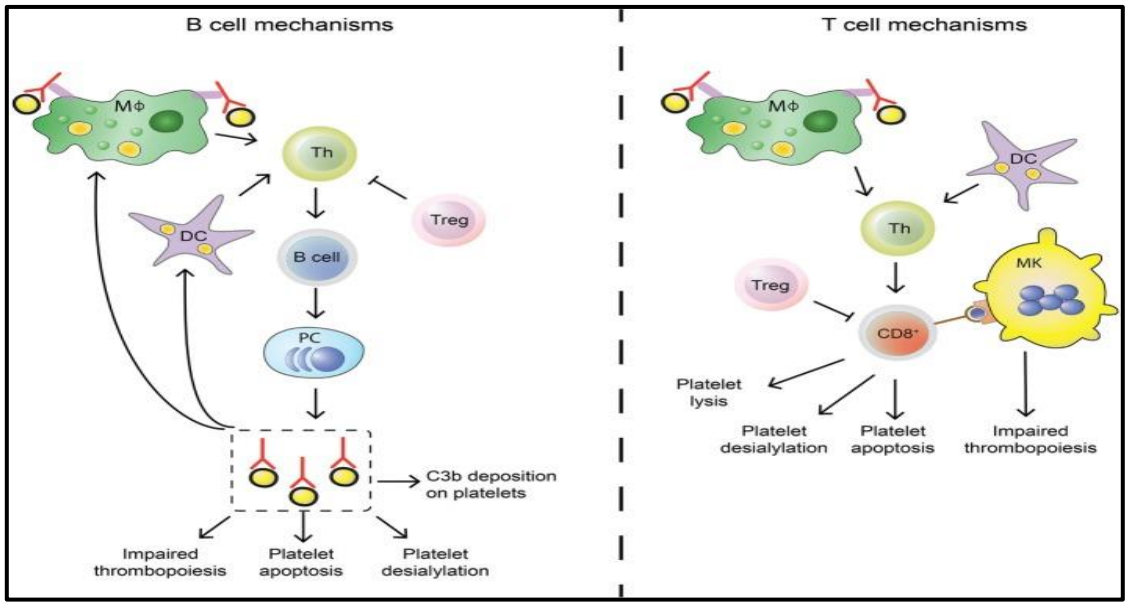

Figure (2): Differences in the actions of B and T cells in ITP. [8].

Programmed cell death -1 role in ITP:

PD-1 is a co-inhibitory receptor produced by a variety of activated immune cells that belongs to the CD28 superfamily. In situations including peripheral tolerance, chronic viral infection, antimicrobial, and tumor immunity, PD-1 receptor activety regulates the balance between lymphocyte activation and repression, hence modulating important immune responses. T cell responses such as proliferation, cytokine generation, and cytotoxicity are all inhibited by the interaction between PD-1 and its ligands (PD-L1 or PD-L2) (10). In autoimmune diseases, viral diseases, and cancer, T follicular helper cells play a crucial role in modulating the humoral immune response. Antigen-specific B-cells that regulate the immune system are known as TFH cells. B-cell responses are also controlled by TFH cells, which could result in the development of specific antibodies. In TFH cells, PD-1 and ICOS are two distinct molecules with closely comparable activeties. TFH cells could have a significant role in controlling platelet antibody formation in patients with ITP. ITP patients had a considerably greater number of CXCR5+CD4+TFH cells in circulation with elevated ICOS or PD-1 expression than healthy controls (12). Furthermore, ITP (+) patients had a considerably greater number of CXCR5+CD4+TFH cells in circulation with elevated ICOS or PD-1 expression as well as considerably higher IL-21 and IL-6 levels in the serum than ITP (-) patients and HC. In addition, IL-21 levels in ITP (+) patients were found to be linked to CXCR-5+CD4+TFH cells with strong ICOS or PD-1 expression. [4]

T-cell immunosuppressive receptors PD1 and CTLA-4, which are involved in T-cell tolerance induction, play a key role in immunological homeostasis. Furthermore, the downregulation of these factors appeared to be linked to autoimmune disease. Self-reactive T cells are suppressed by the activation of PD-1, which also protects against autoimmune diseases. There is a change in PD-1 and PD-L1 levels in ITP, as well as a decr-

ease in SPD-1 and SPD-L1 levels. As a result, there is a link between SPD-1 levels and platelet counts. As a result, In ITP pathogenesis, changing PD-1 and PD-L1 levels appear to play a role. [13].

The PD-1/PD-L1 signaling pathway is critical for immunological balance modulation and peripheral immunological tolerance maintenance. T cell proliferation and cytokine production are inhibited when the PD-1/PD-L1 signaling pathway is activated (12). In C57BL/6 mice, knocking down the PD-1 gene, for example, exacerbates the symptoms of lupus nephritis. also, Collagen-induced arthritis is more severe in PD-1-/- mice than in normal animals. The percentages of PD-1+CD4+T cells and PD-L1+DCs in ITP patients are higher, which is consistent with prior results [14]. However, in chronic ITP, its expression is reduced.

CD41 and CD61 in ITP:

GPIIb (CD41) and GPIIIa (CD61) are two main platelet surface glycoproteins that have been linked to a variety of illnesses. These two glycoproteins form a complex that acts as a receptor for fibrinogen and other platelet-related chemicals, causing platelet aggregation and the creation of platelet plugs. Two genes, ITGB3 and ITGA2B are important for the production of the GPIIb, IIIa complex and are both found on chromosome 17. Glanzmann's thrombasthenia is one of the bleeding illnesses caused by several types of mutations [15].

CD41 is a two-subunit protein that binds to CD61 in the presence of calcium to form a functional sticky protein receptor. When blood vessels are damaged, many intracellular mediators are released, as well as the hemostatic cascade, which activates CD41/CD61 to bind to many proteins, including fibrinogen, fibronectin, and von Willebrand factor, and vitronectin. CD41/CD61 is a specific receptor complex that has been employed as a phenotypic marker for the megakaryocyte-platelet lineage for quite some time. CD41 expression, on the other hand, may not be restricted to platelets. CD41 was reported to be expressed in CD34+CD41+CD42– human cord blood cells with colony-forming cells (CFC) and lymphoid and myeloid repopulating capacity. [16].

As is well known, ITP is an autoimmune illness caused by antiplatelet autoantibodies, which result in increased platelet clearance. The majority of these antibodies target platelet membrane glycoprotein (GP) complexes, specifically GPIIb-/IIIa (CD41/CD61). Platelet production is normal in some ITP patients, whereas it is diminished in others. Antiplatelet antibodies may attach to megakaryocytes, impairing their function or delaying their maturation, and therefore interfering with platelet formation. This could be since CD41/CD61 are expressed on the surface of megakaryocytes. As a result, antiplatelet autoantibodies may obstruct megakaryocyte maturation and platelet release [17]. Autoantibodies may obstruct the GPIIb/IIIa complex on circulating platelets in ITP patients, reducing the number of accessible binding sites. Platelet GPIIb/IIIa inhibitors can also cause ITP. Due to autoantibody coating, platelet surface antigens are recognized at a reduced level. Varon and Karpatkin were the first to publish findings on antigen masking [18].

Conclusion:

The expression of PD-1 on CD4+T- cells is higher in patients with ITP than in healthy people, indicating that PD-1 plays a significant role in the etiology of ITP. The level of expression of CD41 and CD61 on PLT has decreased as a

result of autoantibodies against these glycoproteins covering PLT.

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