Brief overview about IL-1beta(IL-1β) and IL1receptor antagonist (IL1-Ra) and their Possible correlation to Immune Thrombocytopenia in Children

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Abstract

Among genetic factors, polymorphisms in inflammatory cytokine genes, human leukocyte antigen, Fcγ receptors, and tumor necrosis factor are related to ITP. IL-1 is known to be a strong proinflammatory cytokine with multiple biological effects. Since IL-1 was implicated as an important factor for cellular proliferation, it has been reported that IL-1B polymorphisms contributed to the susceptibility of developing gastric cancer and hepatocellular carcinoma. The genes that encode IL-1α and IL-1β are located side by side on chromosome 2. In ITP, IL-1 may be involved in the stimulation of megakaryocytopoiesis, regulation of platelet production, and generation of autoantibodies. It was found that the presence of allele-II of IL-1Ra led to 1.75-fold increase in the probability of ITP development. They also found that both hetero and homozygous types of genotypes of IL-1Ra are associated with ITP.

Keywords: IL-1beta(IL-1β), IL1receptor antagonist (IL1-Ra), Immune Thrombocytopenia

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Introduction:

ITP is a common hematologic disorder that affects patient of all ages, genders and races. Initially known as “idiopathic thrombocytopenic purpura”, an International Working Group (IWG) on ITP recently recommended that this disease be designated “Immune Thrombocytopenia”

(retaining the abbreviation ITP); this terminology recognizes the immune pathogenesis of ITP and the fact that patients with ITP may not uniformly exhibit purpura or bleeding manifestations **(1).**

Immune thrombocytopenia (ITP) is an autoimmune syndrome involving antibody- and cell-mediated destruction of platelets and suppression of platelet production that may predispose to bleeding **(2).**

ITP is defined as a platelet count of less than 100 × 10^9/L (100,000/μL) with no evidence of leukopenia or anemia. This cut off point is new: in the past, ITP was defined as a platelet count of less than 150 × 10^9/L, which is the threshold for a normal platelet count in most laboratories **(3).**

Epidemiology:

In a small number of children, estimated at 1 in 20,000, 1-4 weeks after exposure to a common viral infection, an autoantibody directed against the platelet surface develops with resultant sudden onset of thrombocytopenia. A recent history of viral illness is described in 50-65% of cases of childhood ITP. The peak age is 1-4 year, although the age ranges from early in infancy to the elderly. In childhood, males and females are equally affected. ITP seems to occur more often in late winter and spring after the peak season of viral respiratory illness **(2).**

Acute ITP is more prevalent among children younger than 10 years of age, affects males and females equally, and is more prevalent during the late winter and spring after the peak season of viral respiratory illness **(4).**

Chronic ITP affects adolescents more often than younger children, with females being affected more frequently than males. Unlike acute ITP, it does not show a seasonal predilection. Patients who have chronic ITP are more likely to exhibit an underlying autoimmune disorder, with up to one third having clinical and laboratory manifestations of collagen-vascular disease **(5).**

Incidence in Egypt:

35 million children < 18 years; approximately 1800 new cases of ITP were diagnosed annually in Egypt. Intracranial hemorrhage (ICH) is a rare devastating complication of childhood immune thrombocytopenia (ITP). Incidence of ICH among children with ITP varies markedly in different studies from 0.2 up to 1.0 %. Among genetic factors, polymorphisms in inflammatory cytokine genes, human leukocyte antigen, Fcγ receptors, and tumor necrosis factor are related to ITP.These SNPs may cause disturbance in the Th1 and Th2 cell balance leading to overproduction of inflammatory cytokines. The SNPs in TNF-α gene are associated with increased phagocytic activity of macrophages and T-cytotoxic cells leading to the destruction of platelets via activation of apoptotic pathways. Furthermore, TNF-α and -β are associated with increased serum level of cytokines which plays a crucial role in the regulation of immune systems. Of note, the patient with

TNF- β +252GG genotype was shown to be associated with platelet recovery in ITP patients after the eradication of Helicobacter pylori **(6).**

Moreover, the IFN- γ +874TT was found as a genotype that is associated with increased cytokine production which in turn causes increment of antibody production leading to increased platelet destruction **(7).**

IL-1 is known to be a strong proinflammatory cytokine with multiple biological effects. Since IL-1 was implicated as an important factor for cellular proliferation, it has been reported that IL-1B polymorphisms contributed to the susceptibility of developing gastric cancer and hepatocellular carcinoma **(8).**

The IL-1 family consists of three related genes, IL-1A, IL-1B , and IL-1Ra, and each plays a different functional role in auto- immune diseases and ITP. IL-1B and IL-1Ra are found on chromosome 2q14 within a 360-kb region. IL-1 beta (IL-1β) is a proinflammatory cytokine released by macrophages in systemic inflammatory responses and regulates inflammatory reactions and immune responses by promoting cytokines such as IL-6 and IL-12 **(9).**

In ITP, IL-1 may be involved in the stimulation of megakaryocytopoiesis, regulation of platelet production, and generation of autoantibodies **(6).**

Abnormal serum cytokines levels have been reported in ITP patients . The cytokine genes are polymorphic, which accounts for the different levels of cytokine production. A lot of studies have investigated so far the association between cytokine gene polymorphisms and different immunoinflammatory diseases **(10).**

IL-1B has two diallelic polymorphisms at positions -511 and -31 in the promoter region and at position +3954 in the fifth exon. The polymorphism –31 T>C (rs1143627) in the promoter region affects IL-1B expression. IL-1Ra is a penta-allelic polymorphic site in intron 2 with variable numbers of an 86-base pair (bp) tandem repeat sequence. Pociot and Addas-Carvalho reported that the IL-1B -511 T and +3954 T alleles enhance IL-1 β and IL-1Ra production in humans **(9).**

IL-1

IL-1 is an extremely potent inflammatory cytokine that is involved in myriad immunological responses, spanning both innate and adaptive immunity **(11).** Of the cytokines that bind the primary receptor IL-1RI, there are two similar yet distinct molecules, IL-1α and IL-1β,which are encoded by different genes.

IL-1α and IL-1β

The genes that encode IL-1α and IL-1β are located side by side on chromosome 2 **(12).**

Despite their low level of amino acid sequence homology (27%), IL-1α and IL-1β share a similar three-dimensional structure, consisting of a so-called β-trefoil fold that is formed by 12 β-strands. Both cytokines are mainly produced by stimulated monocytes and macrophages, and to a lesser degree by several other cell types, including neutrophils, keratinocytes, epithelial and endothelial cells, lymphocytes, smooth muscle cells and fibroblasts. IL-1α and IL-1β are synthesized as 31 kDa precursor peptides (pro-IL-1α and pro-IL--1β), which can be cleaved to generate 17 kDa mature forms (mIL-1α and mIL-1β) **(12)**.

Both cytokines lack leader peptides, and are therefore secreted via an unconventional pathway independent of the endoplasmic reticulum and Golgi apparatus. The two IL-1 proteins have different cellular localization patterns and mechanisms of maturation and secretion **(12)**.

Pro-IL-1α can be found as a membrane-associated protein at the surface of several cell types, and seems to be involved in paracrine cell to cell signalling. It can also be cleaved by activation of the calcium-dependent membrane-associated cysteine protease calpain to produce mIL-1α, but this process occurs with relatively low frequently **(12)**.

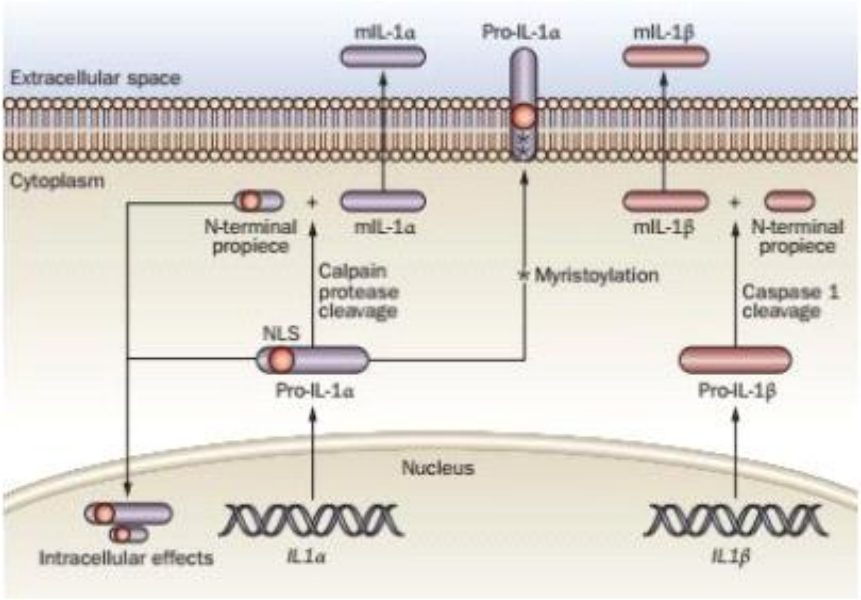

Figure (1): Synthesis, maturation and cellular localization of IL-1α and IL-1β. IL-1α and IL-1β are encoded by two separate genes. Both proteins are synthesized as pro-peptide precursors (pro-IL-1α and pro-IL-1β) without a signal sequence, so are secreted via an unconventional secretion pathway. Pro-IL-1α is biologically active, and can exert both intracellular and extracellular effects. Pro-IL-1α contains a nuclear localization sequence in the N-terminal region and is present at high concentrations in the nucleus. After myristoylation, pro-IL-1α is also expressed as a membrane-bound cytokine, where it is probably involved in cell–cell interactions. Less-frequently, the precursor form can be cleaved by a calpain-like protease to generate secreted mIL-1α and an N-

terminal propiece. Like pro-IL-1α, the N-terminal propiece can exert intracellular activities independently of cell-surface receptor binding. Nuclear translocation seems to be required for the described intracellular effects of pro-IL-1α and the N-terminal propiece. Pro-IL-1β is cleaved by caspase 1 into mIL-1β, which can be secreted as a soluble, active protein. Abbreviations: IL, interleukin; mIL-1α/β, mature IL-1α/β; NLS, nuclear localization sequence.

IL-1α is rarely detected in blood or other body fluids in humans except during severe diseases, in which case it may be released from dying cells. Interestingly, pro-IL-1α also exerts intracellular activities independent of binding with cell surface receptors. The 16 kDa N-terminal moiety of pro-IL-1α contains a nuclear localization sequence (NLS), and nuclear translocation of pro-IL-1α or the cleaved N-terminal pro-peptide are required for these intracellular effects. **(13).**

Pro-IL-1β is biologically inactive, and must be converted to 17 kDa mIL-1β in order to function. IL-1β is processed and released from cells by a mechanism involving caspase 1. Activation of caspase 1 is regulated by a multimeric cytosolic protein complex, called the inflammasome. This complex contains caspase 1, the adapter protein PYCARD (also known as ASC), and a sensor protein belonging to the NOD-like receptor (NLR) family **(12).**

Activation of caspase 1 through the NALP3 inflammasome can be induced by stimulation with microbial molecules derived from both Gram-positive and Gram-negative bacteria, with micro crystals such as silica, asbestos, mono sodium urate (MSU) and calcium pyro-phosphate dihydrate (CPPD), or with P2X purinoceptor 7 agonists, and seems to be mediated through changes in the cytoplasmic ionic milieu and redox status. NALP3 inflammasome activation has also been shown to have an important role in host defense against influenza A virus and in the induction of adaptive immunity against tumors, particularly in the case of dying tumor cells following chemotherapy. **(11).**

Two signals are required for IL-1β release from primary macrophages: first, activation of Toll-like receptors (TLRs), resulting in transcription and translation of pro-IL-1β; and second, NLR-induced IL-1β processing and release through a caspase-1-dependent mechanism involving P2X purinoceptor 7 activation by extra cellular ATP. However, freshly isolated primary human monocytes release mIL-1β after single stimulation with TLR4 or TLR2 ligands, which suggests that IL-1β is differentially regulated in monocytes and macrophages **(14).**

In addition, although IL-1α cleavage is not mediated by caspase 1, its secretion is regulated by caspase 1 activity. Pro-IL-1β can also be cleaved in the extracellular environment by different inflammatory proteases to yield active IL-1β. Unexpectedly, nuclear factor κB (NFκB) activation exerts an inhibitory effect on IL-1β release by macrophages and neutrophils. NFκB inhibits caspase-1-dependent IL-1β processing in macrophages by enhancing the expression of

antiapoptotic genes, whereas in neutrophils, IL-1β secretion is independent of caspase 1 and depends on serine proteases whose activity is in hibited by NFκB-induced gene products **(15).**

Neutrophil-derived serine proteases, such as proteinase 3 and elastase, and mast-cell-derived serine proteases, such as chymase, have been shown to have a major role in caspase-1-independent pro-IL-1β processing in models of joint inflammation and crystal-induced peritonitis. Most interestingly, the adaptive immune system can also downregulate NALP3 inflammasome function and IL-1β secretion by macrophages through negative feedback signals provided by tumor necrosis factor (TNF) family members, such as CD40 ligand expressed on the cell surface of effector and memory CD4+ T cells. Like IL-1β, IL-18 is synthesized as a 23 kDa bio logically inactive precursor peptide that is subsequently cleaved by caspase 1,29 and the biological activity of IL-18 is regulated mainly by caspase-1-mediated pro-IL-18 processing. IL-33, the most recently described member of the IL-1 family of cytokines, is synthesized as a 30 kDa peptide; however, unlike IL-1β and IL-18, it is not processed by caspase 1 and is biologically active as a full-length peptide **(16).**

IL-1α and IL-1β intracellular signalling:

The biological activities of IL-1α and IL-1β are mediated by binding to IL-1 receptor type I (IL-1RI). This receptor is expressed at the surface of a wide variety of celltypes, consistent with the broad spectrum of biological responses induced by IL-1. IL-1RI contains three extra-cellular immunoglobulin domains and an intra cellular domain that shares some homology with other members of the IL-1R and TLR families, known as the Toll-like/ IL-1R (TIR) domain.Binding of IL-1α or IL-1β to the extracellular portion of IL-1RI induces the recruitment of a second receptor chain termed IL-1R accessory protein (IL-1RAcP). The IL-1–IL-1RI–IL-1RAcP ternary complex recruits a number of intracellular adaptor molecules, including myeloid differentiation factor 88 (mYD88), IL-1R-associated kinases (IRAK) and TNF receptor-associated factor 6 (TRAF6), to activate signaling via NFκB, as well as to p38, c-Jun N-terminal kinases (JNKs), extracellular signal-regulated kinases (ERKs) and mitogen-activated protein kinases (mAPKs) **(12).**

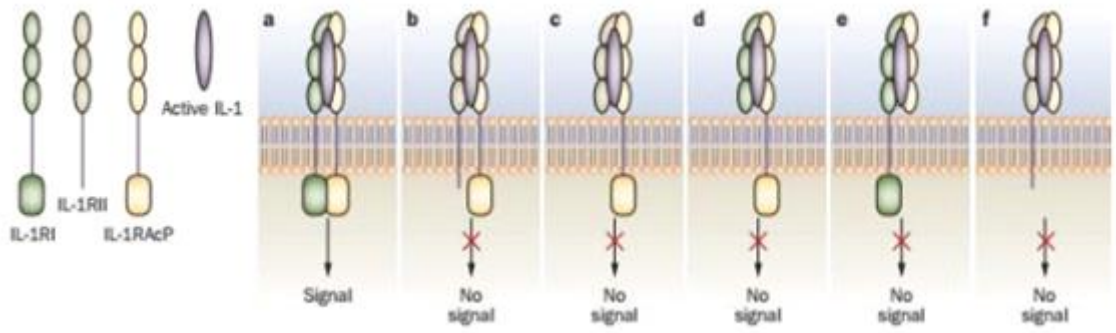

Figure (2): Regulation of IL-1 activity by both membrane-bound and soluble forms of IL-1 receptors. a | The biological activities of IL-1, including membrane-bound pro-IL-1α, mIL-1α and

mIL-1β, are mediated by binding to the cell surface receptor IL-1RI. The binding of IL-1 induces a conformational change in the extracellular component of IL-1RI, enabling its interaction with IL-1RAcP, which is required for intracellular signaling. IL-1RII might only act as a decoy receptor either b | on the cell surface or c | as sIL-1RII in the extracellular environment after enzymatic cleavage of its extracellular domain. sIL-1RII contributes to IL-1 antagonism. d | IL-1RI and e | IL-1RAcP also exist as soluble forms, produced by cleavage of the extracellular domain and alternative splicing, respectively. To date, the physiological role of sIL-1RI is unclear. sIL-1RAcP can form an inactive complex with cell surface IL-1RI bound to IL-1, and f | also increases the potency of sIL-1RII as an inhibitor of IL-1 action. Abbreviations: IL, interleukin; IL-1RI/II, IL-1 receptor type I/II; IL-1RAcP, IL-1 receptor accessory protein; m, mature; s, soluble.

Biological effects of IL-1:

IL-1 (which refers here to both IL-1α and IL-1β) is a proto typical proinflammatory cytokine that stimulates both local and systemic responses. In some circumstances these effects are detrimental, such as in chronic inflammatory diseases and septic shock. However, these responses are also essential in the control and resolution of infections. IL-1 promotes the recruitment of inflammatory cells at the site of inflammation by inducing the expression of adhesion molecules on endothelial cells and through the release of chemokines by stromal cells. The cytokine induces the production of various enzymes, such as phospho lipase A2, cyclo-oxygenase 2 and inducible nitric oxide (NO) synthase, leading to the release of the inflammatory mediators prostaglandin E2 and NO, which contribute to local and systemic responses (12).

IL-1 stimulates the production of several metalloproteinases, which leads to connective tissue breakdown, and inhibits the production of proteoglycans and type II collagen, thereby exerting a global negative effect on articular cartilage. In addition, IL-1 exerts direct and indirect stimulatory effects on the maturation of osteoclasts, and therefore participates in the development of bony erosions in arthritis (13).

The systemic effects of IL-1 include hypotension, fever, neutrophilia, thrombocytosis, and the production of acute-phase proteins. Some of these effects are indirect, mediated through the induction of downstream cytokines and other inflammatory mediators. IL-1 is also involved in the regulation of adaptive immune responses by inducing the differentiation of type 17 T-helper cells and the production of IL-17 in mice and humans (17).

IL-1Ra:

IL-1Ra was the first naturally occurring cytokine to be described that functions as a specific receptor antagonist. IL-1Ra acts as a competitive inhibitor for the binding of IL-1 to its receptor. However, despite the near- equal affinity of IL-1 and IL-1Ra for IL-1RI, a large molar excess (100-fold to 1,000-fold) of IL-1Ra is necessary to block IL-1 activity in vitro and in vivo. These findings

are explained by the high level of expressed IL-1RI on most cells, and the fact that engagement of only a few receptors by IL-1 is sufficient to fully activate its cellular responses **(12).**

IL-1Ra is produced as four different isoforms by using different first exons and alternative mRNA splicing and translation initiation codons. One isoform is secreted (sIL-1Ra), whereas the three others lack a consensus leader peptide and remain intracellular (icIL-1Ra1, icIL-1Ra2 and icIL-1Ra3). These intracellular isoforms can be released by dying cells or in certain other circumstances, and bind to IL-1RI **(18).**

The importance of IL-1Ra in regulating the effects of IL-1 has been clearly demonstrated in knockout mice lacking IL-1Ra, which exhibit excessive inflammatory responses and develop spontaneous joint inflammation, vasculitis or skin inflammation, according to the back- ground into which they have been bred. The occurrence of autoinflammatory manifestations in children deficient in IL-1Ra further supports the key regulatory role of this antagonist **(12).**

IL-1Ra is associated with several inflammatory diseases like ankylosing spondylitis, rheumatoid arthritis, alopecia areata,

Association of IL-1B and IL1Ra Polymorphism

with ITP

Immune thrombocytopenia (ITP) is an autoimmune bleeding disorder in which the platelet autoantigens activate the immune system of the patient causing immune-mediated platelet destruction and/or suppression of platelet production. ITP can be either primary or secondary to other disorders, but the primary cause of the disease is still not well known. Meanwhile, many reports on genetic factors of ITP described several single nucleotide polymorphisms (SNPs), mostly inflammatory cytokine polymorphisms, associated with increased risk of ITP.

Kim, (9). found that IL-4, IL-10, and IL-1Ra poly- morphisms contribute to childhood chronic ITP, while an IL-1β exon 5 polymorphism is associated with childhood ITP

In ITP, IL-1 may be involved in the stimulation of megakaryocytopoiesis, regulation of platelet production, and generation of autoantibodies **(6).**

In the report by **Yadav et al., (19)** in order to rule out ITP associated with secondary causes, patients with human immune deficiency virus, systemic lupus erythematous, and H. pylori were excluded from the study. Thus, direct association between ITP and IL-1B polymorphisms could be elucidated of ITP.

Kim, (9). evaluated the association of polymorphisms in interleukin (IL)-1B-31, IL-1B-511, and IL-1Ra with ITP, and revealed that IL-1B-31 and IL-1Ra were significantly associated with ITP whereas IL-1B-511 failed to show association with ITP.

Patients with ITP and IL-1B-31 polymorphism not only showed an increased susceptibility to ITP, but also had a more severe form of the disease, particularly those with homozygous mutant and variant alleles **(9).**

In another study, **Bizav and Adil (20)** evaluated the relation between several interleukins including IL-Ra with ITP .They reported that the presence of allele-II of IL-1Ra led to 1.75-fold increase in the probability of ITP development. They also found that both hetero and homozygous types of genotypes of IL-1Ra are associated with ITP.

Abnormal serum cytokines levels have been reported in ITP patients. The cytokine genes are polymorphic, which accounts for the different levels of cytokine production. A lot of studies have investigated so far the association between cytokine gene polymorphisms and different immunoinflammatory diseases **(10).**

IL1 Ra, a major member of the IL-1 family (consisting of 11 members in total), is a natural anti-inflammatory molecule that neutralizes the effects of IL-1. The balance between IL-1 and IL-1 Ra is important in maintaining the homeostasis of immune system. As a result, IL-1 Ra polymorphisms may lead to changes in this IL-1 and IL-1 Ra balance and be associated with susceptibility of a variety of autoimmune diseases **(21).**

IL-1 Ra polymorphism is associated with childhood ITP. The genotype I/II was more frequently detected in children with ITP than in controls. More specifically, we found that the presence of allele II seems to increase 2.12 times the risk for development of ITP, thus assuming that IL-1 Ra polymorphism may be involved in the pathogenesis of ITP. The polymorphism under investigation is caused by the variable copy number of an 86-bp sequence, and the repeat region contains three potential protein-binding sites. Therefore, the variable copy number may have functional significance. Furthermore, allele II has been reported to be associated with more severe clinical outcome in several inflammatory and autoimmune diseases **(22).**

The induction of IL-1Ra by IL-1beta is an important counter regulatory mechanism and may at least partially account for the increased IL-1Ra levels found in the carriers of allele II, thus explaining the higher incidence of ITP **(22).**

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