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Review

Pathogenesis of immune thrombocytopenia

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ABSTRACT

Immune thrombocytopenia (ITP) is a rare autoimmune disease due to an abnormal T cell response, notably supported by splenic T follicular helper cells, that stimulates the proliferation and differentiation of autoreactive B cells. The antiplatelet autoantibodies they produce facilitate platelet phagocytosis by macrophages, essentially in the spleen. Macrophages contribute to the perpetuation of the auto-immune response as the main antigen-presenting cell during ITP. $CD8^+$ T cells also participate to thrombocytopenia by increasing platelet apoptosis. Besides this peripheral platelet destruction, inappropriate bone marrow production also exacerbates thrombocytopenia, due to an immune response against megakaryocytes. Moreover, the level of circulating thrombopoietin, the main growth factor of megakaryocytes, is low during ITP. In this review, the major mechanisms leading to thrombocytopenia, the role of the different immune cells and the different targets of treatments are described.
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Contents

Abbreviations: ADP, adenosine diphosphate; AID, autoimmune diseases; AML, acute myeloid leukemia; APRIL, a proliferation inducing ligand; BAFF, B cell activating factor; Breg, regulatory B cells; CMV, cytomegalovirus; DC, dendritic cells; EBV, Epstein Barr virus; FcγR, Fcγ receptor; GP, glycoproteins; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDO, indoleamine 2,3-dioxygenase; ITP, immune thrombocytopenia; MDS, myelodysplastic syndrome; MHC, major histocompatibility complex; moDC, monocyte-derived dendritic cells; MSC, mesenchymal stromal cells; RTX, rituximab; TCR, T cell receptor; TIMP-3, tissue inhibitor of metalloproteinase 3; TFH, T follicular helper cells; TLR, toll-like receptor; TPO, thrombopoietin; TPO-RA, thrombopoietin receptor agonists; TRAP, thrombin receptor activating peptide; Treg, regulatory T cells.

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1. Introduction

Immune thrombocytopenia (ITP) is an autoimmune disease (AID) characterized by a low platelet count (<100 G/L). It causes bleeding, especially in the skin and the mucosa, in 2/3 of patients. The prevalence of ITP in adults is about $10/10^5$ [1] with an incidence rate ranging from 1.6 to $3.9/10^5$/year [2–4]. Adults generally present a chronic course (>1 year in 80%) whereas in children the disease is most often acute. ITP is a diagnosis of exclusion which needs to rule out thrombocytopenia secondary to medications (including heparin-induced thrombocytopenia), disseminated intravascular coagulation, vitamins B9 and B12 deficiency, congenital thrombocytopenia, spleen sequestration, portal hypertension and bone marrow disorders such as myelodysplastic syndromes. Secondary ITP refers to autoimmune thrombocytopenia occurring in the course of other diseases, mainly infections (Human Immunodeficiency Virus (HIV), Hepatitis C Virus (HCV), Epstein Barr virus (EBV), Cytomegalovirus (CMV), *Helicobacter pylori*, other AID (lupus, Evans syndrome, Sjögren's syndrome, antiphospholipid syndrome), hematologic malignancies (mainly non-Hodgkin lymphoma, most particularly chronic lymphocytic leukemia) or primary immune deficiency (common variable immune deficiency (CVID), autoimmune lymphoproliferative syndrome (ALPS)). Guidelines have standardized ITP nomenclature: newly-diagnosed ITP refers to a disease lasting less than 3 months, persistent ITP between 3 and 12 months from diagnosis, chronic ITP when the disease lasts for more than 1 year and refractory ITP if patient is at risk of or displays bleeding despite splenectomy. Severe ITP refers to the presence of bleeding that requires treatment or treatment escalation [5].

Steroids are the first-line therapy and represent a useful diagnostic test, as a transient response is observed in more than 80% of cases. Intravenous immunoglobulin (IVIg) and anti-D immunoglobulin are generally used as emergency rescue therapies with a transient response [6]. Splenectomy remains a cornerstone treatment that should be proposed when ITP lasts more than one year, as the chances of spontaneous remission are nearly null at this time [7]. Importantly, splenectomy gives the highest long-term response rate of about 66% [8]. However, drugs such as rituximab (RTX, off-label use in ITP) or thrombopoietin receptor agonists (TPO-RA) have changed the management of ITP, particularly for persistent ITP, when drugs with a high benefit/risk ratio must be favored [9,10]. These drugs are thus more and more used to postpone splenectomy. Other therapies such as dapsone, danazol, hydroxychloroquine and vinca alkaloids can be useful in specific situations [11]. The aim of this review is to describe the general mechanisms involved in ITP pathogenesis with a focus on the role of the different immune cells; these are summarized in Fig. 1.

2. Triggering the immune response: genetic background and environmental factors

2.1. Genetic predisposing factors

As in other AID, specific genetic backgrounds have been reported to be associated with ITP (Table 1). The major histocompatibility complex (MHC) [12–15], Fcγ receptors (FcγR) [16–21], transcription factors [22], chemokines [23], pro-inflammatory cytokines [24–29] or anti-inflammatory cytokines [27,30,31] together with their receptors [27,28,32] display polymorphisms that are often observed in ITP cohorts, or specifically during the chronic course of the disease. Polymorphisms of regulator proteins such as the phosphatase PTPN22 are also overrepresented in ITP patients [33–35]. Specific epitopes on human platelet antigens (HPA) have also been linked to acute or chronic ITP [36,37]. More recently, variations in the level of some microRNAs, non-coding RNAs that regulate genes at the post-transcriptional level, have been reported in ITP. These variations of microRNAs lead to the dysregulation of cytokines involved in the immune response, such as IFN-γ, IL-21, IL18 or TGF-β [38–40].

However, most of these data were obtained from small cohorts or from patients of specific ethnic origins, and should thus be interpreted carefully. Analyses of exome sequencing are in process, to identify new genes that might be implicated in the development of ITP.

Polymorphisms have also been associated to the response to medications. Indeed, *FCGRA-V/V* polymorphism is overrepresented in responders to RTX [41], while *FCGR2B-I/I* is associated with a better response to IVIg during pediatric ITP [42]. However, treatment choice at an individual level is not yet decided on gene polymorphisms.

2.2. Environmental factors

Different mechanisms participate in the initiation of the autoimmune process triggered by infections (Table 2). Molecular mimicry between infectious components and platelet glycoproteins (GP) has been clearly demonstrated *in vitro*: between the GP120 of HIV or the core envelope 1 protein of HCV and the platelet glycoprotein GPIIb/IIIa [43,44]. By computer analyses, homologies have been observed between the sequences of different viral proteins from *Herpes simplex virus*, *Varicella zoster virus*, EBV, CMV and the GPIIb/IIIa. Interestingly, some peptides derived from these proteins are recognized by antiplatelet antibodies *in vitro* [45]. Molecular mimicry is mainly involved in secondary acute ITP, accounting for 70, 50 and 30% of neonatal CMV, EBV and HIV infections, respectively [45–47]. However, in some cases, the viral infection triggers an autoimmune response that subsequently

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