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Immune Thrombocytopenia: Advances in Pathogenesis and Targeted Therapy

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Abstract: ***Immune thrombocytopenia (ITP), an acquired autoimmune disease characterized by accelerated platelet destruction and impaired platelet production, is clinically heterogeneous and associated with a high risk of bleeding. With the advancement of multi-omics technologies, the medical community's understanding of the pathogenesis of ITP has expanded from a single autoantibody-mediated hypothesis to a multidimensional framework encompassing lymphocyte network dysregulation, megakaryocyte maturation defects, and immune tolerance defects in the bone marrow microenvironment. Innovations in diagnostic approaches, coupled with the emergence of targeted therapies such as TPO receptor agonists, FcRn inhibitors, and multi-targeted kinase inhibitors, are contributing to the development of precision treatment strategies for ITP. Integrated Traditional Chinese and Western Medicine (ITCM) has has shown potential clinical value for its role in comprehensive disease-course intervention, restoration of immune homeostasis, and improvement of the bone marrow hematopoietic microenvironment. This article systematically reviews the core pathological mechanisms and cutting-edge targeted intervention strategies in the field of ITP, evaluates the clinical efficacy of integrated traditional Chinese and Western medicine approaches, and prospectively explores future development pathways guided by molecular subtyping, with the aim of providing high-value academic references for basic translational research and personalized clinical diagnosis and treatment.***

Keywords: Immune thrombocytopenia, Pathogenesis, Precision medicine, Targeted therapy, Integration of traditional Chinese and Western medicine.

1. Introduction

Immune thrombocytopenia (ITP) is a highly heterogeneous acquired autoimmune bleeding disorder characterized by increased platelet destruction and impaired platelet production [1]. According to the International Working Group (IWG), ITP is defined as a peripheral platelet count below 100 × 10^9/L in the absence of other causes of thrombocytopenia [2]. Epidemiological studies have shown that the annual incidence of adult ITP ranges from 2 to 10 per 100,000 population, with relatively higher prevalence among young women and older adults [3]. In addition to bleeding manifestations, chronic fatigue, recurrent relapse, and long-term treatment burden may significantly affect patients' quality of life.

Traditionally, ITP was mainly considered an antibody-mediated disorder characterized by accelerated platelet destruction in the reticuloendothelial system [4]. However, increasing evidence suggests that the pathogenesis of ITP involves both humoral and cellular immune dysregulation, impaired immune tolerance, and abnormalities of the bone marrow hematopoietic microenvironment [5]. Advances in the understanding of these mechanisms have promoted the development of novel therapeutic strategies beyond conventional immunosuppression.

Although glucocorticoids and intravenous immunoglobulin (IVIG) remain standard first-line therapies, their long-term use is associated with relapse, drug resistance, and treatment-related adverse effects. In recent years, targeted therapies aimed at promoting thrombopoiesis and modulating immune responses have expanded treatment options for patients with refractory or relapsed ITP. In addition, integrated traditional Chinese and Western medicine approaches have attracted increasing attention because of their potential role in immune regulation and supportive hematopoietic management.

2. Related Research Progress

2.1 Autoantibody-Mediated Destruction and Remodeling of Clearance Pathways

Autoantibody-mediated platelet destruction is one of the major pathogenic mechanisms of ITP [6]. Clinically, IgG-type autoantibodies against platelet membrane glycoproteins (GPIIb/IIIa and GPIIb/IX) can be detected in a substantial proportion of patients [7]. After binding to their target antigens, the Fc segments of these pathogenic antibodies cross-link with activated Fcγ receptors (FcγRIIA and FcγRIIIA) on the surface of splenic macrophages, triggering downstream signaling cascades [8]. In ITP patients, the overexpression of activated Fcγ receptors and the absence of inhibitory FcγRIIB disrupt the immune homeostasis of the mononuclear-macrophage system, enhancing macrophage-mediated platelet phagocytosis [9]. In addition to the classical Fcγ receptor pathway, platelet desialylation constitutes another independent destruction pathway [10]. Anti-GPIb/IX antibodies can induce the cleavage of sialic acid residues on platelet surface glycoproteins, exposing galactose structures, which are then sensitively recognized by Ashwell-Morell receptors (AMR) on the surface of hepatic parenchymal cells and rapidly internalized and cleared [11]. Because this pathway is independent of Fcγ receptors, it often exhibits primary resistance to conventional corticosteroid and IVIG therapies.

2.2 Autoantibody-Mediated Destruction and Remodeling of Clearance Pathways

T-cell-mediated cellular immune dysfunction pervades the entire course of ITP and plays a dominant role in antibody-negative patients [12]. Peripheral blood from ITP

patients exhibits significant Th1/Th2 cell polarization abnormalities, with Th1 cells exhibit increased secretion of IFN-γ, IL-2, and TNF-α, exacerbating systemic inflammatory cascades [13]. More critically, there is an imbalance in the Th17/Treg axis: Th17 cells, which exert pro-inflammatory effects, are significantly expanded, and the IL-17 they secrete directly contributes to tissue inflammatory damage; the number of regulatory T cells (Tregs)—the core cells responsible for peripheral immune tolerance—is significantly reduced, and Foxp3 expression is downregulated, rendering them unable to effectively secrete the inhibitory factors IL-10 and TGF-β [14]. The failure of Treg function is regarded as a key driver in the transition of ITP from an acute, self-limiting phase to a chronic, persistent phase [15]. Overactivated CD8+ cytotoxic T lymphocytes (CTLs) not only directly lyse peripheral blood platelets via the perforin/granzyme pathway but also induce apoptosis in bone marrow megakaryocytes through the Fas/FasL receptor pathway [16].

2.3 Abnormal B-Cell Activation and Colonization of Long-Lived Plasma Cells

The humoral immune abnormalities in ITP stem from uncontrolled B-cell cloning [17]. Due to functional defects in regulatory B cells (Bregs), the body loses its ability to early eliminate autoreactive B cells [18]. In this process, follicular helper T cells (Tfh) highly express CD40L and secrete IL-21, providing strong support for B-cell proliferation and affinity maturation. The chronic and refractory features of ITP are closely associated with the persistence of long-lived plasma cells (LLPCs) [19]. These cells lack CD20 expression, making them less responsive to anti-CD20 monoclonal antibody therapy. LLPCs home to survival niches deep within the bone marrow. With continuous nutritional support from stromal cells and high levels of B-cell activating factor (BAFF) and proliferative-inducing ligand (APRIL), they serve as persistent sources of autoantibody production, constituting the microscopic anatomical basis for the high recurrence rate of ITP [20].

2.4 Inflammatory Remodeling of the Bone Marrow Microenvironment and Inhibition of Megakaryocyte Maturation

ITP is not only a peripheral depletion disorder but also a disorder of impaired bone marrow production [21]. Bone marrow aspiration often reveals a compensatory increase in total megakaryocyte count, accompanied by a significant reduction in platelet-producing megakaryocytes [22]. This phenomenon may be associated with inflammatory remodeling of the bone marrow microenvironment. High concentrations of TNF-α and IFN-γ directly interfere with signaling along the thrombopoietin (TPO)/c-Mpl receptor axis, inhibiting the development of the megakaryocyte endomembrane system and pseudopod formation. Bone marrow mesenchymal stem cells (MSCs) undergo transcriptional reprogramming, losing their ability to secrete immunoregulatory factors and instead adopting a pro-inflammatory phenotype, thereby impairing the bone marrow microenvironment required for megakaryocyte maturation. [23].

3. Laboratory Diagnosis and Advances in Biomarkers

Current clinical guidelines reiterate that the diagnosis of ITP must be based on strict exclusion criteria [24]. Clinicians must rely on a detailed medical history and laboratory tests to accurately distinguish ITP from secondary causes such as systemic lupus erythematosus, antiphospholipid syndrome, myelodysplastic syndromes, and occult infections (e.g., HIV, HCV, and Helicobacter pylori). Regarding biomarker exploration, Monoclonal Antibody-Specific Platelet Antigen Capture (MAIPA) serves as the standard technique for detecting specific autoantibodies; a positive result for anti-GPIb/IX antibodies often indicates a higher risk of corticosteroid resistance [25]. The immature platelet fraction (IPF), a kinetic indicator reflecting the bone marrow's real-time hematopoietic compensatory capacity, serves as a highly sensitive reference for distinguishing between diseases involving bone marrow failure [26]. High-throughput multi-omics studies have revealed that non-coding RNA networks (miR-155 and lncRNA NEAT1) play a crucial regulatory role in the immune imbalance of ITP, offering potential as novel biomarkers to guide future molecular subtyping and prognostic assessment [27].

4. Clinical Evidence and Evolution of Targeted Treatment Strategies

4.1 Re-evaluation of Conventional Immunosuppression

Glucocorticoids remain the cornerstone of first-line therapy for rapidly reversing immune responses, primarily by downregulating Fcγ receptor expression on macrophages and inhibiting the transcription of pro-inflammatory factors [28]. Since corticosteroids cannot restore long-term immune tolerance, and given the risks of metabolic disorders, osteoporosis, and opportunistic infections associated with prolonged exposure, international guidelines strongly recommend strictly limiting the duration of high-dose corticosteroid therapy (recommended to be kept within 6 weeks) [29]. Intravenous immunoglobulin (IVIG) is primarily used as a bridging therapy for acute episodes of severe bleeding. Because of surgical risks and long-term complications including thrombosis and infection, the role of splenectomy in ITP management has gradually declined with the development of novel therapeutic agents [30].

4.2 Hematopoietic Remodeling with TPO Receptor Agonists (TPO-RAs)

The advent of thrombopoiesis-stimulating agents has expanded therapeutic strategies for ITP. Small-molecule receptor agonists such as eltrombopag, avatrombopag, and the novel TPO-RA hetrombopag bind to the transmembrane or extracellular domains of the c-Mpl receptor, bypassing inflammatory microenvironmental barriers to promote megakaryocyte proliferation and platelet production [31]. Long-term clinical follow-up studies have suggested that approximately 20%–30% of patients achieve treatment-free remission (TFR) following standardized use of TPO-RAs [32]. The underlying mechanism is believed to be closely related to

the indirect restoration of peripheral Treg cell numbers and the remodeling of the bone marrow hematopoietic microenvironment induced by TPO-RAs [33].

4.3 Novel Small Molecules and Monoclonal Antibody-Targeted Interventions

Based on recent advances in the understanding of ITP pathogenesis, multiple novel therapeutic approaches have entered the clinical translation phase. FcRn inhibitors competitively bind to neonatal Fc receptors with high affinity, blocking the endocytosis and recycling of pathogenic IgG antibodies and promoting their rapid degradation in lysosomes, thereby achieving a biologic plasma exchange effect without suppressing cellular immunity [34]. In the field of kinase inhibitors, the Syk inhibitor (fotamatinib) precisely disrupts the downstream signaling cascade of the Fcγ receptor on macrophages, directly impairing their phagocytic and destructive capabilities [35]. Next-generation BTK inhibitors offer the advantage of dual-target inhibition: they both suppress B-cell BCR signaling to reduce antibody production and attenuate macrophage activity, demonstrating broad application potential. Targeted elimination strategies using CD38 monoclonal antibodies against long-lived plasma cells in the bone marrow are currently undergoing active validation in patients with multi-line refractory disease [36].

5. Targeted Regulatory Mechanisms and Clinical Advantages of Integrated Traditional Chinese and Western Medicine Interventions for ITP

Integrated Traditional Chinese and Western medicine treatment represents a distinctive and highly promising approach in the precision management of ITP [37]. Throughout history, medical practitioners have classified this condition under the categories of “purpura” and “blood disorders,” summarizing its pathogenesis as “heat, deficiency, and stasis.” Recent studies have attempted to explore the association between TCM syndrome differentiation and immunopathological alterations in ITP, which may provide additional insights into comprehensive disease management.

5.1 Association Between Traditional Chinese Medicine Syndromes and the Immunopathological Mechanisms of ITP

According to traditional Chinese medicine (TCM) theory, the acute phase of ITP is commonly classified as a “blood-heat” syndrome and is characterized by bleeding manifestations such as petechiae, ecchymosis, epistaxis, and gingival bleeding [38]. Some studies have reported elevated inflammatory cytokines and immune activation during the active stage of the disease, suggesting a potential association between “blood-heat” syndromes and enhanced inflammatory responses. However, direct evidence linking specific TCM syndromes to defined molecular mechanisms remains limited. As the disease progresses, some patients develop symptoms including fatigue and pale complexion, which are generally categorized in TCM as “qi and blood deficiency” or “spleen-kidney deficiency” syndromes. Modern studies indicate that chronic ITP may involve impaired megakaryocyte maturation, hematopoietic dysfunction, and persistent immune imbalance, particularly Th17/Treg dysregulation, which has been associated with chronicity and relapse [39].

In patients with prolonged or recurrent disease, alterations in the bone marrow microenvironment and mild fibrotic changes have also been reported. The TCM syndrome of “blood stasis” may therefore be related to microcirculatory dysfunction, although the underlying mechanisms remain unclear.

Overall, current evidence suggests a potential association between TCM syndrome evolution and the immunopathological changes observed in ITP. However, most studies remain exploratory, and further mechanistic and clinical investigations are still needed.

5.2 Multi-Target Regulatory Effects of Active Compounds and Traditional Chinese Medicine Formulas

In recent years, increasing attention has been paid to the therapeutic potential of traditional Chinese medicine (TCM) formulas and bioactive compounds in the treatment of immune thrombocytopenia (ITP) [40]. Unlike single-target therapies, TCM interventions are generally considered to exert integrated effects through multiple pathways, including immune regulation, suppression of inflammatory responses, and improvement of the bone marrow hematopoietic microenvironment, thereby demonstrating the characteristics of “multi-component, multi-target, and multi-pathway” regulation [41]. Some TCM formulas with functions of reinforcing qi, strengthening the spleen, and tonifying the kidney have been reported to improve immune imbalance, promote megakaryocyte maturation, and enhance platelet production. Modern pharmacological studies have shown that various active compounds derived from TCM may influence signaling pathways such as PI3K/Akt and NF-κB, thereby participating in the regulation of inflammatory responses, apoptosis, and autophagy [42]. However, most current mechanistic studies are still based on cell experiments and animal models, and their clinical relevance remains to be further clarified. At the level of active compounds, astragaloside IV, quercetin, paeoniflorin, icariin, curcumin, and indirubin have all been reported to exhibit immunomodulatory effects [43]. Previous studies suggest that these compounds may improve immune abnormalities associated with ITP by regulating the Th17/Treg balance, suppressing inflammatory cytokine release, and alleviating oxidative stress [44]. In addition, some studies have indicated that these compounds may exert protective effects on the bone marrow hematopoietic microenvironment and megakaryocyte function, thereby contributing to improved megakaryocyte maturation and platelet production [45]. Nevertheless, the current evidence is still largely derived from basic experimental studies, and high-quality clinical evidence remains insufficient.

5.3 Clinical Advantages of Integrated Traditional Chinese and Western Medicine Throughout the Disease Course

In recent years, integrated traditional Chinese and Western medicine approaches have been increasingly applied in the management of immune thrombocytopenia (ITP). Current

studies suggest that, when combined with standard Western medical treatment, syndrome-based traditional Chinese medicine (TCM) therapy may help improve clinical symptoms, reduce relapse rates, and alleviate treatment-related adverse effects. During the acute phase of ITP, glucocorticoids remain the first-line treatment. Some clinical studies have shown that the combination of TCM therapies aimed at clearing heat, cooling blood, and promoting hemostasis may improve bleeding symptoms and reduce gastrointestinal reactions and metabolic disturbances associated with prolonged glucocorticoid use [46]. For patients in the chronic or persistent phase, TCM approaches such as strengthening the spleen, replenishing qi, and nourishing the kidney and blood are commonly used as adjunctive therapies to reduce steroid dependence and maintain platelet stability. Several meta-analyses have suggested that integrated Chinese and Western medicine treatment may be superior to Western medicine alone in improving overall response rates and reducing relapse risk [47]. However, due to variability in the quality of the included studies, these findings still require confirmation through high-quality randomized controlled trials. With the widespread use of thrombopoietin receptor agonists (TPO-RAs) in ITP treatment, sustained remission after drug withdrawal has become an important clinical concern [48]. Some studies have proposed that TCM may contribute to maintaining disease stability through immune regulation and overall functional improvement. Nevertheless, evidence regarding its role in improving treatment-free remission (TFR) remains limited, and further studies are needed to clarify its long-term clinical benefits.

6. Conclusion and Future Perspectives

Research on immune thrombocytopenia (ITP) has expanded considerably in recent years, leading to a more comprehensive understanding of its complex immunopathological mechanisms. Autoantibody-mediated platelet destruction, T-cell dysregulation, long-lived plasma cell persistence, and alterations in the bone marrow microenvironment are all considered important contributors to disease development and progression. Advances in high-throughput technologies and targeted therapies, including small-molecule agents and monoclonal antibodies, have further broadened current treatment strategies. Given the marked heterogeneity of ITP, future studies should focus on establishing high-resolution molecular classification systems based on single-cell transcriptomics and multi-omics approaches to support individualized treatment strategies. In addition, further investigation into the mechanisms underlying traditional Chinese medicine (TCM), particularly its potential immunomodulatory and hematopoietic regulatory effects, may provide additional insights into integrated therapeutic approaches.

Although integrated traditional Chinese and Western medicine treatment has shown potential clinical benefits in ITP management, most current evidence remains preliminary. More well-designed mechanistic studies and multicenter randomized controlled trials are still needed to clarify its long-term efficacy and clinical value.

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