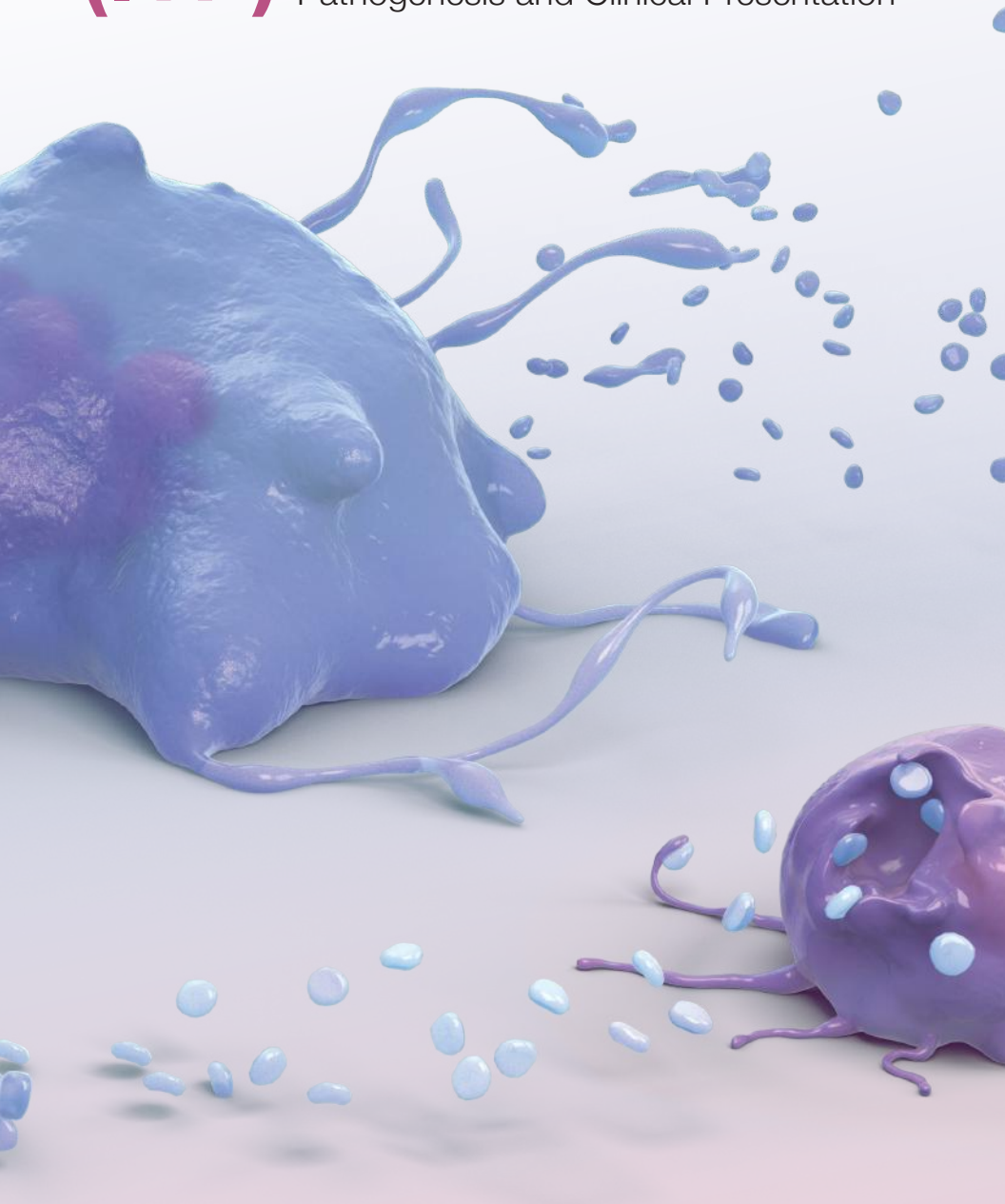
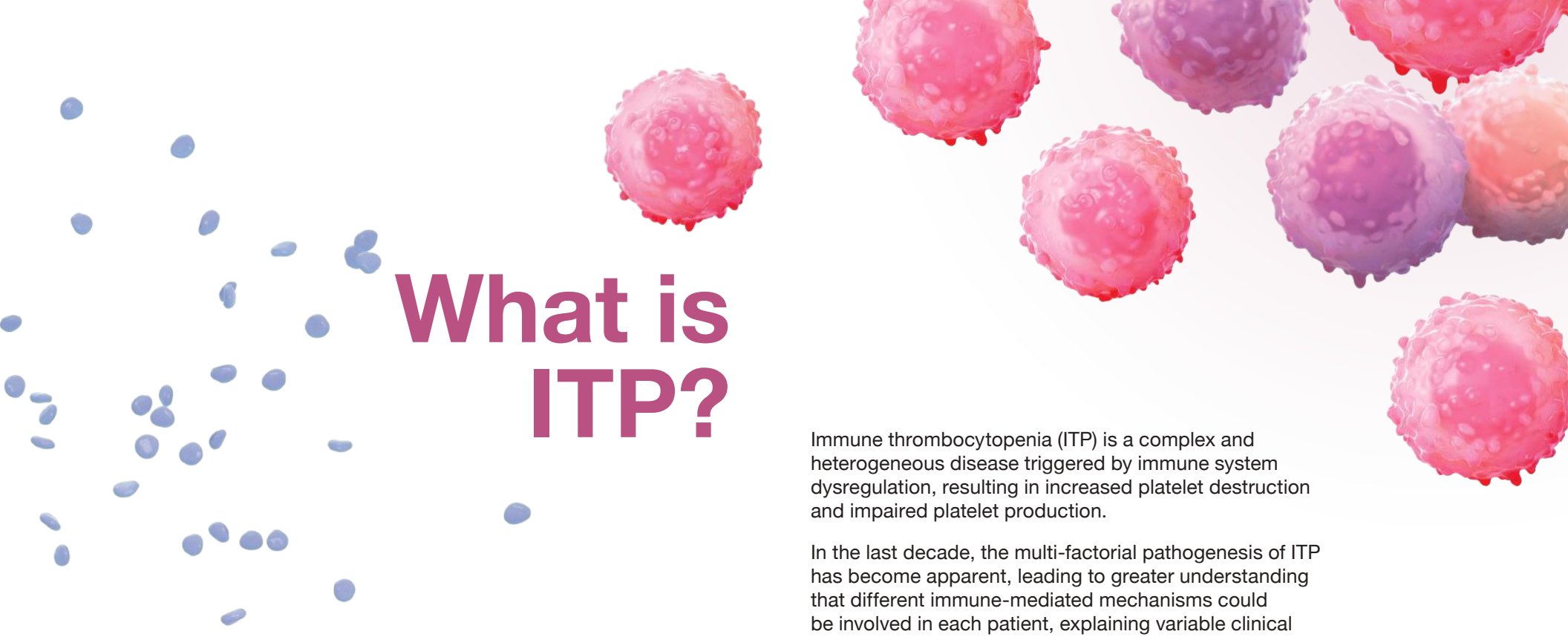
Immune Thrombocytopenia (ITP)

An Autoimmune Disorder of Diverse Pathogenesis and Clinical Presentation





What is ITP?

Immune thrombocytopenia (ITP) is a complex and heterogeneous disease triggered by immune system dysregulation, resulting in increased platelet destruction and impaired platelet production.

In the last decade, the multi-factorial pathogenesis of ITP has become apparent, leading to greater understanding that different immune-mediated mechanisms could be involved in each patient, explaining variable clinical presentation and response to therapies.[1-3]

ITP Basics

Immune thrombocytopenia (ITP) is an acquired autoimmune disorder characterized by low platelet counts (< 100 x 10^9/L) and increased risk of bleeding.[4]

Primary ITP is an isolated thrombocytopenia that occurs in the absence of other identifiable causes of thrombocytopenia.[4] Primary ITP is a diagnosis of exclusion that constitutes about 80% of diagnosed ITP patients.[2]

Secondary ITP is associated with other underlying immune disorders and constitutes about 20% of ITP cases.[2] Secondary causes include autoimmune diseases (systemic lupus erythematosus [SLE], common variable immune deficiency [CVID]), infections (HIV, Hepatitis C, H. pylori), drug-induced thrombocytopenia (DITP) and, rarely, post-vaccination syndrome (eg, measles, mumps and rubella vaccine [MMR]).[4-6]

Other non-immune related causes of thrombocytopenia may include: Chronic liver disease (CLD), hypersplenism, bone marrow suppression (for example, through chemotherapy), and pregnancy (gestational thrombocytopenia).[4-7]

Disease phases, based on disease duration from diagnosis, include:[4]

- **Newly diagnosed ITP** lasts < 3 months following diagnosis
- **Persistent ITP** lasts between 3 and 12 months after diagnosis
- **Chronic ITP** lasts longer than 12 months

Severe ITP is defined by the presence of clinically relevant bleeding of sufficient magnitude to mandate treatment, regardless of disease phase. This includes bleeding symptoms at presentation that require treatment, or occurrence of new bleeding symptoms that require additional therapeutic intervention.[4]

Burden of Disease

Incidence

Immune thrombocytopenia (ITP) affects all ages and genders, with the highest incidence in children (<18 years old) and the elderly (>60 years).[8,9]

The incidence of **ITP in adults** is estimated to be 2.9–3.9 per 100,000 person-years.[8,9] Adult ITP occurs most frequently later in life, with the median age of diagnosis being 56 years.[10] In adults, ITP rarely resolves without treatment, with up to 90% of newly diagnosed cases progressing to later stages of disease.[11]

The incidence of **pediatric ITP** is 1.9–6.4 per 100,000 person-years.[12] ITP is more likely to resolve spontaneously in children (up to 70% resolve within 6 months of diagnosis, and 80% within 12 months of diagnosis).[9,13,14] Children with ITP can present at any age, but its incidence peaks between one and five years, with a highest peak in younger boys.[9]

Primary ITP is distinct from secondary ITP.

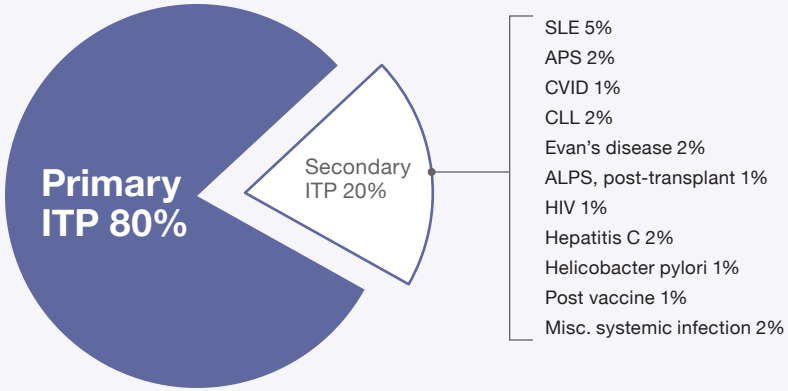


Figure 1. Estimated proportion of causes of ITP.[2] Causes of secondary ITP include: SLE, systemic lupus erythematosus; APS, antiphospholipid syndrome; CVID, common variable immune deficiency; CLL, chronic lymphocytic leukemia; Evan's syndrome; ALPS, autoimmune lymphoproliferative syndrome; HIV, human immunodeficiency virus; Hepatitis C; Helicobacter pylori; Post-vaccine; Miscellaneous systemic infection

Bleeding Risk

The main clinical burden of ITP for adult and pediatric patients is increased risk of bleeding, although presentation of these symptoms varies from patient to patient.[4]

In adult ITP, an inverse correlation has been shown between platelet counts and bleeding risk. Patients with platelet counts under 30 x 10^9/L are at increased risk of serious or life-threatening bleeding with the highest risk for those with counts under 10 x 10^9/L.[7] A similar relationship has been shown in children with chronic ITP.[15]

Most patients with ITP will experience at least one bleeding-related event (BRE) per patient-year. Newly diagnosed, elderly and patients with prior bleeding events were at higher risk for bleeding.[16]

Severe bleeding (other than intracranial hemorrhage [ICH]) occurs in **9.6%** of adults[14] and **20.2%** of children with newly diagnosed or chronic ITP.[14]

Intracranial hemorrhage (ICH) is a rare but dangerous complication in ITP. The incidence of ICH is **1–1.8%** in adults (37% presenting within the first 3 months after diagnosis),[17,18] and **0.6%** in pediatric ITP patients.[18] Prior significant hemorrhage is a risk factor for ICH.[17]

Patients with ITP frequently require hospitalization to receive ITP treatments and to manage BREs,[19] incurring substantial medical costs.[20]

Quality of Life

Adult patients with ITP may experience fear of BREs and fatigue (general, mental, physical), which may limit their daily activities.[21-25] Quality of life of patients with ITP is similar to, or worse than, that of patients with other chronic conditions such as arthritis and diabetes.[21]

Diagnosis

A diagnosis of primary ITP relies on the exclusion of alternative etiologies of thrombocytopenia, as no robust clinical or laboratory parameters are available to establish a diagnosis.[2,6] Diagnosis of ITP can be difficult due to its low incidence,[26] and due to heterogeneity in immune system perturbations that may contribute to variable clinical presentation and responses to treatment.[2]

Major diagnostic concerns in patients with suspected ITP include:[4,27]

1. Distinguishing primary ITP from other non-immune causes of thrombocytopenia, which often have a similar presentation but may require different management approaches.
2. Determining whether ITP is primary or secondary to another underlying immune condition that might also benefit from treatment.

Clinical Manifestations

Presentation varies from patient to patient, from mild bruising tendency to major bleeding. Patients can present with:

Bleeding:[12,15,28]

- Mucocutaneous: skin (petechiae, purpura), oral cavity, gastrointestinal tract
- Mucosal: conjunctival hemorrhage, epistaxis, menorrhagia, gingival, and gastrointestinal
- Intracranial hemorrhage (ICH)
- Internal bleeding

Fatigue[27]

Thrombosis[27]

One third of all adult ITP patients are asymptomatic and diagnosed by chance during work-up for other medical issues.[12,27]

Therapeutic Options

The primary goal of treatment is to sustain platelet counts that are associated with adequate hemostasis, and reduce bleeding risk with minimal side effects. Treatments should be tailored to individual patients, taking into account the patient's age, severity of illness, bleeding risk, comorbidities, lifestyle considerations, and careful evaluation of benefit/risk profile of each therapy.[4] Treatment options may include the following (presented alphabetically, without signifying order of preference):[29]

Reduce platelet destruction	
Immunoglobulin (IVIg, Anti-D)	Blocks Fcγ receptors on macrophages to prevent their recognition of autoantibody-coated platelets.[13,29]
Immunosuppression (corticosteroids)	Suppresses B and T cell-mediated autoantibody production, and impairs the ability of macrophages within the bone marrow to destroy platelets.[13]
Inhibition of B cells	Targets $CD20^+$ B cells to lower production of antiplatelet autoantibodies and block macrophage Fcγ receptors.[13,30]
Nonspecific immunosuppression (eg,azathioprine, cyclosporine)	Nonspecifically inhibits T cells to interfere with immune activation.[13]
Splenectomy	Removes the main site of platelet destruction (fewer macrophages are available to clear autoantibody-coated platelets).[13]
Syk inhibition	Impairs the FcR signaling pathway involved in phagocytosis of autoantibody-coated platelets.[32]
Stimulate platelet production	
Thrombopoietin receptor (TPO-R) agonists	Bind TPO-R to stimulate platelet production, thereby raising platelet counts to outpace excess platelet destruction.[31]

Various underlying autoimmune dysregulations, infections, genetic predisposing factors, and environmental factors have been implicated in ITP.[1] This heterogeneous framework gives rise to the varied impact on platelet turnover, propensity to bleed, and response to ITP-directed therapy.[2]

Unfold to see the big picture of ITP pathogenesis.

The Role of Thrombopoietin (TPO) in Normal Platelet Formation

Thrombopoietin (TPO)—a glycoprotein hormone produced constitutively by the liver—is the **predominant regulator of platelet production**. TPO acts by binding the thrombopoietin receptor (TPO-R) on megakaryocytes and their progenitors to stimulate development and platelet production.[1,34]

Although TPO is produced at a constant rate,[1] its level within the body is inversely correlated with platelet counts in healthy people[34] and is regulated primarily through platelet clearance in the spleen by macrophages.[1]

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Generation — *Liver*

Role in Platelet Formation — *Bone marrow*

Clearance — *Spleen*

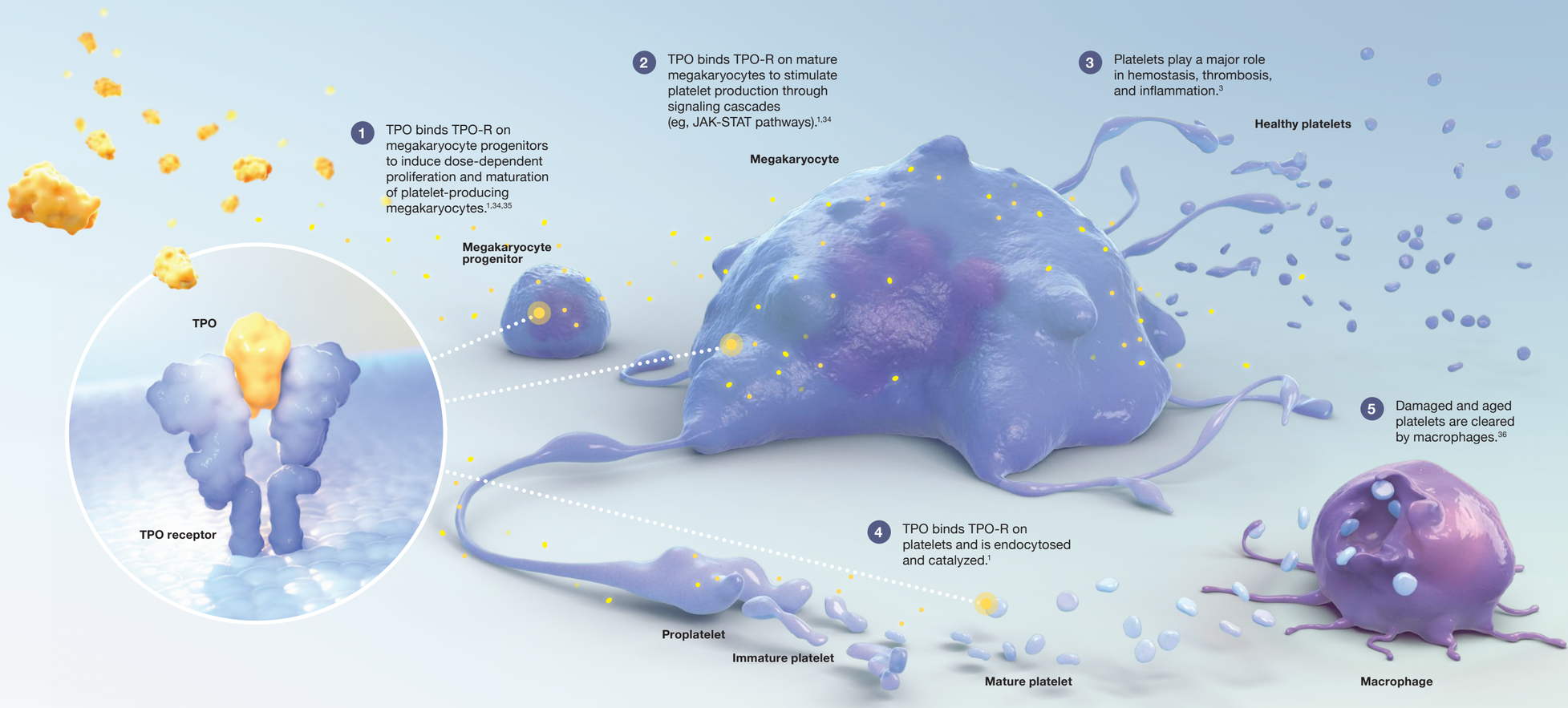
1 TPO binds TPO-R on megakaryocyte progenitors to induce dose-dependent proliferation and maturation of platelet-producing megakaryocytes.[1,34,35]

2 TPO binds TPO-R on mature megakaryocytes to stimulate platelet production through signaling cascades (eg, JAK-STAT pathways).[1,34]

3 Platelets play a major role in hemostasis, thrombosis, and inflammation.[3]

4 TPO binds TPO-R on platelets and is endocytosed and catalyzed.[1]

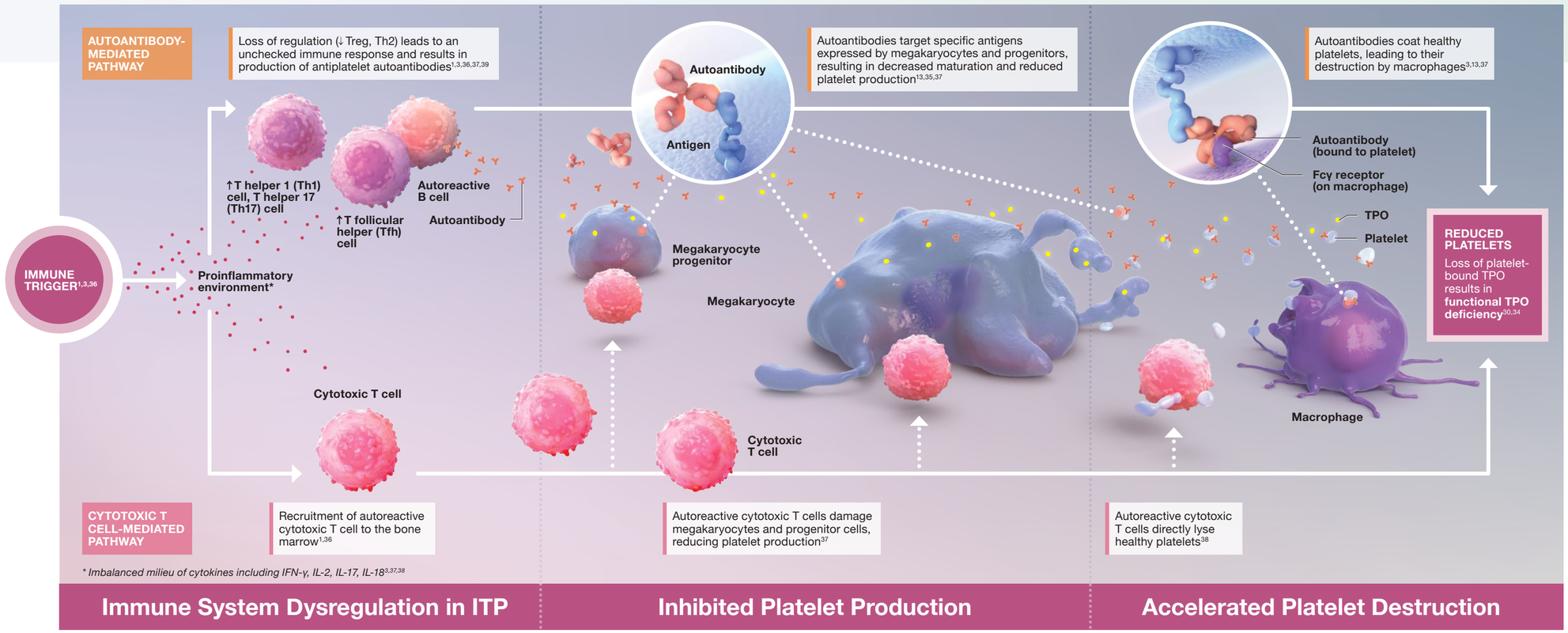
5 Damaged and aged platelets are cleared by macrophages.[36]



ITP Pathogenesis

Immune thrombocytopenia (ITP) is a highly complex autoimmune disease, triggered by immune system dysregulation. **ITP results from autoantibody- and T cell-mediated platelet destruction and impaired platelet production.**[35,37]

Due to the loss of platelet-bound TPO at all stages of the platelet life cycle, patients with ITP have **functional TPO deficiency**, with insufficient levels to overcome immune destruction of platelets.[30,34]



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