The Role of Complement Activation in Immune Thrombocytopenia: Mechanisms, Biomarkers, and Targeted Therapies

Honors Thesis

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Abstract

One of the many innate immune defenses, the complement system, functions to opsonize, or "tag" threats to the host's body for destruction, mediate inflammation, and lyse pathogens (eliminate threats). The complement system is a complicated array of proteins that must undergo various cleavages and binding steps to become functional within a host's immune system. Although this system is tightly regulated by proteins and factors, it can be involved in certain pathologies of the immune system. Immune Thrombocytopenia (ITP) is a disease characterized by autoimmune destruction of host platelets, whose destruction is heavily assisted by involvement of the various complement pathways. There are primary (pITP) and secondary (sITP) classifications of ITP determined by their pathogenesis, which vary in their responsivity to treatment. Low count of platelets that typically function in clot formation results in various symptoms, ranging from minor (petechiae) to life-threatening (intracerebral hemorrhage). In this review of the literature, an analysis of existing research and gaps in knowledge will summarize what areas of the complement system and pITP remain understudied. Sources used for this review of the literature include many recent (2022-present) and older peer reviewed articles, gathered and filtered primarily using the National Institutes of Health (NIH) database. More extensive treatment options and diagnostic techniques will provide a better quality of life for those with pITP, crucial in allowing those with thrombocytopenias to function normally and maintain active lifestyles. A better understanding of how the complement system is involved with autoimmune diseases will lead to the development of inhibitory therapies targeted towards the complement cascade.

Introduction

Innate and Adaptive Immune Systems

The immune system is a complex defense system of tissues, organs, and cells against possible threats to the human body. Lipids, proteins, carbohydrates and lipopolysaccharides are all examples of molecule types that can be antigens; substances that the immune system may recognize as non-self or foreign. Immunogens are foreign antigens that can illicit an immune response. Pathologies can occur when the immune system cannot properly distinguish host and foreign antigens, causing it to mistakenly attack its own structures. There are two branches of the immune system that respond at different rates: the innate immune system and the adaptive immune system (Medina, 2016).

The innate branch of immunity is non-specific and continuously active. Physical (integument, mucosa), chemical (enzymes, pH variability), cellular (mononuclear phagocytes, neutrophils, natural killer cells), and molecular (complement, interferons, cytokines) defenses are enacted by the innate immune system for prevention and destruction of pathogens. This branch is also

responsible for inflammation and pyrexia (fever). One of the functions of inflammation is to allow white blood cells to reach a wound or surface that was exposed to foreign antigens. Degranulation of granulocytes releases histamine and other inflammatory molecules, which increase vascular permeability and dilation. This inflammation signals innate immune cells to respond to where pathogens may be in the body. Pyrexia, or fever, is irregularly increased body temperature caused by pyrogens to stimulate immune activity and inactivate certain microbes and their toxins. Inflammatory cytokines, such as interleukin-1α and interleukin-1β, are pyrogenic (fever causing) molecules that originate from the host immune system. Fever can be induced by exogenous pyrogens, such as lipopolysaccharide (LPS) from bacteria, that originate from a source external to the host. This system responds most quickly to delay the threat, as the adaptive immune system needs more time to become active (Nomula et al., 2022).

Adaptive, or acquired immunity, is the other branch of the immune system. When lymphocytes (B-cells and T-cells) of the adaptive immune system recognize their specific antigen, they can become active. This branch can also recognize familiar antigens and thus has a mechanism for both primary and secondary exposures. This allows secondary or tertiary exposure to the same antigen to have a quicker and stronger immune response (Medina, 2016).

Acquired immunity follows a pathway of relay activation that is communicated through cytokines, or protein molecules that carry "messages" to other cells. When professional antigen-presenting cells (dendritic cells, macrophages, B-cells) engulf a foreign antigen, they can present an epitope for the T-cell on MHC class II receptor and release a cytokine signal to CD4 T-cells. This prompts activation of CD4 T-cells to become T-helper cells. Nucleated cells can also present an epitope for CD8 T-cells on an MHC class I receptor. However, CD8 T-cells and B-cells must receive their cytokine signals from the activated T-helper cells to become activated during the primary response. Activated B-cells (plasma cells secrete antibodies specific to the antigen and activated CD8 T-cells (cytotoxic T lymphocytes) release cytotoxins onto diseased cells to induce apoptosis (Nomula et al., 2022).

Complement Proteins

A molecular defense mechanism of the innate and adaptive immune systems is activation of complement proteins. There are more than 30 individual complement proteins, and one of their purposes is to aid in the killing or neutralization of pathogens. There are three pathways for the activation of complement proteins; classical, alternative, and lectin (as shown in Figure 2) (Sarma and Ward, 2010). When activated, complement proteins will undergo relay or sequential enzymatic reactions to perform their intended function. Complement proteins can perform three main functions: opsonization or “tagging” of pathogens for phagocytosis, mediation of inflammation by anaphylatoxins, and membrane lysis of a pathogen (called the membrane attack complex or MAC) (Shindo et al., 2023).

Complement proteins can play a role in the pathogenesis of autoimmune diseases, such as Immune Thrombocytopenia (ITP). Since the complement system functions to opsonize foreign

cells and form transmembrane pores leading to osmotic lysis, not being able to distinguish self from non-self can be detrimental to proper immune function. C3b, a complement protein, can mistakenly prompt phagocytosis of host cells or induce cellular lysis via the MAC in ITP. This leads to platelet destruction (Najaoui, 2011).

Classical Pathway

The first pathway of complement activation is the classical pathway. Complement first must become activated, and it becomes activated when immunoglobulin G (IgG1 and IgG3) or immunoglobulin M (IgM) recognizes their antigen binding site, or epitope. The immunoglobulins/antibodies form an antigen/antibody complex when they bind to their epitope (Sarma and Ward, 2010). C1q is a recognition protein able to recognize the antigen/antibody complex and activates the classical complement pathway when bound to the Fc domain of the antibody (Sarma and Ward, 2010).

Once activated, the classical pathway can recruit the other molecules of the C1 complex, C1r, and C1s. C2 and C4 proteins are cleaved by an activated C1s (or pentraxin, a protein that performs the same function), resulting in a C3 convertase. When this C3 convertase "C4bC2a" encounters the C3 protein, it will cleave it into C3a and C3b. C3b can perform two functions: amplification of phagocytosis as an opsonin, or binding to C3 convertase to form a C5 convertase. The C5 convertase enzymes are C3bBbC3b (from the alternative pathway) and C4bC2aC3b. Each of the three pathways can form C5 convertases, which cleave C5 proteins into C5a and C5b. Similarly to the cleaved products of C3, the C5b can bind more molecules (C6 and C7) to become a binding site (C5bC6C7) for C8 and many C9 molecules. The many C9 proteins in the C5b-9 complex form a ring embedded in the bacterial membrane, causing cellular lysis (Sarma and Ward, 2010).

Alternative Pathway

The alternative pathway of the complement system is initiated by a slow and continuous "tick over" hydrolyzation reaction of C3 + H_2O, even in the absence of pathogens. The resulting C3b protein from the hydrolyzation reaction can bind to a foreign or non-self-epitope. Factor B, a serine protease, can bind to C3b and then be quickly cleaved off by Factor D to form the "C3bBb" C3 convertase enzyme. This convertase will amplify the complement deposit of activated C3b on the surface of a pathogen, allowing it to greatly function as an opsonin. When C3b proteins bind to the "C3bBb" C3 convertase itself, it will become a "C3bBbC3b" C5 convertase and function similarly to the C5 convertase from the classical pathway when it encounters C5 proteins. Unlike the classical pathway, though, this C5 convertase can also cleave C3 to create the C3a (anaphylatoxin) and C3b (opsonin) molecules. Anaphylatoxins function to induce an inflammatory response, attracting phagocytes, and releasing histamine. Opsonins also attract phagocytes by depositing on the surface of non-self or dead antigens (Sarma and Ward, 2010).

Lectin Pathway

The lectin complement pathway is activated by mannose, a simple sugar found on the surface of bacteria. Mannose-binding lectin and ficolin are proteins that will individually bind to mannose, further activating mannose-associated serine protease 2 (MASP2), another serine protease that acts similarly to an activated C1q of the classical pathway. C4 is cleaved into C4a and C4b, and C2 is cleaved into C2a and C2b by MASP2. C4b and C2a bind to each other to form the same C3 convertase as the classical pathway, C4bC2a. From this point, the classical and lectin pathways similarly form the C5 convertase "C4bC2aC3b" when C3b binds to C4bC2a. This convertase can cleave C3 to make the C3a anaphylatoxin and C3b opsonin or follow the C5 pathway to perform the MAC. MASP-2 deficiencies can prevent activation of this pathway downstream, influencing susceptibility to infections (Sarma and Ward, 2010).

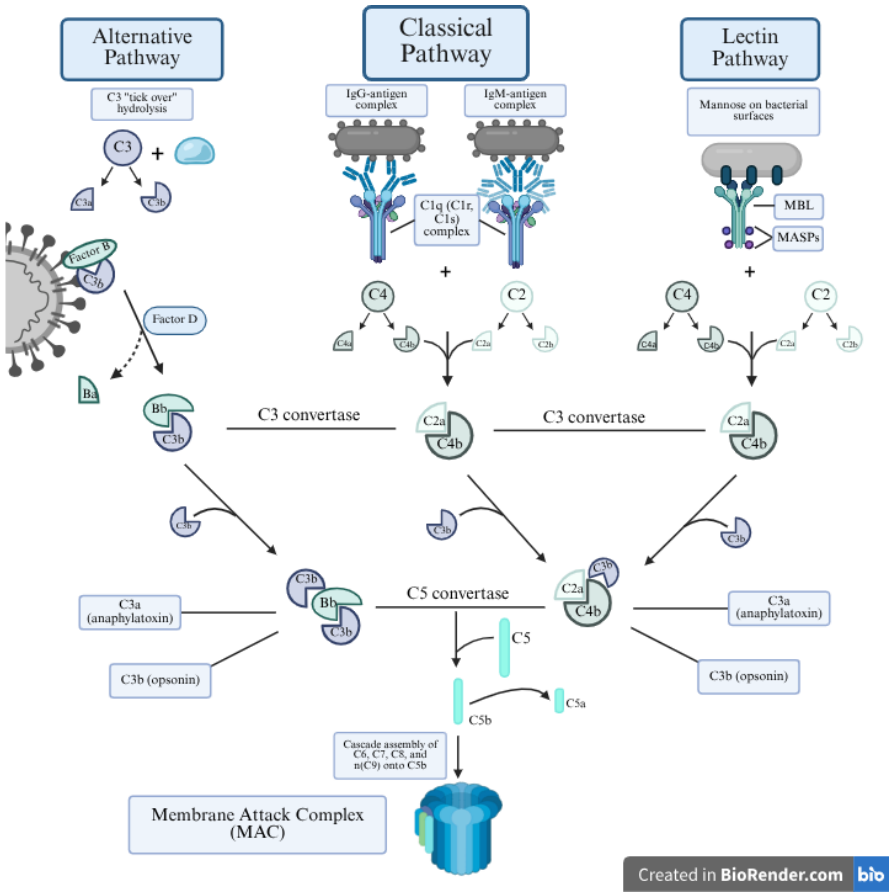

Figure 1: The complement activation cascade, defined by the alternative, classical, and lectin pathways. Inhibitory factors are not included. Created in https://BioRender.com

Immune Thrombocytopenia

Pathophysiology

Immune thrombocytopenia (ITP) is an autoimmune disease that targets the host's own blood platelets. Blood platelets are cells that circulate in the bloodstream, functioning to clot and plug wounds in vessels and tissues. Patients with ITP have platelet counts of <100,000/μL, where normal platelet counts are within the 150,000-350,000/μL range. With low platelet count as seen in patients with ITP, there are easily ruptured capillaries (petechiae), purpura (bleeding underneath the skin), and uncontrolled hemorrhages (rapid blood loss) (Pietras et al., 2024). There is a primary, idiopathic type of ITP, where the root cause cannot be clinically determined. Secondary ITP is associated with underlying conditions like connective tissue diseases (CTDs) or autoimmune diseases (SLEs), but also can be triggered by medications, cancers, or infection. More abnormalities in the complement system have been discovered relating to primary ITP (Shindo, et. al). ITP can occur in both chronic (lasting 12 months or longer) and acute forms (lasting less than 12 months) (Pietras et al., 2024). Becaus this review focuses on immune dysregulation rather than secondary triggers, emphasis is placed on mechanisms relevant to primary ITP unless otherwise specified.

The lifecycle of a platelet begins with its creation, or thrombopoiesis. There are cells that originate from the red bone marrow, called hemocytoblasts. These cells are immature hematopoietic stem cells that can differentiate into all blood cells (erythrocytes, leukocytes, and thrombocytes). Megakaryocytes are the cells that stem from hemocytoblasts that ultimately function for thrombopoiesis. Thrombopoietin (TPO) is a hormone that is produced by the kidneys, bone marrow, and liver, that stimulates hemocytoblast maturation into megakaryoblasts, and eventually megakaryocytes. Megakaryocytes will produce thrombocytes that will circulate in the blood system for ~7-10 days, tending to wounded tissue and vasculature.

The normal function of antibodies in the adaptive immune system is to neutralize, destroy, or tag pathogens. Autoimmune diseases will occur when the immune system mistakes its own cells as foreign, or non-self. The result of this is the memory B-cell/plasma cell synthesis of self-targeted immune cells (autoantibodies) that result in destruction of the host cells or tissues. Complement proteins – specifically the classical pathway – can be involved in the formation of autoantibodies for self-targeted platelet destruction or platelet clearance that occurs in the spleen and liver (Pietras, et al., 2024).

Autoantibodies are synthesized to bind to the platelet membrane glycoproteins (GPs), and these opsonized platelets are then phagocytized and destroyed. Platelet GPs function to adhere to the subendothelial matrix, or intravascular surface, and are also involved in platelet cohesion. GP types that are commonly targeted by complement proteins in ITP are GPIIb/IIIa, GPIb-IX, and (less commonly) GPV complexes. Autoantibodies against these platelet GPs are not found in non-thrombocytopenic individuals (Shindo et al., 2023).

ITP diagnosis is difficult due to a myriad of potential causes of low platelet count. Viral infection stimulates the immune system to create antibodies, but viral antigens can present similarly to platelet surface glycoproteins, signaling their removal and the development of ITP. Platelet destruction can be a result of defects in the production of platelets (thrombopoiesis) from the megakaryocytes of bone marrow cells, an increase in desialylated platelets from hepatocytes, and autoantibodies from lymphocytes. Medications and malignancies can cause ITP. The destructor of blood platelets that drives this paper is the highly active reticuloendothelial system (Allegra et al., 2023).

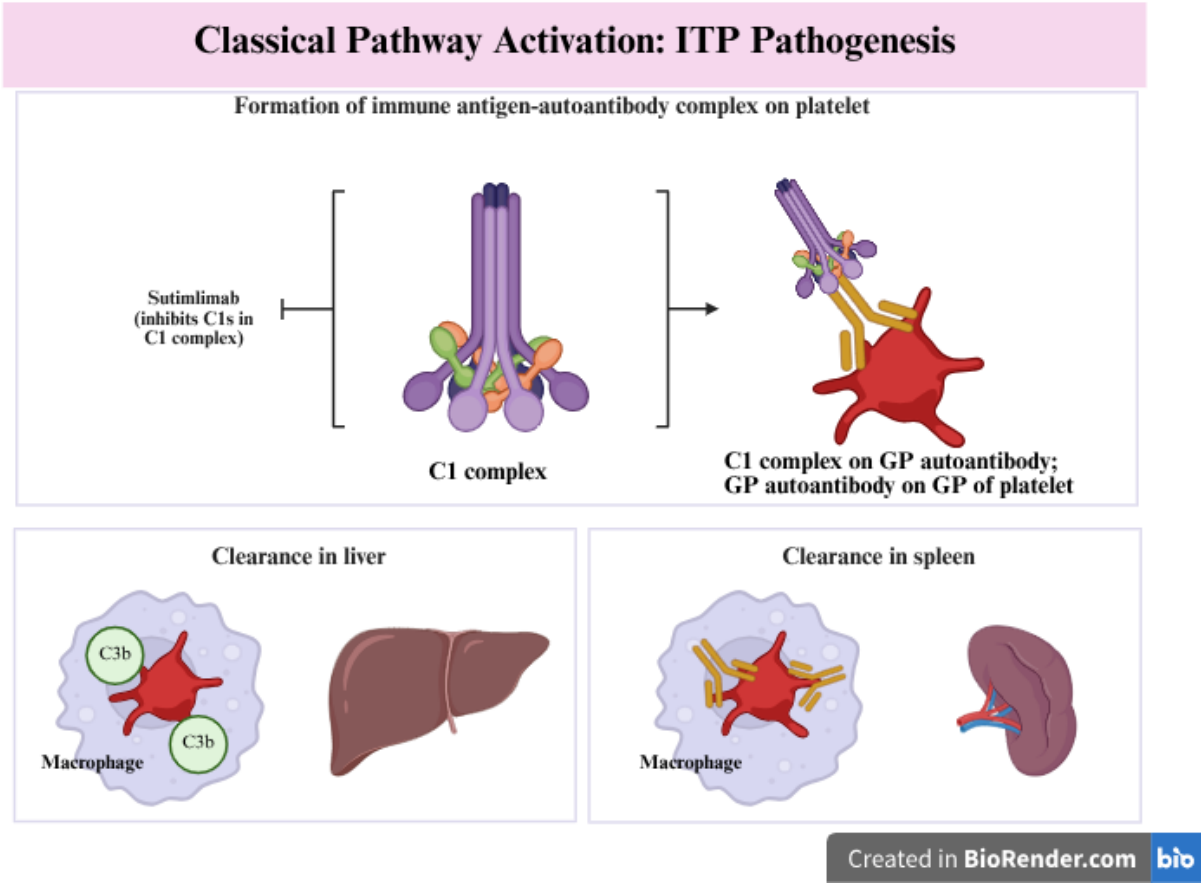

Figure 2: Pathogenesis of ITP from involvement of the classical complement system. Includes inhibitory effect that Sutimlimab has on formation of C1 complex. Formation of the C1-autoantibody-platelet complex (top) for complement-initiated platelet clearance in the liver (left) and spleen (right). Created in https://BioRender.com.

Existing Research

Complement Involvement in Immune Thrombocytopenia

Abnormalities in the complement system include fluctuations in complement protein count in the blood serum and the amount of complement deposited on platelet membranes. Studies that

continuously monitor the activity of the complement system found that most patients with primary ITP demonstrate lower levels of C3, C4, and CH50 (Total Hemolytic Complement; a test that measures complement activity), meaning the immune system is over-utilizing these proteins before the body can create more. ITP patients have greater deposition/opsonization of C1q, C4d, and (slightly heightened) C3b complement proteins on platelet membranes compared to a healthy individual. The greater opsonization of platelets results in heightened binding rate of platelet GPIIb/IIIa and GPIb/IX autoantibodies, ultimately resulting in the destruction of platelets. Additionally, the C5b-9 complement protein involved in the membrane attack complex is found more frequently on platelets of patients with ITP (Shindo et al., 2023).

Anti-platelet autoantibodies are produced to bind to GPIIb/IIIa and GPIb/IX, which can inhibit the megakaryocyte maturation system and increase programmed cell death (apoptosis) in the bone marrow, where thrombopoiesis occurs. Additionally, the activation of the classical pathway by platelet-bound IgG1 and IgG3 antibodies and thus increased C3b deposition strengthens the complement's involvement in ITP. C3b opsonization increases the platelet removal mechanisms in the liver, leading to decreased platelet count alongside the primary platelet clearance from the spleen (Allegra et al., 2023).

Pathological Biomarkers and Diagnostic Testing

The American Society of Hematology (ASH) considers purpura (bleeding under the skin) and isolated thrombocytopenia (less than 100,000/μL of platelets, with normal levels of other blood cells) to be a basis for diagnosis (Pietras et al., 2024). However, the screening of patients suspected to have ITP is primarily done by exclusion, since ITP pathogenesis can have many different origins. Monitoring patient respondence to different treatment types can aid in locating the origin of the disease, such as the reticuloendothelial system, thrombopoiesis, or platelet clearance (Pietras et al., 2024).

Since antiplatelet autoantibodies that bind to GPIIb/IIIa and GPIb/IX are found in patients with ITP, performing tests that target those specific antigens can be a diagnostic biomarker. In a study from 1997, platelet-associated and free plasma autoantibody counts were collected in counts per minute (cpm) and optical density (OD) (Berchtold et al., 1997). The antibody assays used in this study from eight different labs were the Monoclonal Antibody-specific Immobilization of Platelet Antigens (MAIPA) Assay, the Immunobead Assay (IBA), and the Modified Antigen Capture Assay (MACA). The purpose of these tests is to quantify the presence of antigen-autoantibody complexes in human blood plasma with the use of monoclonal, or synthetically made, antibodies (Pietras et al., 2024).

The MAIPA assay is the most reliable of the autoantibody assays for ITP, because it makes it possible to identify glycoprotein GPIIb/IIIa or GPIb/IX autoantibodies. The MAIPA assay is performed using intact platelets, for the strongest example of surface platelet glycoproteins. Patient serum (that may have antibodies specific to the test GP) is added onto the intact isolated platelets, which will form antigen-antibody complexes. Monoclonal (laboratory-made) animal

antibodies (mAb) against the target GP are then added to the serum, which will also from antigen-antibody complexes. These samples are then washed to isolate and capture the animal mAb-GP-patient antibody complexes. Once the complexes are isolated, adding an enzyme-labelled antibody that recognizes the human autoantibodies (IgG or IgM) will create a visible color change (Kiefel, 1992). The reliable detection of these specific autoantibodies is a basis for the diagnosis of ITP. Certain tests that are also specific to the glycoprotein autoantibodies fluctuate greatly in their sensitivity and are not reliable as a diagnostic test. Patients with ITP can also demonstrate synthesis of different autoantibodies (other than GPIIb/IIIa or GPIb/IX) that contribute to their disease (Allegra et al., 2023).

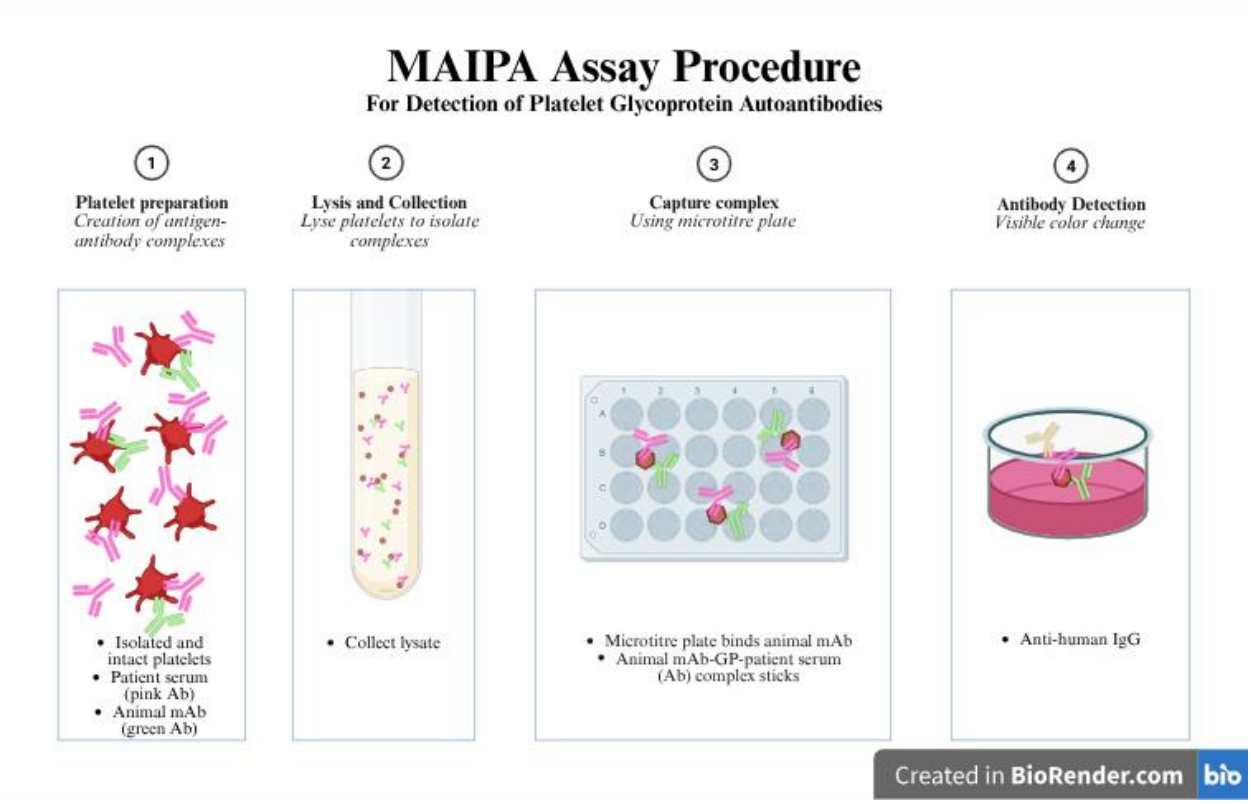

Figure 3: Basic MAIPA assay Procedure for platelet auto-antibody detection. This method is sensitive and specific enough for diagnosis of autoimmune thrombocytopenia. Created in https://BioRender.com

Another test that helps physicians infer the root of thrombocytopenia is a measurement of the immature platelet fraction (IPF), which is the percentage of young platelets in the total platelet count. This value is used to distinguish between consumptive thrombocytopenia, or low platelet count due to insufficient central thrombopoiesis. Thrombopoiesis in the bone marrow becomes more active to compensate for increased platelet destruction, which can be proven by a high IPF percentage in the already low platelet count (~11.7%-13.80% in ITP patients compared to a 3.00% control) (Allegra et al., 2023).

Complement Biomarkers

Certain ITP biomarkers have been heavily associated with the complement system due to their inhibitory or stimulatory effects. β-2-glycoprotein 1 (2-GPI) was found to be of decreased levels in the plasma samples of patients with ITP. 2-GPI is a protein that protects against complement mediated hemolysis by accelerating C3 and C5 protein breakdown and inhibiting the membrane attack complex (MAC). 2-GPI also downregulates c-Jun N-terminal kinase (JNK) phosphorylation, which functions to transcribe normal cellular stress responses, inflammation, and apoptosis (Allegra et al., 2023).

Therapeutic Implications

Treatment for patients with ITP is managed case by case, depending on their medical history, timeline of ITP diagnosis, bleeding severity, and individual platelet count. In first line cases of severe or critical bleeding (often with platelet count<10,000 μL), emergency intravenous immunoglobulin G (IVIG) is administered. This medication quickly elevates platelet count by deactivating the Fc receptor on macrophages, which functions to recognize platelets that are tagged with autoantibodies. IVIG is typically administered alongside a platelet transfusion and glucocorticoids (methylprednisolone, dexamethasone), which assist in lowering autoantibody count. Second-line therapies include thrombopoietin receptor agonists (TPO-RA) to stimulate platelet neogenesis in the bone marrow, rituximab to destroy the immune system's B cells, and splenectomy to stop platelet clearance in the spleen (Pietras et al., 2024).

Complement Related Treatment

Splenectomy has been highlighted as an effective treatment method for ITP cases with high deposition of C3b on platelet surface membranes. This is because the spleen is the primary site of destruction for complement-tagged thrombocytes. In a test trial of a recently developed monoclonal antibody, sutimlimab, 9 of 12 patients demonstrated a sustained increase in platelet count across the treatment plan. Sutimlimab acts to inhibit C1s of the classical complement pathway (Shindo et al., 2023).

Key Findings

Gaps in Knowledge

Many studies have been performed highlighting the role that the classical complement pathway plays in pathogenesis of Immune Thrombocytopenia, but there remain gaps in knowledge associated with all complement pathways, treatment targets, and reliability of diagnostic tests.

Complement Pathways

The classical complement pathway is the most prevalent pathway found to contribute to primary ITP. This claim is reinforced by the effectiveness of sutimlimab, a monoclonal antibody that binds to the C1s protein of the C1 complex in order to inhibit the classical complement pathway. There is high effectiveness in treatments that decrease C3b opsonization and platelet clearance, like splenectomy. However, ficolin, a protein that binds to mannose to activate the lectin

complement pathway, was found to be of lower serum levels in patients with ITP. This indicates that the activation of the lectin pathway plays a role in ITP pathogenesis. Additionally, the active binding mechanism of ficolin causes damage to the platelet membrane, separate from the clearance mechanism or destruction to the platelets that occurs further into the pathway (Allegra et al., 2023).

Despite these conclusions, the literature fails to highlight the lectin pathway's collaboration or individual effect on ITP development and severity. There are medications available that aim to inhibit MASPs (such as narsoplimab and EVO24L), preventing the cleavage of the C4 and C2 complement proteins in the lectin pathway (Bongoni et al., 2025 and Schoettler et al., 2025). However, these medications are not mentioned in relation to ITP treatment across the sources used in this review. This is likely due to the similarities in complement protein products (C3 convertases) across the classical and lectin pathways. Since many cases of primary ITP become refractory, all potential pathogenesis, including the lectin and alternative pathways, should be screened in diagnosis to increase the efficacy and specificity of treatment (Allegra et al., 2023).

Complement Regulatory Factors

Another complement-related abnormality that was highlighted, but underdiscussed as a target for treatment options, were the many complement regulatory factors. Regulatory proteins are essential in protecting host cells by keeping the complement cascade from over-activating and becoming highly destructive towards host cells. These regulatory proteins can be divided into two groups, regulators of the classical/lectin pathways, and regulators of the alternative pathway (Janeway et al., 2001).

Classical/Lectin Pathway Regulators

There are four main regulatory proteins that act on similar steps in the classical and lectin pathways. C1 inhibitor (C1-INH) covalently binds to the activated C1s/C1r proteins of the classical complement pathway, removing it from the C1q protein. Since the C1s protein can only cleave C2 and C4 when bound to C1q, C1-INH decreases the amount of time C1s has to cleave those proteins. C1-INH also restricts spontaneous activation of C1. Acting similarly in the lectin pathway, C1-INH binds to MASP-1/2 to prevent cleavage of C4 and C2. Decay-accelerating factor (DAF) inhibits the C3 convertase formation by displacing C2b from C4b. Complement receptor 1 (CR1) and C4-binding protein (C4BP) create the same result as DAF, only binding C4b to displace C2b. (Janeway et al., 2001 and Sarma et al., 2011).

Alternative Pathway Regulators

The DAF and CR1 are also regulators of the alternative pathway, but function to displace Bb from C3b and inhibit C3 convertase formation. Factor H competes with Factor B to bind to C3b. If Factor B binds, C3bB is created and the complement cascade proceeds. If Factor H binds, it inhibits C3 convertase formation and inhibits the pathway. It can also displace Bb from a formed C3 convertase. Performing the opposite effect, properdin,

(also known as Factor P) helps to stabilize the C3 convertase of the alternative pathway (Janeway et al., 2001 and Sarma et al., 2011).

The final major regulator acts on the membrane attack complex, resulting from all three of the complement pathways. Protectin (also called CD59) is a membrane protein on the cell's surface that inhibits the binding of many C9 proteins to the C5bC6C7C8 complex (Janeway et al., 2001 and Sarma et al., 2011).

Supplementing Factor H has been a recent developing therapeutic development in treatment of complement-related conditions, which is derived from purified human plasma or produced as recombinant Factor H. There is also production of CR1 for therapeutic use, which was found to increase C3 levels and decrease C5b-9 levels in one patient. Drugs that aim to target Factor D, and thus inhibit the alternative pathway, are currently in development. Despite the number of complement regulatory proteins, there have been limited studies demonstrating various degrees of success of these medications in inhibiting complement involvement of conditions. Furthermore, these studies address other conditions with major complement involvement (chronic kidney disease, age-related macular degeneration, hereditary angioneurotic edema), not ITP (Thurman and Quintrec, 2016).

Diagnostic Tests

Diagnostic tests for the detection of platelet glycoprotein autoantibodies vary greatly in their specificity and sensitivity. A variety of studies describing tests for glycoprotein-specific autoantibodies follow differing assay procedures, as well as different controlled variables (subject, type of sample, ranges for testing analysis) (Allegra et al., 2023). Allegra et al. describes standardization of a specific assay and diagnostic ranges, as well as greater scientific development in autoantibody assays to be the most effective strategies to move closer to accurate diagnostic testing of ITP.

Conclusion

When looking towards the future of ITP, development of diagnostic tests and treatments are the next steps for assuring patients a fair quality of life. Although rare, this disease affects humans of all ages, with cases from pediatric to geriatric age groups. Many complications in treatment and thrombocytopenia can lead to morbidity or mortality, and immunosuppressive treatments put patients at a higher risk of other complications, like infection (Pietras et al., 2024). Paying mind to how each pathway of the complement system can be heavily involved in the pathogenesis and severity of the disease allows a targeted therapeutic approach to each special case (Shindo et al., 2023).

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