Immune mediated thrombophilia: Role of innate immunity

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Abstract: Objectives: The aim of this work is to illustrate immune system, hemostasis, thrombosis, inflammation, relations between (hemostasis and immune system, inflammation and immune system) and finally relation between immune system especially the innate immunity and thrombosis. **Data Sources:** Medline database s (PubMed, Medscape and Science direct). **Article Selection:** This article studied the roleof the immune system especially the innate immunity in hypercoagulable state. **Data Synthesis:** Short reviews were made on pathophysiology of hybercoagulability associated with innate immune system dysregulation. **Conclusion**: Despite the innate immunity plays an important role in our immune system, yet its dysregulation is accompanied by different blood diseases, and further elucidation of the underlying defects in its pathways is awaited to develop pathogenesis (hypercoagulability).
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1. Introduction:

Hemostasis resembles a physiologic process that confines blood to the vascular spaces, maintains the fluidity of blood, and stops bleeding when injury to a vessel occurs. We can consider that hemostasis is a complex process based upon interactions among the blood vessels and supporting tissues, endothelial cells, platelets, plasma coagulation proteins, physiologic protease inhibitors and fibrinolytic system. Alteration in hemostatic system can result in significant pathologic bleeding or clotting **(1).**

Thrombophilia is defined as abnormality in blood coagulation process that increases the risk of thrombosis (blood clots in vessels). Such abnormalities can be identified in 50 % of people who have episode of thrombosis (such as deep vein thrombosis in the leg) that was not provoked by other causes. Most of these patients develop thrombosis in the presence of an additional risk factor **(2)**.

We found studies conducted that reveal arelation between the complement system, the main column in innate immunity, and thrombosis. Complement system activation plays an important role in thrombosis. It was cleared that C3 and C5 acts as critical intermediaries linking pathogenic antiphospholipid antibody to white blood cell adhesion and development of thrombosis. So, we can conclude that prevention of complement system associated thrombophilia now is based on introduction of antibodies against C3 or C5**(3).**

For a long time, it was known certain autoimmune disorders, such as (systemic lupus erythematosus, inflammatory bowel syndrome, and behcets syndrome) are linked to an increased risk of vascular thromboembolism and pulmonary embolism. The list of autoimmune diseases or immune mediated disorders linked to increased risk of thromboembolism has grown longer and longer and now also includes (rheumatoid arthritis, celiac disease, hyperthyroidism and wegnersgranulomatosis). Another medical disorders like, antiphospholipid syndrome, hemolytic uremic syndrome, heparin induced thrombocytopenia, thrombotic thrombocytopenic purpura, and disseminated intravascular coagulopathy also are included**(*4*).**

2. Materials and Methods:

Data sources:

We reviewed papers on the influence of innate immunity dysregulation on thrombosis from Medline databases which are (Pub Med, Medscape, and Science Direct). We used complement/ regulation/ complement receptors/ complement dysregulation/ hemolytic uremic syndrome/ Antiphospholipid syndrome/ thrombotic micro-angiopathies. In addition, we examined references recruited from the specialist databases EMF-Portal (http://www.emf-portal.de).

Article Selection:

All the reviews are independently assessed for any updated information about innate immunity dysregulation in blood diseases. They are included if they fulfilled the following criteria:

Inclusion criteria of the published studies:

Published in English language.

Focused on innate immunity dysregulation.

Discussed the relation between innate immunity dysregulation and blood diseases.

Data Synthesis:

Short reviews are conducted on different blood diseases associated with innate immunity dysregulation.

3. Results:

The initial search presented 295 articles, papers and journals about the title of the article with the key words mentioned; extraction was performed, including assessment of quality and validity of papers.122 published articles met the inclusion criteria and are assessed for internal validity. Studies concerning with innate immunity dysregulation in blood disorders were collected; each study was reviewed independently; obtained data is rebuilt in new language and arranged in topics through the article.

4. Discussion:

Immune system

Immune system is the system that protects the body from foreign substances, cells, and tissues by elicitation of the immune response. It includes the thymus, spleen, lymph nodes, special deposits of lymphoid tissue (as in the gastrointestinal tract and bone marrow), macrophages, lymphocytes including the B cells and T cells, and antibodies***(5)***.

Host defense against invading microbial pathogens is elicited by the immune system, which involve two components: innate immunity and acquired immunity. Both components of immunity recognize invading microorganisms as non-self, which triggers immune responses to eliminate them. To date, both components have been characterized independently (***6***)

Types and characters of immunity:

All of usis born with innate (or natural) immunity, a type of general protection. Many of the germs that affect other species don't harm us. For example, the viruses that predisposed to leukemia in cats or distemper in dogs don't affect humans. Innate immunity works both ways because some viruses that make humans ill such as the virus that causes HIV/AIDS don't make cats or dogs sick***(7)*.**

Innate immunity also involves the external barriers of the body, like the skin and mucous membranes (like those of nose, throat, and gastrointestinal tract), which are the first line of defense in preventing diseases from entering the body. If our defensive wall is broken (as through a cut), the skin attempts to heal the break quickly and special immune cells on the skin attack aggressively the invading germs**.** Adaptive or active immunity, which develops throughout our lives, involves the lymphocytes and develops as people are exposed to diseases or immunized against diseases through vaccination.***(8)*.**

Passive immunity is "borrowed" from another source and it remains for a short time. For example, antibodies in a mother's breast milk provide a baby with temporary immunity to diseases the mother has been exposed to. This can help protect the baby against infection during the early years of childhood. Everyone's immune system is different, so some people never seem to get infections, whereas others seem to be sick all the time. As people get older, they usually become immune to more germs as the immune system comes into contact with more and more of them. That's why adults and teens tend to get fewer colds than kids. As we know their bodies have learned to recognize and immediately attack many of the viruses that cause colds(**7*)*.**

The immune system can distinguish between SELF and NON-SELF tissue. It is important because it prevents the system from destroying itself. It is not static but grows and changes with exposure and experience, the system is highly specific. For example, an antibody can distinguish between a P on a molecule and an O substitute. This is both beneficial and bad in that it does not allow for cross protection. There are some notable exceptions to this precept; e.g. identification of smallpox vs. cowpox, and finally the system has memory. The second time an antigen is encountered; the immune system is faster and more effective. Ten (10) to fourteen (14) days after the primary exposure, the immune response peaks. Three days after secondary exposure, the immune response peaks. **(8*)*.**

Inflammation and immunity:

Inflammation is part of the complex biological response of body tissues to harmful stimuli, such as pathogens, damaged cells, or irritants. It resembles a protective response involving immune cells, blood vessels, and molecular mediators. The function of inflammation is to eliminate the initial cause of cell injury, clear out necrotic cells and tissues damaged from the original insult and the inflammatory process, and to initiate tissue repair***(9)*.**

Inflammation can be classified as either *acute* or *chronic*. *Acute inflammation* is the initial response of the body to harmful stimuli and is achieved by the increased movement of plasma and leukocytes (especially granulocytes) from the blood into the injured tissues. A series of biochemical events propagates and matures the inflammatory response, involving the local vascular system, the immune system, and various cells within the injured tissue. Prolonged inflammation, known as *chronic inflammation*, leads to a progressive shift in the type of cells present at the site of inflammation, such as mononuclear cells, and is characterized by simultaneous destruction and healing of the tissue from the inflammatory process.(***10*****).**

Hemostasis and thrombosis:

Haemostasis is responsible for maintenance of blood in fluid state within the blood vessels and prevents excessive blood loss after vascular injury. Haemostasis depends on balanced interactions between different components: blood vessels, platelets, plasma coagulation factors and fibrinolytic system. Any exaggeration or deficiency in one of these components may lead to either hemorrhage or thrombosis.***(11).***

Thrombosis is defined as formation of a blood clot in the circulatory system during life. It may be arterial or venous thrombi. Arterial thrombi are composed primarily of platelets. Whereas fibrin is the predominant component of venous thrombi**.*(12).***

Virchow first postulated that a triad of conditions predispose to thrombus formation. This triad is applied to both arterial and venous thrombosis**.** Virchow triad should consider (abnormal vessel wall, abnormal blood flow, and finally abnormal blood constituents as abnormalities in platelet function, coagulation and fibrinolysis**.*(13)*.**

Furthermore, a variety of antibodies have been found in the pathogenesis of venous and arterial thrombosis in a variety of syndromes including antiphospholipid syndrome(APS), thrombotic thrombocytopenic purpura (TTP), and heparin induced thrombocytopenia with or without thrombosis (HIT/T), hymolitic uremic syndrome (H.U.S).***(14)***

Antiphospholipid syndrome

Antishospholipid syndrome is a form of immune mediated thrombophilia, presenting as recurrent thrombotic events and pregnancy loss, in association with positive laboratory tests for antiphospholipid antibodies (aPL) in the form of lupus anticoagulant (LA) or anticardiolipin antibodies (aCA)**.*(15).***

The prevalence of (aPL) is 1-5 % of young, healthy people, this prevalence increases in elderly, especially in those with chronic diseases. In SLE, the prevalence of (aPL) is much higher and may reach up to 30% of patients**.** Several hypotheses have been proposed to explain the cellular and molecular mechanisms by which (aPL) promote thrombosis.***(16).***

Heparin induced thrombocytopenia(HIT)

Heparin-induced thrombocytopenia (HIT) is a common immune mediated disorder which occurs in 1% to 5% of patients treated with unfractionated high-molecular weight heparin. In the typical case of HIT, the patient developed mild to moderate thrombocytopenia or a 40% drop in the platelet count 5 to 10 days after beginning heparin therapy. About 20% to50% of these patients develop life threatening thrombi.***(17).***

There is increasing evidence indicating that HIT is caused by formation of antibodies to a complex of platelet factor 4(PF4) with heparin that activate platelets, monocytes and vascular endothelium leading to thrombin formation, which in turn amplifies the prothrombotic cascade**.*(18).***

There are two types of HIT. Type 1 HIT presents within the first 2 days after exposure to heparin and the platelet count normalizes with continued heparin therapy. Type 1 HIT is a non immune disorder that results from the direct effect of heparin on platelet activation, type 2 HIT is an immune-mediated disorder that typically occurs 4-10 days after exposure to heparin and has life- and limb-threatening thrombotic complications. In general medical practice, the term HIT refers to type 2 HIT***(19).***

Thrombotic microangiopathy (TMA)

Abbreviated **TMA**, is a pathology that results in thrombosis in capillaries and arterioles, due to an endothelial injury. It may be shown in association with thrombocytopenia, anemia, purpura and renal failure. The classic TMAs are hemolytic uremic syndrome and thrombotic thrombocytopenic purpura. Other conditions with TMA include atypical hemolytic uremic syndrome, disseminated intravascular coagulation, scleroderma renal crisis, malignant hypertension.(*20).*

A-Thrombotic thrombocytopenic purpura

Thrombotic thrombocytopenic purpura is an uncommon multisystem disorder; it may be associated with predisposing conditions such as pregnancy, cancer, bone marrow transplantation and HIV infection. An abnormal interaction between the vascular endothelium and platelets tends to produce thrombosis, endothelial proliferation and micro-angiopathichaemolysis.***(21).***

Abnormalities in von willebrand factor (vWF) have roles in pathogenesis of TTP in many patients. Plasma exchange with fresh frozen plasma

replacement has profoundly affected the prognosis of acquired TTP, decreasing the mortality from greater than 90% to approximately 20% in current series. Many aspects including the pathogenesis and the diagnostic work up of the clinical syndromes associated with immune mediated thrombosis remains to be elucidated***(22)***.

Thrombotic thrombocytopenic purpura was originally characterized by a pentad of thrombocytopenia, micro angiopathic haemolytic anemia (MAHA), fluctuating neurological signs, renal impairment and fever, often with insidious onset. However, TTP can present without the full pentad; up to 35% of patients do not have neurological signs at presentation, renal abnormalities and fever are not prominent features. The revised diagnostic criteria state that TTP must be considered in the presence of thrombocytopenia and (MAHA) alone***(23).***

B-Hemolytic uremic syndrome (HUS)

Hemolytic-uremic syndrome (HUS) is a clinical syndrome characterized by progressive renal failure that is associated with microangiopathic (Coombs-negative) hemolytic anemia and thrombocytopenia. HUS can be considered the most common cause of acute kidney injury in children and is increasingly recognized in adults***(24).***

Gasser et al first described HUS in 1955. In 1988, Wardle described HUS and TTP as distinct entities, but in 1987, Remuzzi suggested that these two conditions are varied expressions of the same entity. Confirmation that HUS and TTP are clearly different diseases, despite their clinical similarities, followed the discovery of the von Willebrand factor (vWF)–cleaving metalloprotease ADAMTS-13 (A disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13). Researchers subsequently recognized the etiologic link between TTP and congenital deficiencies of ADAMST-13 or formation of acquired antibodies to ADAMST-13.***(25).***

Hemolytic-uremic syndrome (HUS) is classified into two main categories, depending on whether it is associated with Shiga-like toxin (Stx) or not. Shiga-like toxin is so called because it was initially identified in studies of *Shigelladysenteriae*, but this toxin is also elaborated by *Escherichia coli*.***(26).***

Typical HUS (Shiga-like toxin–associated HUS [Stx-HUS]) is the classic, primary or epidemic form of HUS. Stx-HUS is largely a disease of children younger than 2-3 years and often results in diarrhea (denoted D+HUS). One fourth of patients present without diarrhea (denoted D-HUS). Acute kidney injury occurs in 55-70% of patients, but they have a favorable prognosis, and as many as 70-85% of patients recover renal function.***(27)***

C-Disseminated intravascular coagulopathy (DIC):

Disseminated intravascular coagulation (DIC) is characterized by systemic activation of blood coagulation that results in generation and deposition of fibrin, leading to micro vascular thrombi in various organs and contributing to multiple organ dysfunction syndrome (MODS). On the other hand Consumption and subsequent exhaustion of coagulation proteins and platelets (from ongoing activation of coagulation) may induce severe bleeding***(28)***

DIC exists in both acute and chronic forms. Acute DIC develops when sudden exposure of blood to procoagulants (eg, tissue factor [TF], or tissue thromboplastin) generates intravascular coagulation. Compensatory hemostatic mechanisms are quickly overwhelmed, and, as a consequence, a severe consumptive coagulopathy leading to hemorrhage develops.(***29)***

Acute DIC occurs in obstetric calamities such as placental abruption (abruptio placentae) and amniotic fluid emboli. Amniotic fluid is shown to be able to activate coagulation in vitro, and the degree of placental separation correlates with the extent of the DIC, suggesting that leakage of thromboplastinlike material from the placental system is responsible for the occurrence of DIC. ***(28)***

Abnormalities of blood coagulation parameters are readily identified, and organ failure frequently results in chronic DIC which reflects a compensated state. It may develop when blood is continuously or intermittently exposed to small amounts of TF. Compensatory mechanisms in the liver and bone marrow are not overwhelmed, and there may be little obvious clinical or laboratory indication of the presence of DIC. Chronic DIC is more frequently observed in patients with solid tumors and in those with large aortic aneurysms***(28).***

Conclusion:

Increasing knowledge about the immune system has taught us about both the protective and harmful roles in blood disease. In the course of this review, it has become clear thatinnate immunity dysregulation has been early recognized to be a central event in hypercoagulability, and peripheral markers for complement activation. TLRs and NETs must be tested routinely for different idiopathic and acquired blood diseases. An increasing number of inherited blood diseases due to acquired factors with genetic predisposed for innate immunitydysregulation. Therapeutic strategies for reestablishing innate immunity regulation must be implented.

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