



Coevolution of the coagulation and immune systems

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Abstract

Background Higher organisms rely on the coagulation and immune systems to fight disease-causing pathogens and other foreign invaders in the body. Coagulation has an important role as a barrier against foreign bodies, including bacteria, viruses, and protozoa. The protective responses associated with the coagulation and immune systems can protect the host organism from a wide range of pathogens, such as viruses, parasites, fungi, and even bacteria.

Aim The purpose of this paper was to review available research on the evolution of the coagulation and immune systems.

Materials and methods The study analyzed evidence from studies that have examined the coagulation and immune systems in the context of evolutionary processes. The articles used in the review were identified from the PsycINFO, CIHAHL, PubMed, Web of Science, and CIHAHL databases.

Results Studies have shown that both the coagulation system and the early immune system originated from the same initial system in early organisms. Some researchers argue that hemocytes from lower organisms are the common link from which the immune system and coagulation system developed.

Discussion and conclusion Simple organisms have hemocytes that can carry out both immune response and coagulation processes. Evolution led to the separation of these processes in higher organisms. Furthermore, this divergence resulted in the emergence of thrombocytes and plasmatic coagulation subsystems. These observations explain why there is some form of overlap between immunity and hemostasis, even in advanced organisms such as vertebrates. Several phenomena in clinical medicine related to coagulation and immunity can be explained by this overlap and are consistent with the hypothesis of the coevolution of coagulation and the immune system.

Keywords Coevolution · Coagulation · Immune system · Complement system

Introduction

The immune and coagulation systems play key roles in the survival of vertebrates, which have remarkable adaptive immune systems that can successfully recognize pathogens and initiate a protective response [1–3]. The protective response mechanism can protect the organism from a wide range of pathogens, such as viruses, parasites, fungi, and even bacteria [4–6]. Importantly, the adaptive immune

system is so effective that it can accurately recognize pathogens that previously invaded the body and repel a second invasion [7–9]. In other cases, the immune system initiates new responses when a strange and lethal pathogen interferes with bodily function. Furthermore, the innate immune response uses self-defense to protect an organism from pathogens.

These protective systems are hereditary in nature and may differ between individuals. Despite this, the adaptive and innate immune responses play a key role in limiting and preventing the invasion of pathogens [1, 2]. The blood coagulation system plays an important role as a barrier against foreign bodies, including bacteria, viruses, and protozoa (see Fig. 1).

This delicately balanced process relies on extracellular proteins that protect tissues and cells in the body. Similar to the immune system, the coagulation system has undergone

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Examples of common structures in hemostasis and inflammation

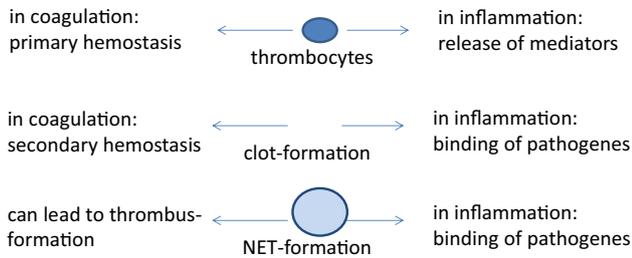


Fig. 1 This diagram exemplarily shows the coevolution of coagulation and inflammation. The same structures and cascades have functions in inflammation and in hemostasis

significant evolution and development in response to events that occur around the world and to various habitats [1].

Previous studies have attempted to depict how the immune and coagulation systems have developed through evolution and the manner in which such changes have improved the survival of organisms in a given habitat [1]. The purpose of this review is to examine available evidence on the evolution of the coagulation and immune systems.

Methodology

As noted earlier, the aim of this study is to review research evidence on the evolution of the coagulation and immune systems.

Thus, this study involved the analysis of evidence and results from previous reports that have examined coagulation and immune systems in the context of evolutionary processes. Because our study is based on a secondary approach to research, it was imperative to locate articles that could help address the current research problem. The articles were retrieved from different electronic databases that provide information on different health and medical issues. These databases included PsycINFO, CIHAHL, PubMed, Web of Science, and CIHAHL. Search terms and phrases such as “coagulation,” “immune system,” “evolution,” “adaptive immune system,” and “vertebrate blood coagulation” were used to identify articles that were relevant to this research topic.

Evolution is a complex process that has attracted the attention of researchers and experts around the world. Furthermore, several studies have been performed over the years to explore the evolution of various systems, such as the coagulation and immune systems. However, because evolution tends to be a continuous process, it is imperative to gather up-to-date evidence that could provide a clear picture of how the coagulation and immune systems have developed.

To this end, the search was limited to articles published in the five electronic databases between 2007 and 2017.

Results

The search conducted in this study revealed that several reports have examined the evolution and development of the coagulation and immune systems. A review of these studies showed that researchers regard the coagulation and immune systems to be critical for the survival of organisms in a competitive habitat where they are also exposed to a wide range of pathogens and threats. In addition, these systems have allowed organisms to survive and develop in complexity and numbers. Further review showed that evolution has played a critical role in the development and function of the coagulation and immune systems. Thus, attempts have been made to examine the exact manner by which the two systems have evolved and how such changes help organisms survive in various habitats.

Evolution of the coagulation system

Coagulation is the process through which blood changes from a liquid to a gel or semisolid clot, resulting in blood loss cessation and hemostasis [9, 10]. Furthermore, coagulation can prevent further damage to tissues and facilitate the repair of damaged areas. The coagulation system relies on a wide range of mechanisms, such as platelet activation, aggregation, adhesion, and fibrin maturation, to create clots and prevent further blood loss [11].

Evidence has shown that coagulation in vertebrates, particularly in humans, is a balanced process involving extracellular proteins that influence clot formation. Furthermore, this process entails a delicate balance between the requirement for blood to flow and the desire to form a polymeric gel at the wound site to prevent further blood loss [10, 11]. Thus, questions have always arisen regarding when and how this complex process evolved. Researchers have reported that most of the proteins in the body are related to each other via gene duplication [11, 12]. The relationships between the proteins involved in the blood clotting process and the manner in which they are influenced by gene duplication have been an area of interest. Furthermore, attempts have been made to explore how evolution has affected protein–protein interactions as well as the assemblage of factors critical to clot formation.

Evolution of the immune system

The principal elements and mechanisms of the adaptive immune system are known. Researchers have indicated that the immune system comprises a lineage of lymphocytes that

can successfully identify, recognize, and respond to different antigenic determinants derived from pathogens and toxins [13, 14]. Research has shown that human beings evolved and developed superior immunological memory and innate immunity to thwart and survive recurrent infections and pathogens [15, 16].

At times, however, the immune mechanism and processes show changes [17]. The first changes occur when the fetus transitions into an infant, which is then followed by significant changes when an individual matures into an adult [18, 19]. In other cases, immunological memory is abated and becomes less important as an individual grows older [20]. These events show that the immune system, similar to the coagulation system, undergoes evolution [20–22]. Some studies have shown that the immune system has been molded by evolution in response to acute infections and the pathogens that people have encountered at different points during their lives.

Origin and evolution of the immune and coagulation systems

Virtually every type of organism has at least one method of defense that helps fight against foreign pathogens and disease-causing organisms [23–25]. In the case of advanced animals such as vertebrates, the defense entails a complex group of actions and responses that identify, isolate, and eliminate the disease-causing organism. This protective system has continuously evolved from simpler defense mechanisms and has undergone profound changes in response to the prevailing environment [20, 26].

While examining the evolutionary path that has been followed by the defense mechanism in such animals, researchers often focus on different organisms, genes, and systems. It is, however, worth noting that in many organisms, the defense mechanism comprises tissues and cells that may not lend themselves to fossilization; therefore, it is not easy to trace the evolution of immunity from paleontological records [27–29]. However, because all animals have some ability to recognize self and to identify and repel foreign substances and organisms, it is possible to examine the immune capacity of these animals based on their relative position in the evolutionary tree [6, 30, 31]. Furthermore, extrapolating the reasonable evolutionary path and history of defense systems and mechanisms in various organisms is conceivable.

Discussions on the defense mechanism in most organisms often revolve around immunity and hemostasis. Traditionally, these two systems have been viewed as distinct and separate. This may be true in higher organisms such as vertebrates, but in lower organisms, immunity and hemostasis are mediated by the same cells known as hemocytes. Jenne et al. stated that both the coagulation system and the early immune system originated from the same initial system

in early organisms [32]. The author added that it is from hemocytes in lower organisms that the immune system and coagulation system developed [32]. This concept explains why there is some overlap between immunity and hemostasis, even in advanced organisms such as vertebrates. Thus, an understanding of the evolution of the coagulation and immune systems starts with an examination and review of hemocytes and how they have contributed to the emergence of these two systems.

Hemocytes are primordial immune cells with the ability and capacity to initiate cellular and humoral immune responses in the body. These cells can identify foreign organisms and invaders of the body through several recognition patterns and scavenger receptors [33–35]. When subsets of hemocytes are activated, they rapidly degranulate and release antimicrobial peptides, such as anti-LPS factor, tachyplesin, and big defensin [32, 36].

These molecules can bind to, sequester and kill invading organisms and pathogens. Research further shows that hemocytes have excellent phagocytic abilities. Once these cells bind to the foreign pathogen, they rapidly internalize the invaders and shield the host from further damage [36–38]. Researchers have also argued that some hemocytes can produce compounds and substances such as melanin to encapsulate and kill the invading organism [32, 39–41].

In addition to exerting these vital immune functions, hemocytes have been shown to release different procoagulation factors, such as factors C and G, that can influence the coagulation process following tissue injury [42]. These factors usually interact with hemolymph proteins in the presence of calcium ions to initiate the coagulation process. In this regard, it is evident that coagulation is a process mediated by the cross-linking of various soluble proteins with different receptors on the surface of hemocytes [32, 43, 44].

This process results in the generation of large cellular aggregates that contribute to tissue healing [32]. Importantly, coagulation is not always initiated by tissue damage alone [45, 46]. In other cases, the presence of molecules that can be detected by the components of the hemolymph can initiate the coagulation process; one such molecule is LPS [46, 47]. In such cases, the resulting clot will trap and eventually kill the invading pathogen [48–50]. This process further shows the overlap between immunity and hemostasis and provides evidence on the possible evolutionary path preceding the coagulation and immune systems.

The available evidence showing the overlap between immunity and hemostasis alludes to a common origin and possible differentiation that occurred as a result of evolution. Jenne et al. argued that evolution led to the splitting of immunity and hemostasis into two unique systems that became specialized to carry out unique functions in the body [32]. The two major components that have been identified in previous studies are thrombocytes and plasmatic coagulation

[32, 51, 52], both of which have unique features and characteristics that allow them to effectively carry out their functions. Furthermore, both components help the body respond to invading organisms and repel disease-causing organisms. Thus, they play a critical role in safeguarding the health and well-being of organisms.

Thrombocytes

Compared to the lower organisms where the hemocytes are responsible for both hemostasis and immunity, higher organisms such as vertebrates have developed multiple cell types to carry out these functions. Thrombocytes, also known as platelets, were the first subset to develop as a result of the evolution of hemocytes. They are small anucleated cells present in the circulation and play a significant and specialized role in protecting the body from foreign invasion.

These cells are usually formed in the bone marrow from megakaryocytes and play a critical role in thrombosis and hemostasis. Although attempts have been made to separate hemostasis and immunity in higher animals and for different cell types, available evidence suggests that this may not be feasible. The argument is that thrombocytes express various cell surface immune receptors as well as a wide range of adhesion molecules that allow them to participate in both the immune response and hemostasis. Thus, the ability of thrombocytes to modulate, activate, and participate in a wide range of immune and coagulation processes makes this group of cells unique [53].

Evidence shows that thrombocytes express a broad spectrum of immune receptors that can aid the immune response. Some of the commonly identified receptors include Toll-like receptors (TLR1-9), complement receptors, and coreceptors. In other cases, these cells release signaling molecules that play an important role in the immune response. Most of these receptors are functional after they engage in ligand binding.

The downstream effects of ligand binding to their target receptors include the identification of pathogens and the initiation of a response to neutralize them [54]. In this process, the cells protect the body from disease-causing organisms and maintain good health. Research further shows that there are three types of vesicles in thrombocytes: dense bodies, α -granules, and lysosomes [55, 56]. The contents of these vesicles facilitate vasoconstriction, proinflammatory cytokine production, inflammation modulation, and platelet aggregation [57, 58].

In addition, the vesicles can release enzymes such as collagenase and β -glucuronidase. These enzymes are critical in the immune response because they support pathogen clearance, extracellular matrix breakdown, and platelet thrombi clearance.

Thrombocytes also facilitate the coagulation process. Under normal circumstances and conditions, thrombocytes circulate in the body in the form of quiescent discs [59]. However, upon damage to the blood vessel endothelium as well as the underlying structures, these cells will adhere to exposed extracellular matrix components such as collagen. Chemical damage, changes in shear stress, partial blocking of blood vessels and mechanical injury can damage the endothelium [32, 60]. During hemostasis, there are distinct phases that define the thrombocyte response. First, the cells will adhere to the damaged endothelium. Second, the shape of the cells may change from the disc-like structure to a spiny sphere due to surface exposure of membrane invaginations [60]. Third, the cells recruit other thrombocytes to the injured site and aggregate to form a thrombus. Finally, the contents of the intracellular granules are released, which augments the thrombotic process.

Thrombocytes show that there is a clear overlap between immunity and hemostasis. The same cells and molecules are used for both. This similarity results in immune functions of several coagulation molecules and cells. A short overview of this overlap is given in Table 1.

Plasma-based coagulation

The second major process that emerged as a result of evolution was the plasmatic coagulation system. This system relies on coagulation factors and proteins to change the state of blood from liquid into a gel or semisolid clot to prevent further blood loss following injury [61]. The coagulation factors and proteins are critical components of the plasmatic coagulation system and lead to a complex set of reactions that result in the successful conversion of soluble fibrinogen into insoluble strands of fibrin [62]. A number of coagulation factors and proteins involved in plasmatic coagulation have been identified, and their roles and functions have been examined [62, 63]. These factors play unique roles in the body to facilitate the coagulation process. For instance, Factor III is regarded as a procoagulant glycoprotein that can initiate coagulation *in vivo*. These proteins can be activated through vascular injury, activation of tissue factor, sepsis, inflammation, hypoxia, and malignancy.

Evidence has shown that most coagulation proteins and clotting factors are precursors of a group of proteolytic enzymes [42, 62, 64]. These proteolytic enzymes usually circulate in an inactive form in the body. The proteins usually undergo post-translational modification that allows them to bind calcium and other cations involved in the coagulation process [45, 65]. This activity explains why the administration of vitamin K antagonists, such as warfarin, or vitamin K deficiency can hinder the coagulation process [42].

The plasmatic coagulation system in higher animals, such as vertebrates, often consists of a wide range of enzyme

Table 1 Examples of the immunologic functions of coagulation molecules

Coagulation molecule or coagulation cell	Immunologic function
TREM-1 receptor on neutrophils stimulated through platelets	Release of inflammatory chemokines
Tissue factor	Activation of PAR2 Activation of mitogen-activated protein kinase family
Tissue factor pathway inhibitor 1/2	Antimicrobial activity
High molecular weight lininogen	Precursor of peptides with antimicrobial activity
Bradykinin	Inflammatory mediator (chronic)
Factor Xa	Activation of PAR receptors Precursor of peptides with antimicrobial activity
Thrombin	Activation of PAR receptors Precursor of peptides with antimicrobial activity
Activated protein C	Activation of PAR1 receptor
Neutrophil extracellular traps (nets)	Immobilization of pathogens Activation of the coagulation system Adhesion, activation, and aggregation of platelets
Thrombocytes	Release chemokines and immune mediators
Clot formation	Can be used to immobilize pathogens has developed from a pathogen immobilization

This table shows the close relationship between the coagulation system and the immune system

activation events where a serine protease acts on both the profactors and proenzymes [66]. Furthermore, it involves a cascade of responses related to proteolysis. The ultimate result of the chain reactions and responses is the polymerization of fibrin and the formation of a clot [67]. Similar to processes within immune systems, the processes that define the plasmatic coagulation system are protective in nature [60]. In particular, these processes usually help prevent excessive blood loss [68, 69]. It is, however, worth stating that aberrant plasmatic coagulation can also contribute to the formation of unwanted blood clots in blood vessels and lead to disability and death [42, 69].

The liver is the main producer of humoral coagulating factors, while most immune cells originate from bone marrow. The liver is important for both the coagulation system and for the immune system, as this organ hosts most immune cells, but not the reproduction of immune cells, in humans. Because immune cells originate from stem cells, these stem cells have been translocated into the bone marrow during evolution. The reason for this translocation of the stem cells into the bone marrow is most likely due to the improved protection from UV and gamma radiation given by the bones. The stem cells are very important for the human body and for the correct function of the immune system and need to be protected from radiation.

Evidence from patient care and clinical chemistry

Evidence for the coevolution of coagulation and immune system also comes from everyday clinical practice as well as from laboratory medicine. Thus, solid explanations for clinically

relevant laboratory phenomena and laboratory observations are available. Laboratory assessment of blood counts revealed that the number of thrombocytes increases when patients have an infection. This is relatively common in everyday clinical practice and shows the link between and coactivation of the coagulation and immune systems.

Further interplay of both systems is observed in hemolytic uremic syndrome (HUS) and thrombocytopenic thrombotic purpura (TTP). In these diseases, not only activation of the plasmatic-based coagulation but also the complement factors (e.g., C3) are decreased, which indicates that both systems are activated in parallel and that the complement and coagulation systems are interdependent.

A very important coactivation of both systems also occurs upon inflammatory “meltdown” during sepsis. In this process, bacteria enter the bloodstream, which leads to activation of the complement system; this often serves as a complication to the activation of the plasmatic coagulation system.

This phenomenon can be explained by the foreign molecules present on the surface of the pathogens (bacteria). However, the plasmatic coagulation and complement systems are blocked by the same inhibitor, namely, the C1-esterase inhibitor. If there is a decrease in the levels of the C1-esterase inhibitor, both systems will be activated.

Conclusion

The concept of evolution has been used to trace and understand the history of organisms and plants and identify changes that have occurred over the years. Life on earth

started millions of years ago, and it is imperative to state that the similarities observed by present-day organizations tend to indicate the existence of common ancestors from which all species diversified via evolution. These ancestors include single-cell organisms, archaeobacteria, and eukaryotes.

Evolution has also been used to examine the development and specialization of the coagulation and immune systems in different animals. The purpose of this paper was to examine evidence on the evolution of these systems. This review highlights the hypothesis that the coagulation and immune systems originated from the same system in early organisms. Simple organisms have hemocytes, which can carry out both immune response and coagulation processes. Later, evolution led to the separation of the coagulation and immune functions in higher organisms.

This shift led to the emergence of thrombocytes and plas-matic coagulation subsystems. Although thrombocytes can carry out both coagulation and immunity functions, the plas-matic coagulation system specializes in primary hemostasis.

With the hypothesis of coevolution, we can also explain several phenomena found in patient care (clinical medicine).

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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