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Bi-directional activation of inflammation and coagulation in septic neonates

Antonio Del Vecchio [a,*], Mauro Stronati [b], Caterina Franco [a], Robert D. Christensen [c]

[a] Division of Neonatology, Neonatal Intensive Care Unit, Di Venere Hospital, Bari, Italy
[b] Neonatal Intensive Care Unit, Maternal-Infant Department, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
[c] Women and Newborns Program, Intermountain Healthcare, Salt Lake City, Utah, USA

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ABSTRACT

Neonatal sepsis is frequently accompanied by significant and sometimes life-threatening coagulopathy. More complete understanding is needed of the molecular and cellular mechanisms underlying the interaction of the inflammatory and hemostatic systems. Such information may help focus future studies toward novel ways to improve the outcome of neonates who develop septic coagulopathy.

1. Introduction

Complex and balanced physiological systems exist for regulating inflammation and hemostasis. Overlap in these two intricate systems occurs because the vascular endothelium and platelet–endothelial and neutrophil–endothelial interactions are central to both systems [1]. Because of this overlap in regulatory mechanisms, it is understandable that activation of inflammatory pathways due to sepsis can lead to significant pathological changes in coagulation. Indeed, neonatal sepsis is often accompanied by significant and sometimes life-threatening coagulopathy [2].

Among ill and preterm neonates, sepsis and coagulopathy are common and often devastating pathological entities, with the two conditions frequently occurring simultaneously. However, the exact mechanisms involved in the inflammation/hemostasis interaction, and means of preventing morbidity from coagulopathy during neonatal sepsis, remain largely undiscovered. This review will focus on developmental aspects of inflammation and coagulation, with the intent of describing a basis for future experimental and clinical studies aimed at improving the outcomes of neonates who develop coagulopathy during sepsis.

2. Inflammation, sepsis, and coagulation

Invasion of microbial pathogens into normally sterile tissues results in activation of the innate immune response, triggering a chain of events including the production and secretion of cytokines and chemokines and the activation of macrophages and monocytes. The activated proinflammatory and anti-inflammatory cytokine network is closely linked with other physiological systems including the coagulation–fibrinolytic system, production and regulation of acute-phase and heat-shock proteins, interactions of neutrophils with vascular endothelium and interactions of platelets with vascular endothelium, hypothalamic–pituitary–adrenal axis activation, cell apoptosis, increased nitric oxide (NO) production, and the oxidant-antioxidant pathways [3] (Fig. 1).

Gram positive and Gram negative bacteria, viruses, fungi, and protozoa, can immediately affect the coagulation system of neonates. An example of such is the significant link between elevated markers of inflammation at birth (elevated C-reactive protein and elevated leukocyte left shift) and an elevated fibrinogen concentration [4]. Since fibrinogen, central to coagulation, is an acute phase reaction, it is predictable that during perinatal infection the fibrinogen concentration initially rises. However, fibrinogen can be consumed when overwhelming sepsis proceeds to DIC, thus the fibrinogen concentration can increase very early during infection and then fall as the infection evolves into septic coagulopathy.

Recent studies show a bidirectional cross-talk between the systems regulating inflammation and coagulation, and some of the mechanisms involved in this cross-talk are becoming clear. For instance, after microbial invasion, cellular pattern recognition receptors (PRRs) such as Toll-like receptor (TLR)-4 and CD-14, become expressed on the surface of monocytes and macrophages. When bacteria interact with these PRRs, proinflammatory cytokines are released. At this stage coagulation also becomes activated, although the mechanisms by which this occurs are just beginning to be understood [3].

Three pathways have been proposed by which bacteria and proinflammatory cytokines activate coagulation: (1) cytokine induction of tissue factor (TF) expression and TF-mediated thrombin generation, (2) inflammation-induced down-regulation of the protein C (PC) system, and (3) inhibition of fibrinolysis. These three changes are expected to result in a net procoagulant state with increased fibrin deposition [1].

As inflammation initiates coagulation, so the coagulation can activate inflammation. An example of the latter occurs when the procoagulant enzyme thrombin activates the acute inflamma-

* Corresponding author: Antonio Del Vecchio, Division of Neonatology, Neonatal Intensive Care Unit, Di Venere Hospital, Via Ospedale Di Venere 1, 70121 Bari, Italy. Tel.: +39 080 5015012; fax: +39 080 5015016.
E-mail address: a.delvecchio@asl.bari.it (A. Del Vecchio).

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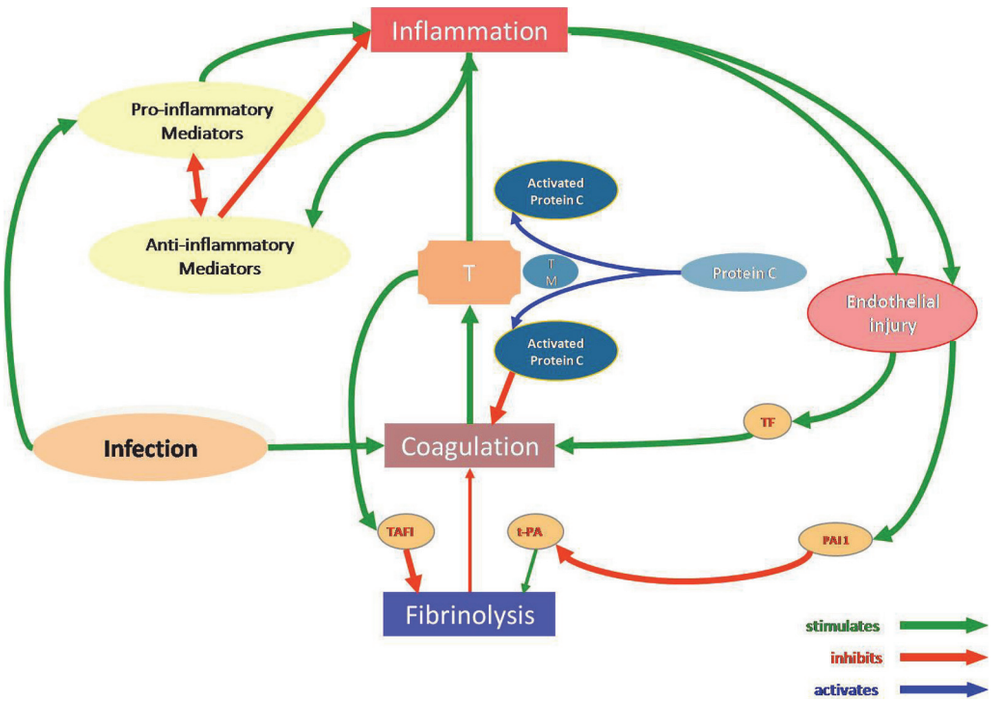

Fig. 1. Schematic representation of the interaction between infection, inflammation and coagulation. Invasion of the host by microbial pathogens causes the response of the innate immune system which activates a chain of events that results in the production and secretion of cytokines and chemokines involving other homeostatic pathways, including coagulation and fibrinolysis. The onset of sepsis seems to result from a combination of uncontrolled cascades of coagulation, fibrinolysis and inflammation. PAI, plasminogen activator inhibitor; T, thrombin; TAFI, thrombin activatable fibrinolytic inhibitor; TF, tissue factor; TM, thrombomodulin; t-PA, tissue plasminogen activator.

tory response by way of intracellular signal transduction initiated through protease activated receptors (PARs) on endothelial cells. It is apparent that activation of hemostasis and inflammation can synergize, in ways still being discovered. The apparent purpose of this synergy is to facilitate the recognition and elimination of invading pathogens and to limit the damage done during this process [3].

Inflammation up-regulates TF synthesis in endothelial cells, monocytes/macrophages and dendritic cells, and induces TF expression on the surface of mononuclear cells, endothelial cells and parenchymal cells, including heart, lung, brain and kidney. The responsible cytokines appear to be predominantly IL-6, TNFα, IL-1, and IL-12. TF binds and activates factor VII which, initiating the extrinsic clotting pathway via factor X, and catalyzes the cleavage of prothrombin (factor II) to thrombin, cleaving fibrinogen to fibrin.

IL-1 and TNFα can work in an additional way as procoagulant cytokines. Furthermore, leukocytes, endothelial cells, vascular smooth muscle cells and platelets can shed microparticles of TF in the plasma that are implicated in activation of both coagulation and inflammation in sepsis. These microparticles have the role of transferring TF to cells that do not produce TF and can be considered part of a mechanism of amplification of signals generated during sepsis.

Furthermore, the interaction between platelets, leukocytes, and endothelium can produce a pro-coagulant effect enhanced by inflammation. Endotoxin, pro-inflammatory mediators including platelet activating factor, and thrombin itself activate platelets and granulocytes that further stimulate monocyte TF expression.

Severe infection impairs the function of the PC system, as a result of decreased synthesis of protein C by the liver, increased consumption of protein C, and impaired activation of protein C by diminished thrombomodulin expression on endothelial cells. Thus the widespread formation of fibrin is further facilitated. PC activated form (APC) inhibit thrombin generation through irreversible inhibition of factors Va and VIIIa, and also acts as inhibitor of fibrinolysis by enhancing the function of two fibrinolysis inhibitors: thrombin activatable fibrinolytic inhibitor (TAFI) and plasminogen activator inhibitor type I (PAI-1) [5].

Fibrinolysis is considerably involved in the inflammation–coagulation balance. Pro-inflammatory cytokines stimulate PAI secretion by endothelium, and the consequent depression of the fibrinolytic system impairs fibrin removal within circulation. Even though defective late fibrin removal may exacerbate organ damage in sepsis, the inflammation-induced inhibition of fibrinolysis can be considered a rational part of the host defense [5].

Since a crosstalk between inflammation and coagulation exists, the activation of the coagulation system can in turn notably affect the inflammatory response. Proteases released during activation of the clotting cascade have been reported to maintain and reinforce inflammatory reactions, and, during severe sepsis, contribute to multiple organ failure and death.

Components of the thrombin/fibrin pathway can also modulate inflammation, as they can affect the inflammatory cell responses. In most cases, endothelial cells, platelets and monocytes/macrophages become activated and secretion of IL-1 and IL-8 increases [6].

The PC pathway, independently of its anticoagulant function, also has anti-inflammatory effects; it has been recently reported that APC acts as a therapeutic drug for severe sepsis [5].

In addition, we can suppose that in the course of severe infection or sepsis patients with thrombophilia may suffer from more severe coagulopathy, and sepsis result in a more serious clinical course and an adverse outcome.

3. Fetal and neonatal development of the coagulation system

Hemostasis evolves *in utero* and physiologic concentrations of coagulation proteins gradually increase with gestational age. In the 1980s Andrew introduced the term “developmental hemostasis” to describe the age-related physiological changes of the coagulation system as it develops progressively from fetal, to neonatal, to pediatric, to adult systems [7].