Review Article

Complement and coagulation cascades in trauma

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Trauma remains a major cause of death throughout the world, especially for patients younger than 45 years. Due to rapid advances in clinical management, both in the acute and prehospital settings, trauma patients survive devastating injuries at unprecedented rates. However, these patients can often face life threatening complications that stem from the robust innate immune response induced by severe hemorrhage, leading to further tissue injury rather than repair. The complement and coagulation cascades are key mediators in this disordered reaction, which includes the development of trauma-induced coagulopathy. There is increasing evidence that cross-talk between these two pathways allows rapid amplification of their otherwise targeted responses and contributes to overwhelming and prolonged systemic inflammation. In this article, we summarize the initial steps of innate immune response to trauma and review the complex complement and coagulation cascades, as well as how they interact with each other. Despite progress in understanding these cascades, effective therapeutic targets have yet to be found and further research is needed both to improve survival rates as well as decrease associated morbidity.

Key words: Coagulation, complement, DAMPs, PAMPS, trauma

INTRODUCTION

TRAUMA REMAINS AMONG the leading causes of death throughout the world. 4.9 million deaths in 2016 were caused by injuries, 29% of which were road accidents.[1] In the USA alone, unintentional injuries became the third leading cause of death across all ages with an annual death rate of 47.4 per 100,000 US standard population[2] or 1 in 17 deaths overall.[3] This staggering death rate persists despite major clinical advances in trauma care, particularly over the past 20 years, including use of tourniquets, permissive hypotension, point of care ultrasonography, tranexamic acid, high ratio massive transfusions, and of course all efforts to act within the limits of the "golden hour".[4] Additionally, a strong association remains between risk of road traffic-related death and a country's income level. The average rate of death in low income countries (27.5/100,000 population) is 3.3 times higher than the rate seen in high income countries (8.3 deaths/100,000). Furthermore, the number of road traffic deaths has not decreased in any low income country across the globe since 2013 compared with reductions in 48 middle and high income countries.[5]

The rapid evolution in early definitive control of hemorrhagic injuries has allowed severely injured patients to survive their initial injuries at unprecedented rates. However, these patients also sustain extreme hypoperfusion/reperfusion injuries that are then worsened by the complex innate immune response to severe injury. These nuanced immune responses are protective in cases of mild or moderate tissue injury and cumulatively operate to kill pathogens, clear tissue damage, and initiate local healing. For example, rapid activation of the complement and coagulation cascades serves to protect against invading pathogens and limit further bleeding, respectively (Fig. 1). When these cascades are overamplified by severe injury, the imbalanced response rapidly leads to destruction, rather than repair, of the injured tissue. This exaggerated and disordered response can result in multi-organ dysfunction syndrome (MODS) which is frequently fatal. In addition, intrinsic feedback loops of immune activation simultaneously induce a compensatory anti-inflammatory response[6] characterized by cytokines and cytokine antagonists such as interleukin-10 (IL-10),

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Received 11 Mar, 2019; accepted 19 Mar, 2019; online publication 25 Apr, 2019

Funding information

United States Air Force Medical Support Agency (FA8650-15-2-6595).

transforming growth factor-β, and IL-1Ra. These mechanisms are meant to restore local homeostasis and are thought to vary by tissue environment.[7] However, severe injury disrupts the innate immune balance, resulting in rapid and profound immune dysregulation including, but not limited to, decreased expression of human leukocyte antigen – DR isotype in macrophages, suppressed Toll-like receptor responses, increased regulatory T cell populations, and premature apoptosis of immune effector cells.[8] This leaves severe trauma patients especially vulnerable to nosocomial infection[9] as well as subsequent sepsis, the latter of which is the leading cause of delayed mortality in trauma patients.[10]

For patients requiring more than 2 weeks of surgical intensive care, another potential complication is the development of persistent inflammation–immunosuppressive catabolism syndrome. This syndrome is associated with loss of monocyte–macrophage function, decreased effector T cells, suppressed cytokine generation, and elevated amounts of myeloid-derived suppressor cells. The clinical manifestations of decreased protein catabolism with immunosuppression include poor wound healing and consequently an increased risk of infection, slow functional decline, and a higher rate of mortality.[11]

DAMAGE-ASSOCIATED MOLECULAR PATTERNS INITIATE IMMUNE DYSREGULATION

THE INITIAL STEP of over-activation of innate immunity is thought to start with release of endogenous

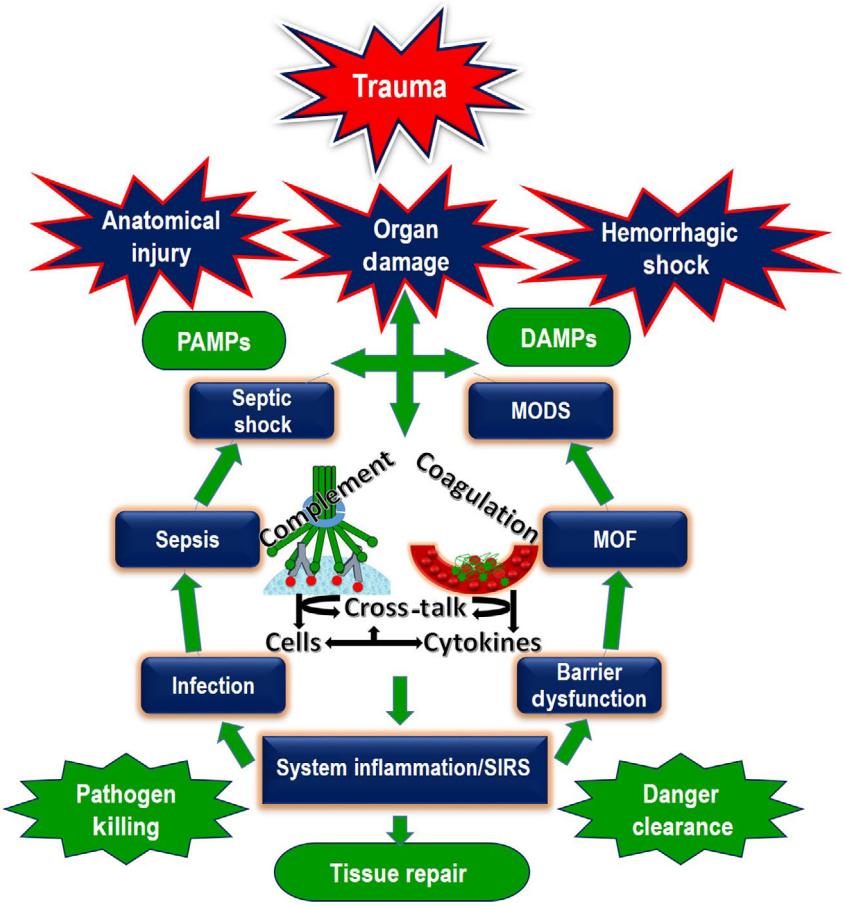

Fig. 1. Uncontrolled response of the complement and coagulation cascades intensify trauma-instigated organ damage. Trauma causes anatomical injury, hemorrhagic shock, and organ damage. These injuries induce early activation of the complement and coagulation cascades and their molecular cross-talking pathways, which results in clearance of danger molecules and kills the invading microorganisms and damaged cells. DAMP, danger-associated molecular pattern; MODS, multiple organ dysfunction syndrome; MOF, multiple organ failure; PAMP, pathogen-associated molecular pattern; SIRS, systemic inflammatory response syndrome.

damage-associated molecular patterns (DAMPs), including mitochondrial DNA and peptides, from mechanically damaged or necrotic cells into the extracellular environment.[12] Damage-associated molecular patterns can be directly detected by pattern recognition receptors, such as nucleotide oligomerization domain-like receptors and Toll-like receptors on the surface of dendritic cells, natural killer lymphocytes, macrophages, and neutrophils.[13] Recognition of DAMPs by pattern recognition receptors will induce a similar inflammatory response as that provoked by pathogen-associated molecular patterns (PAMPs) from microbial pathogens. For example, monocytes release IL-6 after recognition of nuclear DNA and IL-8 after mRNA exposure.[14] Damage-associated molecular patterns display receptor redundancy in that they can stimulate multiple receptors and therefore activate several signaling pathways.[14] For this reason, DAMPs can trigger massive pro-inflammatory cytokine release including IL-1, IL-6, IL-8, IL-12, interferon I/II, and tumor necrosis factor-α.

Clinically, plasma levels of specific DAMPs will increase proportionally with greater injury severity. For example, mitochondrial DNA concentration has been correlated with clinical outcomes such as systemic inflammatory response syndrome (SIRS) severity and presence of MODS.[12,15,16] High-mobility group box 1, normally a nuclear chaperone protein that regulates DNA transcription, is leaked from necrotic cells and/or released by activated/stressed cells in a time-dependent manner, peaking 6 h after injury but remaining elevated for at least 24 h. High-mobility group box 1 plasma levels at 30 min post-trauma correlated not only with the injury severity score and serum base deficit but were predictive of SIRS, coagulopathy, MODS, and death.[17]

EARLY ACTIVATION OF COMPLEMENT AND COAGULATION

DAMAGE -associated molecular patterns directly stimulate immune cells, including neutrophils and monocytes, through cell surface receptors who then release pro-inflammatory cytokines. In addition to immune cell stimulation, DAMPs can be detected by the inflammatory fluid-phase pathways composed of soluble macromolecules, known as the "first line of defense", which then rapidly activate their protein cascades, including the serine protease system which contains the kinin, complement, and coagulation cascades.[18,19] Acidic environments, as seen in tissue hypoperfusion, can also trigger cross-talk between the complement and coagulation cascades as well as activation of the alternative pathway.[20]

Activated neutrophils can promote local coagulation by releasing neutrophil extracellular traps. C5a in particular can provoke a prothrombotic response by increasing the expression of functionally active tissue factor (TF) in circulating leukocytes,[21] which triggers thrombin formation. The subsequent platelet thrombi lead to endothelial cytokine release and further neutrophil activation. In addition, ischemia will induce glycocalyx shedding into the bloodstream, releasing syndecans with antithrombotic properties as well as a platelet activating factor, and increasing vascular permeability. Additionally, DAMPs play a role in trauma-induced endotheliopathy by activating expression of endothelial adhesion molecules that then assist leukocyte adhesion.[22,23] Subsequent perivascular edema impairs oxygen transport and prolongs tissue hypoxia. Hypercomplementemia in trauma patients similarly worsens local hypoxia as C4d deposition on erythrocytes impairs cell membrane deformability[24] and limits microvascular perfusion. Local acidosis can also impair nitric oxide release, promoting vasoconstriction and platelet adhesion, further decreasing oxygen delivery. This in turn creates further hypoxia-mediated cellular stress, promoting the generation of more DAMPs and thus more complement generation and subsequent coagulopathy.

THE COMPLEMENT CASCADE IN TRAUMA

THE COMPLEMENT SYSTEM represents one of the phylogenetically oldest cascade systems in humans and consists of over 50 proteins which can be found as circulating macromolecules, expressed on cell surfaces or as intracellular proteins.[25] The early phase of tissue trauma is characterized by activation of cellular and molecular effectors of the innate immune system, including complement activation and recruitment and activation of neutrophils.[26,27] The complement system is key in the recognition and elimination of invading pathogens, also in the removal of self-derived danger such as apoptotic cells, and it supports innate immune responses and the initiation of the general inflammatory reactions.[25,28,29] After severe tissue injury, exposure of innate immunity to damaged cells and molecular debris is considered a main trigger of the post-traumatic danger response. However, the effects of cellular fragments (e.g., histones) on complement activation remain puzzling.[30]

Complement system activation after tissue injury occurs through the classical, lectin, and alternative pathways. The classical pathway recognizes uncoated or immunoglobulin-coated antigens initiated by the C1q molecule in complex with the proteases C1r and C1s. The lectin pathway is activated by the recognition of microbial carbohydrates through mannose binding lectin, collectins, or ficolins followed by instigation of the mannose-binding lectin-associated serine

proteases. Mannose-binding lectin-associated serine proteases and C1r and C1s then cleave C4 and C2 to generate C4bC2a, which is a C3 convertase of the classical or lectin pathway. Last but not least, the alternative pathway contains a unique activating mechanism consisting of hydrolyzing relatively inert C3 to C3(H_2O), which exposes new binding sites for Factor B. Factor B is then cleaved by Factor D to generate the C3 convertase of alternative pathway C3bBb. Both C3 convertases – C4bC2a and C3bBb – catalyze the proteolysis of C3 into C3a and C3b and the subsequent cleavage of C5, either by the classical/lectin pathway C5 convertase C4bC2aC3b, or the alternative C5 convertase C3bBbC3b, into C5a and C5b.[25,31–33]

Damage-associated molecular patterns can also activate the alternative pathway through properdin-mediated de novo C3 convertase assembly,[32] leading to rapid production of C3a and C5a.[18,19] Both C3a and C5a are potent chemoattractants for phagocytic cells that in turn release their cache of proteases, reactive oxygen species, and cytokines/chemokines to mediate local tissue damage.[34,35] Finally, the generation of C5b by cleavage of C5 initiates the terminal complement pathway with membrane attack complex (MAC) formation. The MAC is formed by self-association of C5b along with C6 through C9 and leads to the formation of a large membranolytic complex capable of lysing prokaryotic and eukaryotic cells.[32] Extensive prior studies have clearly shows that trauma activates complement, both locally at the injury site and systemically. Early research revealed not only that complement molecules deposit on the surface of erythrocytes after trauma[24] but also the cascade is activated at the level of C3 in serum of trauma patients, and the extent of activation correlates with the severity of injury.[36–38] It was also reported that the intracellular activation of C3 is accountable for intestinal tissue injury during mesenteric ischemia.[39] However, C3a, a pro-inflammatory molecule, promotes intestinal stem cell function and regeneration.[40] Together, the degree of post-traumatic complement cascade activation has been shown to be a defining modulator of the innate immune response and, ultimately, clinical outcomes.

ROLE OF COAGULATION IN TRAUMA

THE COAGULATION CASCADE is another key immediate response to traumatic injury in order to stem local bleeding but rapidly becomes dysfunctional in hemorrhagic shock. Hypothermia, acidosis, and resuscitative hemodilution have been considered the primary contributors to coagulopathy manifestations following trauma, known as the lethal triad.[41,42] Hemostasis is a complex process that is dependent upon a number of interactions including coagulation cascades, fibrinolytic proteins, and platelets.[43] Coagulation is initiated at the site(s) of injury or trauma to maintain hemostasis, to prevent exsanguination, and to protect the vital organs. Coagulation is also important in providing a matrix in the later phases of healing.[44]

Coagulation is comprised of two converging pathways, extrinsic and intrinsic. The extrinsic pathway, also called the TF pathway, is essential for normal thrombus formation and is initiated by TF, which binds to factor VII or activated factor VIIIa that subsequently activates factors IX and X.[43,45,46] Once the extrinsic pathway is triggered, further activation of factor IX in the TF/FVII complex is inhibited by TF pathway inhibitor. Freshly activated factor IXa adheres to its cofactor, factor VIIIa, resulting in the activation of factor X to Xa. Thrombin is then generated via the cleavage of prothrombin by the prothrombinase complex that arises from the common pathway via the activation of factor Xa which binds its cofactor, activated factor Va and calcium on the phospholipid surface. Importantly, only minor thrombin activation occurs via the extrinsic pathway but that minute thrombin activation is critical to induce the coagulation cascade which further triggers and expands thrombin generation through the intrinsic pathway.[43]

Activation of factor XI to factor XIa and additional thrombin generation via factor IXa and factor VIIIa is involved in the intrinsic pathway activation.[43] The intrinsic or contact activation pathway, while not essential to coagulation, initiates through autoactivation of factor XII which when activated, stimulates factors XI, IX, VII, and X activation.[43,46] Both the extrinsic and intrinsic pathways lead to activation of factor X and the production of thrombin which is a catalyst for the conversion of fibrinogen to fibrin and initiates platelet activation.[46]

Thrombin generated by the extrinsic and intrinsic pathways can activate platelets that in turn release additional procoagulant moieties from their alpha granules, which are then expressed on the activated platelet surface.[47] These moieties include fibrinogen, factor XI, factor IX, factor V, factor XIII, and von Willebrand factor.[48] In addition, platelets can bind C3b through their expression of p-selectin to trigger the formation of C5a and the membrane attack complex.[49] Furthermore, C5a can be generated by thrombin while factors FXa and FXIa can cleave C3 and C5 to generate C3a and C5a.[50] Additional enzymes of the coagulation pathway, including FIXa and kallikrein, directly activate C5 independently from C3; kallikrein also activates C3 and Factor B and generates human coagulation factor (F) FXIIa, which in turn can activate C1r.[51] Thus, severe trauma leads to a complex series of interactive events that initiate coagulation and induce platelet activation and complement activation.

CROSS-TALKING OF COMPLEMENT AND COAGULATION

CONVENTIONALLY, THE COMPLEMENT and coagulation systems are described as descendants of a common ancestral pathway. Both proteolytic cascades are composed of serine proteases with common structural characteristics, such as highly conserved catalytic sites of serine, histidine, and aspartate following tissue injury, both systems activate complex inflammatory networks[52] and show some similar characteristics regarding the specialized functions of their activators and inhibitors. Specifically, the clotting factor FXIIa can activate the complement factor C1r and thereby initiate the classical pathway of complement activation.[34] Conversely, the C1 esterase inhibitor suppresses three complement pathways (classical, lectin, and alternative) as well as the intrinsic coagulation cascade (kallikrein and FXIIa).[53,54] Recently, it was shown that thrombin is capable of generating the complement activation product C5a that can be cleaved by thrombin in the absence of C3a.[55] Another study proposed that thrombin and plasmin could contribute to unconventional complement activation during liver regeneration even in the absence of C4 and during inhibition of factor B.[56] Activation of the coagulation cascade in systemic inflammation is accompanied by an intense activation of the complement system, resulting in the generation of the anaphylatoxins C3a and C5a.[57,58] The generation of anaphylatoxins C3a and C5a provides potent chemoattractants for phagocytes and neutrophils, and recruits these immune cells to the site of injury to help in elimination of invading pathogens by opsonization for phagocytosis (C3b, C4b) and chemotaxis of leukocytes (C3a, C5a), and by direct lysis of pathogens through the membrane attack complex (MAC, C5b-9).[29,59–61] The anaphylatoxins further induce degranulation of mast cells, basophils, and eosinophils and mediate the hepatic acute-phase response.[62,63]

CONCLUSIONS

THIS REVIEW STRENGTHENS the argument that activation of the complement and coagulation cascades after tissue injury are highly interconnected. The molecules that participate in the intercommunication between the complement and coagulation systems could serve as biomarkers of tissue injury. As both systems activate complex inflammatory networks and show many analogous characteristics regarding the specialized functions of their activators and inhibitors, complement and coagulation modulating therapies ideally will gain a place in an evolving armamentarium of trauma treatment approaches.

ACKNOWLEDGEMENT

UNITED STATES AIR Force Medical Support Agency (FA8650-15-2-6595).

DISCLOSURE

Approval of the research protocol: N/A.
Informed consent: N/A.
Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A.
Conflict of interest: None.

REFERENCES

1 Global Health Estimates. Disease Burden by Cause, Age, Sex, by Country and by Region, 2000–2016. Geneva, Switzerland: World Health Organization, 2016; 2018.
2 Kochanek KD, Murphy S, Xu J, Arias E. Mortality in the United States, 2016. NCHS Data Brief 2017; 293: 1–8.
3 Heron M. Deaths: leading causes for 2016. Natl Vital Stat. Rep. 2018; 67: 1–77.
4 King DR. Initial care of the severely injured patient. N. Engl. J. Med. 2019; 380: 763–70.
5 Global status report on road safety 2018: Summary. Geneva, Switzerland: World Health Organization, 2018. Contract No.: WHO/NMH/NVI/18.20.
6 Xiao W, Mindrinos MN, Seok J *et al*. A genomic storm in critically injured humans. J. Exp. Med. 2011; 208: 2581–90.
7 Matzinger P, Kamala T. Tissue-based class control: the other side of tolerance. Nat. Rev. Immunol. 2011; 11: 221–30.
8 Tschoeke SK, Ertel W. Immunoparalysis after multiple trauma. Injury 2007; 38: 1346–57.
9 Papia G, McLellan BA, El-Helou P *et al*. Infection in hospitalized trauma patients: incidence, risk factors, and complications. J. Trauma 1999; 47: 923–7.
10 Pfeifer R, Tarkin IS, Rocos B, Pape HC. Patterns of mortality and causes of death in polytrauma patients–has anything changed? Injury 2009; 40: 907–11.
11 Gentile LF, Cuenca AG, Efron PA *et al*. Persistent inflammation and immunosuppression: a common syndrome and new horizon for surgical intensive care. J. Trauma Acute Care Surg. 2012; 72: 1491–501.
12 Zhang Q, Raoof M, Chen Y *et al*. Circulating mitochondrial DAMPs cause inflammatory responses to injury. Nature 2010; 464: 104–7.
13 Manson J, Thiemermann C, Brohi K. Trauma alarmins as activators of damage-induced inflammation. Br. J. Surg. 2012; 99: 12–20.
14 Vourc'h M, Roquilly A, Asehnoune K. Trauma-induced damage-associated molecular patterns-mediated remote organ

injury and immunosuppression in the acutely ill patient. Front Immunol. 2018; 9: 1330.
15 Simmons JD, Lee Y-L, Mulekar S *et al*. Elevated levels of plasma mitochondrial DNA DAMPs are linked to clinical outcome in severely injured human subjects. Ann. Surg. 2013; 258: 591–6.
16 Stover Cordula M, Gu X, Yao Y *et al*. The plasma mitochondrial DNA is an independent predictor for post-traumatic systemic inflammatory response syndrome. PLoS ONE 2013; 8: e72834.
17 Cohen MJ, Brohi K, Calfee CS *et al*. Early release of high mobility group box nuclear protein 1 after severe trauma in humans: role of injury severity and tissue hypoperfusion. Crit. Care 2009; 13: R174.
18 Burk AM, Martin M, Flierl MA *et al*. Early complementopathy after multiple injuries in humans. Shock 2012; 37: 348–54.
19 Ganter MT, Brohi K, Cohen MJ *et al*. Role of the alternative pathway in the early complement activation following major trauma. Shock 2007; 28: 29–34.
20 Kenawy HI, Boral I, Bevington A. Complement-coagulation cross-talk: a potential mediator of the physiological activation of complement by low pH. Front Immunol. 2015; 6: 215.
21 Markiewski MM, Nilsson B, Ekdahl KN, Mollnes TE, Lambris JD. Complement and coagulation: strangers or partners in crime? Trends Immunol. 2007; 28: 184–92.
22 Zhao Y-Y, Sun S, Sursal T *et al*. Mitochondrial DAMPs increase endothelial permeability through neutrophil dependent and independent pathways. PLoS ONE 2013; 8: e59989.
23 White NJ, Ward KR, Pati S, Strandenes G, Cap AP. Hemorrhagic blood failure: oxygen debt, coagulopathy, and endothelial damage. J. Trauma Acute Care Surg. 2017; 82(6S Suppl 1): S41–9.
24 Muroya T, Kannan L, Ghiran IC *et al*. C4d deposits on the surface of RBCs in trauma patients and interferes with their function. Crit. Care Med. 2014; 42: e364–72.
25 Arbore G, Kemper C, Kolev M. Intracellular complement – the complosome – in immune cell regulation. Mol. Immunol. 2017; 89: 2–9.
26 Keel M, Trentz O. Pathophysiology of polytrauma. Injury 2005; 36: 691–709.
27 Stahel PF, Smith WR, Moore EE. Role of biological modifiers regulating the immune response after trauma. Injury 2007; 38: 1409–22.
28 Griffiths MR, Gasque P, Neal JW. The regulation of the CNS innate immune response is vital for the restoration of tissue homeostasis (repair) after acute brain injury: a brief review. Int. J. Inflam. 2010; 2010: 151097.
29 Elward K, Gasque P. "Eat me" and "don't eat me" signals govern the innate immune response and tissue repair in the CNS: emphasis on the critical role of the complement system. Mol. Immunol. 2003; 40: 85–94.
30 Huber-Lang M, Ignatius A, Brenner RE. Role of Complement on Broken Surfaces after Trauma. Immune Responses to Biosurfaces. Cham, Switzerland: Springer International Publishing, 2015; 43–55.
31 Walport MJ. Complement. N. Engl. J. Med. 2001; 344: 1058–66.
32 Ricklin D, Hajishengallis G, Yang K, Lambris JD. Complement: a key system for immune surveillance and homeostasis. Nat. Immunol. 2010; 11: 785.
33 Kolev M, Le Friec G, Kemper C. The role of complement in CD4+ T cell homeostasis and effector functions. Semin. Immunol. 2013; 25: 12–9.
34 Amara U, Flierl MA, Rittirsch D *et al*. Molecular Intercommunication between the complement and coagulation systems. J. Immunol. 2010; 185: 5628–36.
35 Neher MD, Weckbach S, Flierl MA, Huber-Lang MS, Stahel PF. Molecular mechanisms of inflammation and tissue injury after major trauma-is complement the "bad guy"? J. Biomed. Sci. 2011; 18: 90.
36 Kapur MM, Jain P, Gidh M. The effect of trauma on serum C3 activation and its correlation with injury severity score in man. J. Trauma 1986; 26: 464–6.
37 Kapur MM, Jain P, Gidh M. Estimation of serum complement and its role in management of trauma. World J. Surg. 1988; 12: 211–6.
38 Satyam A, Andreo K, Lapchak PH *et al*. Complement deposition on the surface of RBC after trauma serves a biomarker of moderate trauma severity: a prospective study. Shock 2019. (in press). https://doi.org/10.1097/SHK.0000000000001348
39 Satyam A, Kannan L, Matsumoto N *et al*. Intracellular activation of complement 3 is responsible for intestinal tissue damage during mesenteric ischemia. J. Immunol. 2017; 198: 788–97.
40 Matsumoto N, Satyam A, Geha M *et al*. C3a enhances the formation of intestinal organoids through C3aR1. Front Immunol. 2017; 8: 1046.
41 Martini WZ. Coagulation complications following trauma. Mil. Med. Res. 2016; 3: 35.
42 Kashuk JL, Moore EE, Millikan JS, Moore JB. Major abdominal vascular trauma – a unified approach. J. Trauma 1982; 22: 672–9.
43 Periayah MH, Halim AS, Mat Saad AZ. Mechanism action of platelets and crucial blood coagulation pathways in hemostasis. Int. J. Hematol. Oncol. Stem Cell Res. 2017; 11: 319–27.
44 Velnar T, Bailey T, Smrkolj V. The wound healing process: an overview of the cellular and molecular mechanisms. J. Int. Med. Res. 2009; 37: 1528–42.
45 Keragala CB, Draxler DF, McQuilten ZK, Medcalf RL. Haemostasis and innate immunity – a complementary relationship. Br. J. Haematol. 2018; 180: 782–98.
46 Teller P, White TK. The physiology of wound healing: injury through maturation. Surg. Clin. North Am. 2009; 89: 599–610.

47 Ofosu FA. The blood platelet as a model for regulating blood coagulation on cell surfaces and its consequences. Biochemistry (Mosc.) 2002; 67: 47–55.
48 Fukami MH, Holmsen H, Kowalska MA, Niewiarowski S. Platelet secretion. In: Colman RWHJ, Marder VJ, Clowes AW, George JN (eds). Hemostasis and Thrombosis: Basic Principles and Clinical Practice. Philadelphia, PA: Lippincott Williams & Wilkins, 2001; 561–73.
49 Eisinger F, Patzelt J, Langer HF. The platelet response to tissue injury. Front. Med. 2018; 5: 317.
50 Amara U, Rittirsch D, Flierl M *et al*. Interaction between the coagulation and complement system. Adv. Exp. Med. Biol. 2008; 632: 71–9.
51 Conway EM. Complement-coagulation connections. Blood Coagul. Fibrinolysis 2018; 29: 243–51.
52 Rittirsch D, Flierl MA, Ward PA. Harmful molecular mechanisms in sepsis. Nat. Rev. Immunol. 2008; 8: 776.
53 Davis AE, Mejia P, Lu F. Biological activities of C1 inhibitor. Mol. Immunol. 2008; 45: 4057–63.
54 Ghebrehiwet B, Silverberg M, Kaplan AP. Activation of the classical pathway of complement by Hageman factor fragment. J. Exp. Med. 1981; 153: 665–76.
55 Huber-Lang M, Sarma JV, Zetoune FS *et al*. Generation of C5a in the absence of C3: a new complement activation pathway. Nat. Med. 2006; 12: 682–7.
56 Clark A, Weymann A, Hartman E *et al*. Evidence for non-traditional activation of complement factor C3 during murine liver regeneration. Mol. Immunol. 2008; 45: 3125–32.
57 Hecke F, Schmidt U, Kola A, Bautsch W, Klos A, Kohl J. Circulating complement proteins in multiple trauma patients–correlation with injury severity, development of sepsis, and outcome. Crit. Care Med. 1997; 25: 2015–24.
58 Levi M, Poll T, Büller HR. Bidirectional relation between inflammation and coagulation. Circulation 2004; 109: 2698–704.
59 Stahel PF, Barnum SR. The role of the complement system in CNS inflammatory diseases. Expert Rev. Clin. Immunol. 2006; 2: 445–56.
60 Alexander JJ, Anderson AJ, Barnum SR, Stevens B, Tenner AJ. The complement cascade: Yin-Yang in neuroinflammation–neuro-protection and -degeneration. J. Neurochem. 2008; 107: 1169–87.
61 Guo R-F, Ward PA. Role of C5a in inflammatory responses. Annu. Rev. Immunol. 2005; 23: 821–52.
62 Klos A, Tenner AJ, Johswich K-O, Ager RR, Reis ES, Köhl J. The role of the anaphylatoxins in health and disease. Mol. Immunol. 2009; 46: 2753–66.
63 Mastellos D, Morikis D, Isaacs SN, Holland MC, Strey CW, Lambris JD. Complement. Immunol. Res. 2003; 27: 367–85.