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Complement therapeutic strategies in trauma, hemorrhagic shock and systemic inflammation – closing Pandora's box?

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ABSTRACT

After severe trauma, the immune system is challenged with a multitude of endogenous and exogenous danger molecules. The recognition of released danger patterns is one of the prime tasks of the innate immune system. In the last two decades, numerous studies have established the complement cascade as a major effector system that detects and processes such danger signals. Animal models with engineered deficiencies in certain complement proteins have demonstrated that widespread complement activation after severe injury culminates in complement dysregulation and excessive generation of complement activation fragments. Such exuberant pro-inflammatory signaling evokes systemic inflammation, causes increased susceptibility to infections and is associated with a detrimental course of the disease after injury. We discuss the underlying processes of such complementopathy and recapitulate different intervention strategies within the complement cascade. So far, several orthogonal anti-complement approaches have been tested with varying success in a large number of rodent, in several porcine and few simian studies. We illustrate the different features among those intervention strategies and highlight those that hold the greatest promise to become potential therapeutic options for the intricate disease of traumatic injury.

Contents

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1. Introduction

In analogy to Pandora's box that floods the world with evil, severe tissue trauma and hemorrhagic shock overflow the injured body with vast amounts of damaged tissue and inflammatory mediators. So far, no means seem to exist to stop this fatal process. Trauma-hemorrhage exposes the body to various danger- and pathogen-associated molecular patterns (DAMPs and PAMPs, resp.) [1], often resulting in a systemic inflammatory reaction through an immediate release of pro- and anti-inflammatory mediators [2,3]. Clinically, this generalized inflammation is known as "systemic inflammatory response syndrome" (SIRS). SIRS is diagnosed when at least two of the following criteria are met: (i) temperature of more than 38 °C or less than 36 °C; (ii) heart rate of more than 90 beats per minute; (iii) respiratory rate of more than 20 breaths per minute or arterial carbon dioxide tension ($PaCO_2$) of less than 32 mmHg; (iv) abnormal white blood cell count (>12,000/μL or <4000/μL or >10% immature [band] forms) [4]. Whenever SIRS is associated with a bacterial infection, this inflammatory syndrome is classified as sepsis. Pathomechanistic insights of how such a generalized inflammation is initiated and propagated in response to trauma or traumatic-hemorrhagic shock still remain to be elucidated in detail.

Soon after trauma, exposure to PAMPs/DAMPs extensively challenges the "first line of defense" which comprises leukocytes [3] and the two cross-talking serine protease systems of the coagulation and complement cascade [5,6]. Especially activation of the complement system quickly senses damaged tissue and danger molecules with attachment of C1qrs and C3b opsonisation, and generation of the anaphylatoxins C3a and C5a translates these signals into an effective cellular danger response [7]. The subsequent cellular oxidative burst reaction leads to release of reactive oxygen radicals (ROS) and tissue- and barrier-degrading proteases from neutrophils (PMN) which, together with vasoactive mediators (e.g. ROS, thrombin), increase the permeability of membranes and the microvasculature. Complement activation products also trigger extensive release of pro-inflammatory cytokines that in turn contribute to systemic inflammation and generalized capillary leakage. The resultant fluid shift into the interstitial space leads to tissue edema and development of multi-organ dysfunction syndrome (MODS) and is responsible for the high mortality rates that occur in later stages after severe trauma (Fig. 1). Organ or multiple organ failure with incidences of 37.2% and 22.1%, respectively, are indeed

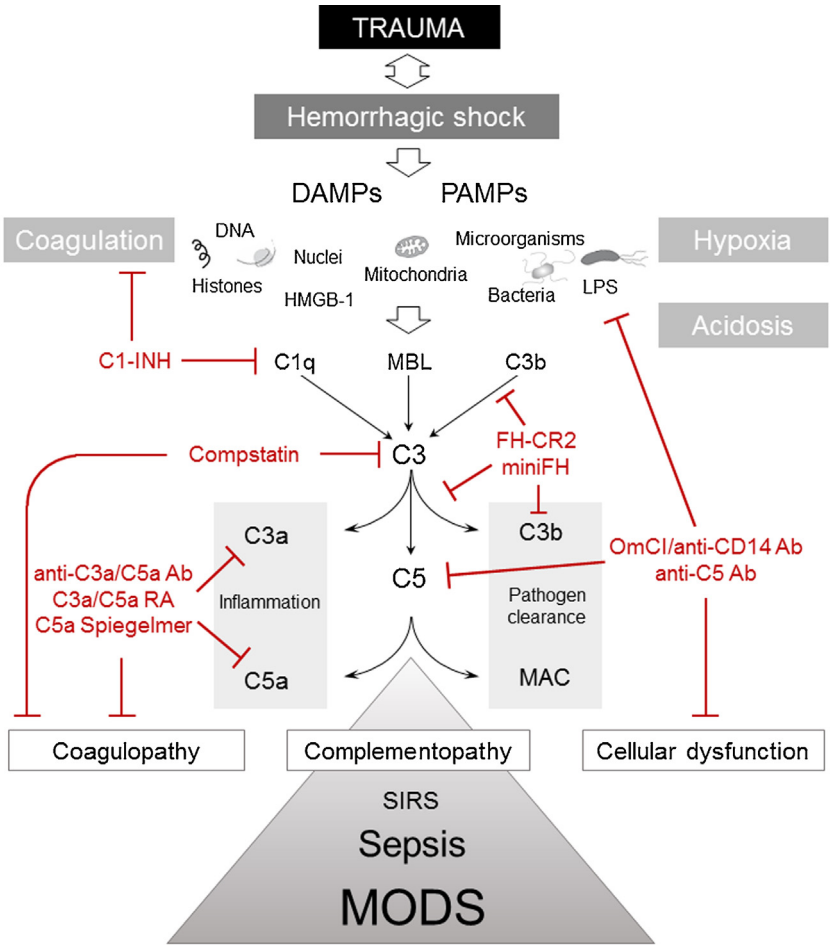

Fig. 1. Therapeutic targets of current complement inhibitory strategies in the posttraumatic inflammatory immune response.
Various pathways of the complement cascade are activated after trauma and hemorrhagic shock by DAMPs/PAMPs, coagulation factors, hypoxia and acidosis. The complement activation products drive inflammation and pathogen clearance. Complications after severe tissue injury with its associated systemic inflammatory response syndrome (SIRS) manifest as coagulopathy, complementopathy and cellular dysfunction and finally culminate in sepsis and multi-organ dysfunction syndrome (MODS). Therapeutic complement strategies can effectively address specific levels of the complement cascade to beneficially modulate the posttraumatic fluid-phase innate immune response and presumably improve outcome.
Abbreviations: Ab, antibodies; C1-INH, C1-esterase inhibitor; DAMPs, damage-associated molecular patterns; FH-CR2, complement receptor 2-Factor H fusion protein; HMGB-1, high-mobility-group protein B1; LPS, lipopolysaccharides; MBL, mannose-binding lectin; miniFH, mini-Factor H; MODS, multi-organ dysfunction syndrome; OMCI, *Ornithodorosmoubata* complement inhibitor; PAMPs, pathogen-associated molecular patterns; RA, receptor antagonist; SIRS, systemic inflammatory response syndrome.