COMPONENT IN TRAUMA–TRAUMATISED COMPLEMENT?

Markus S. Huber-Lang1 | Anita Ignatius2 | Jörg Köhl3,4 | Marco Mannes1 | Christian Karl Braun1,5

1Institute of Clinical and Experimental Trauma–Immunology, University Hospital of Ulm, Ulm, Germany
2Institute of Orthopaedic Research and Biomechanics, University Hospital of Ulm, Ulm, Germany
3Institute for Systemic Inflammatory Research, University of Lübeck, Lübeck, Germany
4Division of Immunobiology, Cincinnati Children’s Hospital Medical Centre, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA
5Department of Paediatrics and Adolescent Medicine, University Hospital of Ulm, Ulm, Germany

Correspondence
Markus Huber-Lang, Institute of Clinical and Experimental Trauma–Immunology, University Hospital of Ulm, Helmholtzstr. 8/2, Ulm 89081, Germany.
Email: markus.huber-lang@uniklinik-ulm.de

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1 | INTRODUCTION TRAUMA

Trauma can hit any individual at any time over a lifetime and thus represents a major burden to the individual patient and societies globally (James et al., 2018). The term "trauma" originates etymologically from the Greek word "traumatos" meaning "wound" and represents any injury and resulting in defective tissue. The term "complement" comes from Latin and means rather the opposite, “something which completes a whole.” It describes that in the context of “trauma,” “complement” may help to complete the whole, that is, to heal defects and regain integrity. The complement system is not only locally activated in wounds (Bekeschus et al., 2018) but also systemically (Fosse et al., 1998; Ganter et al., 2007; Hecke et al., 1997). In general,

Abbreviations: C1INH, C1 esterase inhibitor; CH50, total haemolytic complement activity; CRegs, complement regulators; CRg, complement receptor Ig; DAMP, damage-associated molecular pattern; FSAP, factor VII activating protease; MASP, mannose-binding lectin-associated serine protease; MBL, mannose-binding lectin; mTT30, complement receptor 2-conjugated inhibitor; NGAL, neutrophil gelatinase-associated lipocalin; PAMP, pathogen-associated molecular pattern; PAR, protease-activated receptor; sC5b-9, soluble C5b-9.

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trauma results in the rapid generation of damage-associated molecular patterns (DAMPs) and exposure to external and internal pathogen-associated molecular patterns (PAMPs), which trigger a complex innate and adaptive immune response (Huber-Lang, Lambris, & Ward, 2018; Karasu, Eisenhardt, Harant, & Huber-Lang, 2018). Upon activation, the complement cascade efficiently acts in recognising, marking and clearing the trauma-caused debris, DAMPs and PAMPs, and helps to initiate the regenerative processes. Clinical and experimental trauma settings have previously shown that the degree of complement activation is dependent on injury severity and pattern (Fosse et al., 1998). In the case of life-threatening polytrauma and/or traumatic haemorrhagic shock, the complement response can be excessive, eventually leading to the depletion and dysfunction of the complement factors (Banerjee et al., 2018; Cudjoe et al., 2019; Hecke et al., 1997). Therefore, a balanced innate immune reaction, including of the complement response, is crucial for post-traumatic cell and organ functions and the final outcome (Huber-Lang et al., 2018).

The aim of this review was to summarise basic findings and highlight the most recent insights in the interplay between the complement system and traumatised tissue and vice versa. Furthermore, some research gaps are indicated, and future complement-modulatory strategies are provided for the trauma setting.

2 TRAUMATISED TISSUE—TRIGGER MECHANISMS FOR COMPLEMENT ACTIVATION

The complement cascade functioning as the “master alarm and clearance” system of innate immunity consists of more than 30 proteins, which can be serially activated by three different pathways. The classical pathway is triggered by the identification of antibodies and C-reactive protein bound on “foreign” or damaged cells by its recognition unit C1q, which upon binding activates consecutively the associated proteases, complement C1r and C1s. Latter cleaves C4 into C4a and C4b, which covalently attaches to nearby surfaces and serves as binding partner for C2, which is then cleaved by the same protease, finally forming the C3-converter C4b2a. The functional similar lectin pathway recognises via mannose-binding lectin (MBL) and ficolins conserved microbial surface carbohydrates like mannose and N-acetyl glucosamine and subsequently also activates C4 by the action of MBL-associated serine proteases (MASPs), leading eventually to the same C3 convertase complex. As the name implies, the third pathway is activated alternatively by a permanent low-level activation of C3, thus serving as a platform for the formation of a different initial C3-converter C3(H2O)Bb. All pathways converge at the proteolytic activation of C3 into the anaphylatoxin C3a and the opsonin C3b. The former was originally described as a pro-inflammatory mediator, as it induced histamine secretion from mast cells via binding to its receptor C3a (Klos et al., 2009). In contrary, C3a also dampens neutrophil mobilisation after intestinal ischemia reperfusion injury (Wu et al., 2013), thus changing the delineation for C3a from a “pure pro-inflammatory mediator” to an “inflammatory mediator” (Coulthard & Woodruff, 2015). The further course of complement activation is then determined by the origin of the surface that has been initially tagged. Negative surface-bound (e.g. CD55) or fluid-phase (e.g. factor H) complement regulators (CRegs) stop the progression on host surfaces mainly by the acceleration of convertase decay or by facilitating the degradation of the opsonins into inactivated forms. However, these surface-fixed degradation products (e.g. iC3b and C3dg) serve as further ligands for several CRegs such as the complement receptors 1–4 (CR1–4) or the complement receptor Ig (CR1g), which are spread on a wide range of immune cells, thus promoting the involvement of the cellular immunomodulatory functions. On the other hand, the progression of the cascade on altered or foreign surfaces is even intensified by the alternative pathway “amplification loop.” New formed C3b serves as a platform for further AP C3 convertases, consequently increasing the C3b density. This leads downstream to the formation of the C5 convertases C4b2a3b and C3bBb3b, which activate the terminal pathway through the cleavage of C5 into the anaphylatoxin C5a and C5b, which represents the starting point for the membrane attack complex C5b-9 (Figure 1) (for review, see Hajishengallis, Reis, Mastellos, Ricklin, & Lambris, 2017; Ricklin, Hajishengallis, Yang, & Lambris, 2010). Upon membrane attack complex generation, which morphologically forms a membrane pore, the targeted cell is lysed and killed, while sublytic concentrations of the complex can facilitate intracellular signalling and cell activation, for instance a NF-κB-dependent transcription of IL-8 on endothelial cells (for detailed review, see Xie, Jane-Wit, & Pober, 2020). Like its upstream relative C3a, C5a also acts as a small signalling molecule by its binding to two different receptors, C5a1 (CD88) and C5a2 (C5L2). While C5a1 receptor is mainly pro-inflammatory, the precise role of C5a2 receptor is not well understood and currently hotly debated (Li, Lee, Kemper, & Woodruff, 2019).

Following severe tissue trauma with subsequent exposure to various DAMPs and/or PAMPs, the alternative pathway appears to be predominantly activated (Ganter et al., 2007). However, it is a matter of ongoing debate as to which trigger mechanisms induce complement activation post trauma. In general, it is well established that traumatised tissue with microenvironmental hypoxic and acidic conditions can activate complement (Kenawy, Boral, & Bevington, 2015). The generation of blood plasma soluble C5b-9 (sC5b-9), the soluble terminal complement complex, has been shown to be increased upon tissue injury alone but is significantly more increased by the presence of additional haemorrhagic shock and even further after additional cardiac decompensation (Paredes et al., 2018), indicating tissue damage plus perfusion disturbances are a crucial trigger for complement activation.

The release of mitochondria and mitochondrial debris from destroyed cells drives complement activation. In severe tissue trauma, enhanced mitochondrial DAMPs concentrations have been reported (Zhang et al., 2010). Mitochondria, which, based on the endosymbiotic theory, represent ancient microorganisms, may be sensed as “ancient PAMPs” by MBL, L-ficolin and M-ficolin, resulting in excessive complement cascade activation and measurable C3 consumption (Brinkmann et al., 2013).

Reperfusion injury in the context of trauma with the generation of ROS may also add to complement activation (Lucchesi, 1993; von...
Zabern, Hesse, Nolte, & Haller, 1987). Trauma-released nucleosomes and coagulation factors, including factor VII activating protease (FSAP), a serine protease, can generate anaphylatoxin C5a in humans after polytrauma (Kanse et al., 2012). We and others have proposed that exogenous serine proteases of the coagulation system, which may accumulate locally in damaged tissues, including thrombin and plasmin, at high concentrations can cleave complement factors (Amara et al., 2010; Ganter et al., 2007; Hoth, Wells, Jones, Yoza, & McCall, 2014). Further, exogenous proteases that are systemically enhanced early after polytrauma include cathepsin D, which can cleave native C5 and generate biologically active anaphylatoxins (Huber-Lang et al., 2012). Moreover, an apoptosis–complement crosstalk has been proposed, because enhanced post-traumatic blood concentrations of granzyme B, a serine protease, which is secreted by natural killer (NK) cells and cytotoxic T-cells and induces apoptosis in target cells, could generate C5a in vitro (Perl, Denk, Kalbitz, & Huber-Lang, 2012).

Another trigger might be the activation of the classical pathway via natural IgM antibodies, which bind to neoepitopes exposed after trauma, as demonstrated in the experimental setting of rodent spinal cord injury (Narang et al., 2017). Classical pathway activation can also occur via C-reactive protein, an acute phase protein that is regularly enhanced in the blood during the first days after trauma and particularly during infectious complications.

Following severe trauma and during traumatic haemorrhagic shock, glycocalyx structures are cleaved off from traumatised or hypoxic endothelium and shed into the circulation (Ostrowski & Johansson, 2012). Consequently, complement activation may theoretically occur on the injured endothelial surface because of the loss of glycosaminoglycans and the associated lack of factor H control of self–non-self discrimination (Jokiranta et al., 2005; Li et al., 2015; Meri, 2016). Mechanical "microtrauma" to erythrocytes has also been shown to result in a loss of sialylation, again a precondition for less factor H anchoring, and in turn triggers complement activation (McNamee, Tansley, & Simmonds, 2018). When considering "macrotrauma," it is noteworthy that the deposition of complement activation products on the surface of erythrocytes is associated with trauma severity and may be also due to loss of anticomplementary...
control (Satyam et al., 2020). However, further research needs to define which are the prominent triggers, routes, and dynamics of complement activation and whether new cleavage products with novel functions appear during trauma.

### 3 | POST-TRAUMATIC ACTIVATION OF THE COMPLEMENT AND COAGULATION SYSTEMS

Severe trauma may result in an overwhelming activation of the coagulation cascade, leading to the formation of microthrombi in the vasculature and simultaneously to a fatal consumption of coagulation factors ultimately causing bleeding and contributing to the downward spiral of shock (Brohi, Singh, Heron, & Coats, 2003; Dobson, Letson, Sharma, Sheppard, & Cap, 2015). As both the complement and the coagulation systems depend on the acting of proteases, manifold interactions between the two are conceivable, and some of them have been extensively studied over the past years. However, some results have been recently challenged (Keshari, Silasi, Lupu, Taylor, & Lupu, 2017; Schmidt & Verschoor, 2017) and the implications of those, mostly in vitro generated findings for the trauma patient, are far from clear.

Severe trauma was demonstrated not to only trigger the classical and lectin pathways (Burk et al., 2012) but also activate the alternative pathway (Ganter et al., 2007). Both the extent of thrombin generation and membrane attack complex formation correlate in trauma patients (Ganter et al., 2007). These findings are in accordance with recent works, associating complement activation with coagulopathy (Vollrath, Marzi, Herminghaus, Lustenberger, & Relja, 2020) after sepsis.

Several coagulation factors have been shown to directly activate the complement system. Thus, it has been a scientific paradigm that several proteases of the haemostatic system such as thrombin and plasmin but also factor Xa may cleave C3 and C5 to yield the pro-inflammatory anaphylatoxins C5a and C3a (Amara et al., 2008). Furthermore, thrombin may act out a pro-coagulatory role through atypical complement fragments of C5 (Krisinger et al., 2012), although the biological impact of these in vitro findings remain elusive. Thrombin, which as a central clotting product and is abundantly generated during trauma, has been shown to cleave C5 on an alternative, highly conserved site, which in turn generates 35 and 24 kDa intermediate C5a-like molecules and an 80 kDa C5b-like “C5bT.” Of note, C5bT could form a C5b(T)-9 membrane attack complex that was more potent in its lytic activity than the classical C5b-9 complex (Krisinger et al., 2012). Synchronously to pro-coagulatory actions, the anticoagulatory fibrinolytic system becomes also activated after severe tissue trauma, which may destabilise and eventually dissolve a formed clot and thereby aggravate bleeding complications (Dobson et al., 2015; Gando, 2009). In this context, the key driver of the fibrinolytic system, plasmin, can significantly cleave iC3b, a degradation product of the opsonin C3b, at various so far unknown sites, generating novel biologically active C3c-like and C3dg-like molecules (Foley et al., 2015). More recently, factor XII was shown to initiate the classical pathway via activation of C1 esterases (Didiasova, Wujak, Schaefer, & Wygrecka, 2018). As a main driver of both, contact activation of haemostasis and a key molecule in thromboinflammation (Ekdahl et al., 2016), factor XII may be a promising target for future studies addressing the complement-coagulation crosstalk in the setting of trauma-induced systemic inflammation. Additionally, kallikrein, another mediator of contact activation, cleaves C3 and factor B, thereby linking the alternative pathway and contact-triggered haemostasis (Irmscher et al., 2018). Conversely, high molecular weight kininogen and factor XII may bind to the C1q receptor on membrane surfaces, further enhancing the activation of the contact system (Keragala, Draxler, McQuilten, & Medcalf, 2018). This may have practical implications in the trauma patient beyond tissue injury, as surgical treatment and central lines may add to the detrimental co-activation of the blood protease cascades.

For the lectin pathway, mainly MASPs have been described to cross-react with complement components. Thus, MASPs have been shown to activate prothrombin and to bind to endothelial cells via the protease-activated receptor 1 (PAR1) (Debrezeni et al., 2019; Jenny, Dobó, Gál, & Schroeder, 2015). Similarly, MASPs leads to clot formation in vitro (Gulla et al., 2010; Krapur, Wallis, Presanis, Gál, & Sim, 2007). Accordingly, results from a recent clinical study on sepsis and disseminated intravascular coagulation associated reduced MASp1 levels with impaired thrombin generation (Larsen et al., 2019), although the study was merely descriptive and could not provide an explanation for the pathophysiological mechanism. In the setting of microbe invasion, MBL not only binds to surface patterns of infectious agents but also serves as a linker to fibrinogen and fibrin, possibly leading to the capture of the intruder on the one hand and to the local activation of the complement and coagulation cascade through MASPs on the other hand (Endo et al., 2010). Besides the well-established protease activity of MASPs promoting thrombin formation, activated platelets in turn may provide a platform for lectin pathway activation via binding of ficolins, thus integrating both cellular and humoral mechanisms in the crosstalk (Kozarcanin et al., 2016). Although traditionally associated with pathogen invasion, marked lectin pathway activation is also observed early after trauma (Burk et al., 2012; De Blasio et al., 2019), thus potentially offering a rapidly acting pro-coagulatory trigger in severely injured patients.

Paralleled by the findings of a direct coagulation-complement crosstalk in the fluid phase, evidence has emerged in recent years that platelets as cellular representatives of haemostasis do intimately interact with complement components as well. A recent work demonstrated complement deposition and a complement-triggered platelet aggregation after trauma (Atefi et al., 2016). Thrombocytes seem to be affected by complement activation on various levels of the cascade. Human platelets have been shown to express complement receptors with a functional relevance in health and disease (Nording et al., 2016; Patzelt et al., 2015; Sauter et al., 2018). Moreover, the surface expression of both receptors (C3aR and C5aR1), can be markedly up-regulated after activation with ADP or collagen (Martel et al., 2011; Sauter et al., 2018).

In the experimental setting, platelets are activated through C3a-C3a receptor interactions as measured by increased Ca2+-influx and enhanced adhesion. These effects seem to be at least in part
mediated intracellularly by PI3K and Ras family GTPases (Sauter et al., 2018; Sauter et al., 2019). This effect could be reproduced in animal models of haemorrhage and thrombosis, as in C3a receptor and C3 knockout mice which had a significantly prolonged bleeding time and, on the other hand, showed ameliorated impact of induced thrombosis on the myocardium and the brain (Sauter et al., 2018). C3 deficiency accordingly leads to impaired thrombus formation in a murine thrombosis model (Subramaniam et al., 2017). However, the functional impact of these findings in trauma patients still needs to be determined, as complement receptor blockade of ex vivo blood could not alter clot formation attributes as obtained by thrombelastography (Samuels et al., 2020). Furthermore, while the role of the C3a receptor could be at least experimentally established, the role of the C5a1 and C5a2 receptors on platelets remains elusive. Sauter et al. (2018) could not determine a relevant role of the C5a3 receptor in their study and the effect of C5-deficiency on thrombus formation was shown to be contradictory (Subramaniam et al., 2017).

Besides the central receptors C3a and C5a1 receptor, other receptors and surface molecules have been described as functional relevant for platelet-associated haemostasis. Upon activation, surface CD62P is increased and this selectin can bind C3b (Peerschke, Yin, & Ghebrehiwet, 2010). This interaction initiates the activation of the complement system and the formation of the membrane attack complex (del Conde, Crúz, Zhang, López, & Afshar-Kharghan, 2005). Furthermore, a functional receptor for C1q has been described on the platelet surface that could play a role in the platelet-mediated binding of oposinised bacteria (Peerschke, Murphy, & Ghebrehiwet, 2003). This close interaction of platelets and the complement system in the clearance of bloodstream pathogens is also reflected by the dependency of thrombocyte–bacteria association on C3 (Verschoor et al., 2011). Whether there is an affinity of pro-coagulatory receptors on the surface of thrombocytes for complement components, as recently shown for the PAR1 and PAR4 on endothelial cells (Debrezzeni et al., 2019; Wang, Ricklin, & Lambris, 2017), will have to be addressed in future research. Although it may be tempting to speculate that all these mechanisms shown mainly for the setting of infection and sepsis hold true for traumatic tissue injury, well-crafted studies are necessary to further elucidate the pathophysiology of a platelet–complement crosstalk after multiple injuries.

4 | EARLY TRAUMA MANAGEMENT—DRIVER OF COMPLEMENT ACTIVATION AND ALTERATION?

Early anaesthesiological, surgical management and damage control are crucial for the stabilisation of vital functions in severely traumatised patients and for improved outcome and quality of life. However, the benefits of early interventions may also be malefic for the innate immune response and the clinical course in severely traumatised patients.

Life-saving algorithms address the underlying trauma-induced pathophysiology and mainly aim to rapidly transfer oxygen into the cells. Securing the airways, for example by tracheal intubation, and support of breathing, for example by mechanical ventilation, can result in (additional) ventilator-induced lung injury, which activates central complement components (Chen, Xia, Shang, & Yao, 2018; Liu et al., 2013). Initial volume resuscitation, which is necessary to stabilise haemodynamics, may hyperdilute complement factors and thus compromise their proper function. Blood products, including whole blood and fresh frozen plasma, contain complement factors, which are dependent on the isolation protocol and storage conditions of the products, may contain complement activation products of variable quantity and quality (Cardigan et al., 2001; Sgehatchian & Samama, 2012; Sonntag, Stiller, Walla, & Maier, 1997).

In a porcine haemorrhagic shock model, CH50, a marker for haemolytic complement activity, dropped during the shock phase, indicating excessive complement activation before reperfusion was applied. Resuscitation with plasma expanders, however, caused an additional 20% of complement consumption, whereas, as predicted, whole blood transfusion subsequently increased CH50 values (Szebeni et al., 2003). Interestingly, in the same model, the lactic acidotic environment resulted in the enhanced generation of the anaphylatoxin C5a, suggesting that normalising the pH balance is crucial to avoid further complement activation during haemorrhagic shock (Szebeni et al., 2003). This reflects the clinical priority to avoid the lethal triad of acidosis, low temperature and coagulopathy.

To prevent or treat trauma-induced coagulopathy, defined transfusion protocols are used, and early tranexamic acid application can be indicated. However, tranexamic acid can activate the complement cascade with C5a generation (Barrett et al., 2019; Barrett & Yaffe, 2020). By contrast in a rat polytrauma model, enhanced systemic C5a concentrations were even reduced by tranexamic acid (Wu, Dubick, Schwacha, Cap, & Darlington, 2017). In general, anticoagulants like heparin may alter complement stimulation.

For haemodynamic and organ monitoring of severely injured patients, various catheters are set in place, although any kind of artificial surface, even small, activates not only the contact and coagulation but also the complement system (Mollnes, 1998). Life-saving surgical procedures include the stopping of major bleeding, debris removal and decompression of compressed tissues (e.g. intracranial haematoma, haemato-/pneumothorax and compartment syndromes). Although vital, these procedures can act as a “second hit,” which generates further tissue trauma and adds to the innate immune challenge and complement activation as a crucial part. To stabilise bone fractures or reconstruct damaged joints, highly sophisticated osteosynthesis materials have been developed. Nevertheless, besides the additional tissue trauma (Lackner et al., 2020) and potential blood loss, the osteosynthesis material itself may activate the complement system locally if not also systemically (Mödinger, Teixeira, Neidlinger-Wilke, & Ignatius, 2018). Furthermore, after wound debridement the wound dressing with various materials may more or less locally activate complement (Denzinger et al., 2019) (Figure 2).

Intensive care, accompanied by infectious and organ complications, may require (temporal) an organ replacement therapy, including haemodialysis or extracorporeal oxygenation. In turn, these procedures activate complement mainly via large artificial surfaces (Millar, Fanning, McDonald, McAuley, & Fraser, 2016).
The complement components are constitutively produced mainly in the liver and kidneys but also in other organs. Overall, abundant amounts of central complement components, including C3, are provided, which can immediately mount a sufficient complement response upon activation. However, in the case of severe trauma, complement factors become depleted, similar to coagulation factors. Furthermore, direct or remote injury and/or hypoxic conditions of the complement-producing organs will prevent de novo synthesis and impair, if not stopped, the delivery of complement components. This is reflected by the considerably decreased CH50 after multiple trauma, which is even indicative of the final outcome (Burk et al., 2012). In addition to early systemic activation, this decreased complement functionality, which persists up to 5 days after injury, coined the word of trauma-induced “complementopathy” (Burk et al., 2012). Later reports supported this paradigm and accordingly also reported low C3 and C5 levels after trauma (Li et al., 2019). In addition to early systemic activation, this decreased complement functionality, which persists up to 5 days after injury, coined the word of trauma-induced “complementopathy” (Burk et al., 2012).

On the receptor level, there is a loss of the anaphylatoxin receptor C5a1 receptor on neutrophils early after severe trauma, which is indicative for trauma complications, including the development of infections (Amara, Flierl, et al., 2010; Morris et al., 2011). As to the amount of the receptor that is shed via microvesicles (Karasu et al., 2018), internalised and degraded or recycled remains unclear.

However, the C5a signal processing appears to be altered, resulting in altered neutrophil functions, including altered electrophysiological features as observed in porcine traumatic haemorrhagic shock (Messerer et al., 2018).

On the tissue level, it is also likely that a decrease or loss of membrane-bound CRegs may indirectly support complement activation. During hypoxic conditions (in the experimental context of murine tracheal transplantation), hypoxia-inducible factor 1-α has been shown to reduce CD55 and thereby support endothelial deposition of active C3 as a major molecular signature of tissue microvascular injury (Khan et al., 2020). In polytrauma patients, the Creg profiles of leukocytes were also altered, with decreased CD46 and enhanced CD55 expression values, indicating less control and thus facilitation of complement activation after severe tissue injury (Amara et al., 2010). Another aspect of trauma-induced modified complement function is the altered regeneration of injured organs. In murine partial hepatectomy, C3 and its activation products are necessary for liver tissue regeneration (Markiewski et al., 2009; Strey et al., 2003). Recent reports propose also intracellular C3 (of Paneth cells) as essential for intestinal epithelial regeneration after an acute gastrointestinal injury (Ye et al., 2019). Therefore, C3 depletion or degradation by severe trauma might reduce a C3-related signal for the induction of regenerative processes and healing. Future research needs to further elucidate these mechanisms in the context of trauma.

**FIGURE 2** Early therapeutic approaches - driver of complement alterations. Initial therapeutic interventions for stabilising the patients’ state lead to dysregulated complement functionality
to systemic complement activation products. Furthermore, complement-tagged (opsonised) debris and extracellular vesicles with complement factors can act as triggers for innate immune and cellular reactions (Karasu et al., 2018) and as modulators of complex organ crosstalk and dysfunction (Rittirsch, Redl, & Huber-Lang, 2012). Following initial inflammation, complement activation products also induce regenerative processes (Zhang et al., 2017). In leukocytes isolated from polytrauma patients, an integrated clinic-transcriptomic approach revealed enhanced C5 expression levels particularly in those who later developed post-traumatic nosocomial infections (Rittirsch et al., 2015). In addition, studies in humans and mice indicated that haemorrhagic shock primes neutrophils in a C5a-dependent manner for ROS generation, which in turn contributes to experimental endothelial barrier loss and organ injury (Barrett et al., 2018). To limit this review to the most important complement actions after trauma, we focus on the major vital organs: brain, heart, lungs, liver and kidney (see also Figure 3).

### 6.1 Brain

The function of complement after traumatic brain injury and spinal cord injury has recently been reviewed in detail, proposing a Janus-faced role of complement post injury (Hammad, Westacott, & Zaben, 2018; Roselli, Karasu, Volpe, & Huber-Lang, 2018). Since then, several new aspects have emerged. In a 5-year study on trauma patients, sC5b-9 serum concentrations were significantly enhanced after isolated traumatic brain injury but remarkably not in traumatic brain injury patients with additional femur shaft fracture. Because no time course was provided, the underlying mechanism needs further elucidation (Parry et al., 2020). The first evidence in human brain tissues, obtained from traumatic brain injury patients in comparison to non-traumatic brain injury patients, clearly indicated a significant role of the lectin pathway after trauma in immunohistological and ELISA analyses with elevated concentrations of MBL, ficolin-1, -2 and -3, MASP-2 and MASP-3, and iC3b/C3b as well as terminal complement complex inside and outside brain vessels in all contused areas (De Blasio et al., 2019).

In a rodent traumatic brain injury model, the multifunctional astrocytes in the brain switched their function towards a toxic, disruptive astrocyte phenotype (A1) with the damage marker glial fibrillary acidic protein and C3 as characteristic features and a morphologically more complex pattern of arborization as early as 7 days after traumatic brain injury (Clark et al., 2019). To what extent C3 is involved in the arborization remains unclear. A recent report also highlighted the

**FIGURE 3** Effects of complement activation on vital cross-talking organs post trauma. Systemic activation of the complement system affects the function of several organs. In the heart, trauma causes an alteration in the anaphylatoxin receptor expression levels as well as increased complement deposition. *In vitro* analysis revealed C3a- and C5a-mediated impairment of cardiomyocyte functions. In the brain, strong lectin pathway activation occurs, eventually leading to increased terminal pathway activation as measured by increased sC5b-9 serum concentrations. Trauma induces an elevated expression of complement proteins, an effect that even retains over weeks ("complement scar"). Post-traumatic increased complement deposition can be also detected in the kidney. However, blockage of the cascade at the level of C3 or even upstream by the C1 esterase inhibitor can preserve renal function. Trauma-mediated complement activation seems to interfere with the balance between liver injury and regeneration. Complement activation characterised by C3 deposition and membrane attack complex formation can be limited by the application of decay accelerating factor (DAF) or cobra venom factor (CVF), thus improving the hepatic injury score. Increased systemic anaphylatoxin levels correlate with acute/adult respiratory distress syndrome and can cause in a long-term lung fibrosis. Blast-induced thorax trauma induces an up-regulation of C3 in lung tissues. Oxygenation requirement and the resulting hyperoxic state result in alveolar cytokine accumulation as well as in the up-regulation of C5a3 receptor in lung tissues.
effects of ageing on the astrocyte-specific response post traumatic brain injury. Up to 7 days after murine traumatic brain injury, C1q expression in astrocytes was up-regulated in older but not (or significantly less) in younger mice. For C3, the pattern was almost reversed (Early, Gorman, Van Eldik, Bachstetter, & Morganti, 2020), suggesting a differential complement response after traumatic brain injury depending on the advance in age.

A site-directed approach has been previously reported. A D59-2a-CRIg dimer was designed to inhibit the membrane attack complex assembly at the injured sites of C3b/iC3b deposition. It was found to promote recovery in a murine traumatic brain injury model, the outcome being assessed by a neurological score, and inhibit several inflammatory reactions including inflammasome activation after trauma (Ruseva, Ramaglia, Morgan, & Harris, 2015).

In addition to triggering and modulating the neuroinflammatory response after traumatic brain injury (Alawieh, Langley, Weber, Adkins, & Tomlinson, 2018), complement also appears to be involved in long-term effects. In this regard, the canonical complement system, particularly C2 and C3, was up-regulated in the hippocampal and cortex regions after several weeks and up to 6 months in rat post traumatic brain injury (Boone et al., 2019). These long-term effects of altered complement expression in the defined brain areas could almost be considered as a "complement scar." Whether these effects of traumatic brain injury on complement may be directly involved in cell survival, neurodegeneration, and neuroplasticity remains to be further characterised. In translation to the clinical setting of traumatic brain injury, elevated MBL, C3 and C9 levels were detected in serum also up to 6 months post trauma (Bao et al., 2018), overall suggesting a wider window of therapeutic opportunities than previously appreciated.

For spinal cord injury, a differential role of the C5a₁ and C5a₂ receptors has been proposed. In murine spinal cord injury, genetic loss of the C5a₂ receptor resulted in an enhanced lesion volume, reduced myelin sparing and poor outcome. In contrast, specific blockade of C5a₂ receptor improved morphological and neurological outcome after spinal cord injury and, of note, could also reverse the C5a₂ receptor knockout-induced aggravation of the spinal repair (Biggins, Brennan, Taylor, Woodruff, & Ruitenberg, 2017). This further points out the potential ambivalent role of C5a depending on the addressed receptors.

### 6.2 Heart

While the concept of a complement-triggered cardiomyopathy accompanying sepsis has long been established with many pathophysiological mechanisms revealed (Fattahi et al., 2017; Hoesel et al., 2007; Kalbitz et al., 2016; Niederbichler et al., 2006), only recently has evidence emerged for complement-mediated cardiomyocyte impairment after trauma and haemorrhagic shock.

Interaction of C5a with its respective receptor leads to functional impairment of cardiomyocytes in terms of reduced sarcomere shortening and altered calcium homoeostasis (Hoesel et al., 2007; Kalbitz et al., 2016; Niederbichler et al., 2006). Additionally, C5a appears to alter connexin 43 expression in vitro (Lackner et al., 2020). Quantitative and spatial alterations of connexin 43, the most important component of the cardiac gap junction, could already be observed at very early time points after experimental trauma (Braun et al., 2017; Kalbitz et al., 2017), thereby potentially linking early cardiomyocyte injury and complement activation after trauma. However, recent studies suggest that cardiomyocytes react differently to the systemic inflammation in sepsis and in trauma. In a rodent model of blunt thorax trauma, an increase of C5a₁ receptor expression 24 h after trauma was associated with morphological and functional damage of heart cells (Kalbitz et al., 2017). Moreover, studies of experimental burn injury and sepsis proposed an up-regulation of C5a₁ receptor expression on cardiomyocytes as a hallmark of the complement-related reaction of cardiac cells to inflammatory damage (Hoesel et al., 2007; Niederbichler et al., 2006). In a recent complex porcine polytrauma study, the C5a₁ receptor content of cardiomyocyte lysates was decreased 72 h after trauma, whereas the C5a₂ receptor was unaffected, indicating a differential regulation and/or function (Kalbitz, Schwarz, et al., 2017). The role of C3a and its respective receptor in post-traumatic cardiomyopathy has not yet been defined. While (murine) heart cells have been shown to express the C3a receptor (Tornetta, Foley, Sarau, & Ames, 1997), conclusive studies on the role of C3a–C3a receptor interaction in the setting of severe tissue trauma and the concomitant systemic inflammation are rare. In vitro, C3a appears to have similar effects as C5a on human cardiomyocytes in terms of impaired calcium utilisation and increased oxygen consumption (Lackner et al., 2020). In the same study, C3a altered the expression of fatty acid-binding protein 3 and the key Ca²⁺-pump sarco/endoplasmic reticulum Ca²⁺-ATPase in cardiomyocytes, both being crucially involved in the homoeostasis of heart function (Lackner et al., 2020).

While these findings promise new strategies to target trauma-induced cardiomyopathy, the clinical relevance still needs to be determined. With the availability of specific complement inhibitors, carefully designed experimental and clinical studies are now warranted to address the question whether the interaction between the complement system and the heart plays a significant role in post-traumatic cardiac injury.

### 6.3 Lungs

Already four decades earlier, enhanced systemic complement activation with the generation of the potent chemoattractant C5a and resultant pulmonary recruitment of leukocytes was correlated to the development of adult respiratory distress syndrome (ARDS) (Hammerschmidt, Weaver, Hudson, Craddock, & Jacob, 1980). In addition, when complement regulatory proteins, including the membrane attack complex-inhibitor CD59, are under-expressed, complement activation may drive inflammation, endotheliopathy and development of pulmonary microthrombi clinically manifested as acute lung injury and adult respiratory distress syndrome...
(Chang, 2019). Direct trauma to the lungs with its large alveolar and endothelial surfaces frequently results in disruption of the blood-air barrier and thus directly provides complement factors by bleeding into the alveolar space and additional development of a hypoxic/anoxic microenvironment (Huber-Lang et al., 2018). Generation of C5a as a consequence of lung contusion was found in bronchoalveolar lavage fluids and correlated in humans to the extent of the damaged pulmonary volume (Hoth et al., 2014).

Blast-induced thorax trauma in rats with bilateral lung contusion caused a significant C3 up-regulation in injured lung tissues as early as 10 min after trauma, as detected by a hypothesis-free microarray analysis (Ehrnsthaller et al., 2015). In the same thorax trauma model, there was a time-dependent activation of complement determined by reduced CH50 values and increasing C5a-dependent chemotactic plasma activity (Flierl et al., 2008). When enhanced oxygen concentrations are needed for adequate oxygenation, for example, after severe bilateral lung trauma or during severe acute/adult respiratory distress syndrome, hyperoxia results in alveolar cytotoxicity and leukocyte accumulation, enhanced lung expression of C5a receptor and morphological signs of pulmonary inflammation, all of which are inhibited by a small peptide C5a antagonist (Xu, Tian, & Xie, 2014).

Regarding the terminal complement pathway, sC5b-9 formation preceded the development of acute/adult respiratory distress syndrome in the setting of human sepsis and appeared more sensitive for the prediction of acute/adult respiratory distress syndrome than the anaphylatoxins (Langlois & Gawryl, 1988).

A long-term effect of trauma-induced acute lung injury and acute/adult respiratory distress syndrome is particularly the development of lung fibrosis. There is evidence that C3a and C5a are main contributors to the development and progression of lung fibrosis via inflammation, mesenchymal stimulation, and matrix synthesis (Gu et al., 2016). Therefore, one could speculate that the enhanced pulmonary (and systemic) anaphylatoxin concentrations post trauma may also contribute to lung fibrosis in the long term.

Finally, any extrapulmonary injury, traumatic haemorrhagic shock, and ischaemia and reperfusion injury can contribute to the fluid-phase complement and cellular innate immune responses and worsen classical signs of lung injury (Huber-Lang et al., 2018).

6.4 Liver

The liver as the major metabolic organ and centre of complement production is frequently affected by direct or indirect trauma. It has been proposed that complement activation can influence the balance between liver injury and regeneration (Marshall, He, Zhong, Atkinson, & Tomlinson, 2014; Strey et al., 2003). Most effects of complement on the liver have been described in the setting of ischaemia and reperfusion (Arumugam, Shiels, Woodruff, Granger, & Taylor, 2004) but not in a trauma context. In a model of partial hepatectomy and ischaemia–reperfusion stress, injury site-targeted complement inhibition by CR2-CD59 was not only protective but significantly enhanced hepatocyte proliferation (Marshall et al., 2014). Remarkably, CR2-CD59 application could prevent in vivo mitochondrial depolarisation and lead to recovery of the ATP stores (Marshall et al., 2014). In blast-induced whole-body injury in rats, the liver displayed inflammatory cell infiltration, local thrombi, necrotic areas, apoptotic events and marked hepatocyte degeneration associated with CH50 reduction and C3 depletion (Yang et al., 2019). In mice, C3 deposition of hepatocytes was found after traumatic haemorrhagic shock, whereas C3-deficient littermates did not display shock-induced enhanced liver enzymes (Cai et al., 2010). In a porcine model of traumatic haemorrhagic shock with resuscitation strategy by hetastarch (in lactated electrolyte solution) application, there was an early development of hepatic injury, as determined by hepatocyte hydropic alteration, necrosis/apoptosis, and vascular congestion as well as inflammatory infiltration. By contrast, application of the decay accelerating factor (CD55), which prevents the assembly of the C3/C5 convertases, resulted in a significantly improved hepatic (and renal) injury score (Dalle Lucca et al., 2013).

Trauma modelling in rats with femur fracture and haemorrhagic shock (with a mean arterial pressure of 30 mmHg for 90 min) resulted in clear signs of hepatic injury reflected by spotty necrotic areas, albuminoid and vacuolar degeneration, hepatic infiltration of inflammatory cells, Kupffer cell proliferation, and enhanced liver enzymes (Wang et al., 2018). The trauma-induced remote morphological and functional changes of the liver as well as the outcome were significantly improved when complement C3 and C5 were inhibited by cobra venom factor injection (Wang et al., 2018). Furthermore, C5b-9 deposition on liver cells and hepatic C5a generation occurred after traumatic haemorrhagic shock, both of which were reduced upon cobra venom factor injection (Wang et al., 2018), indicating that complement activation may result in detrimental hepatic effects after severe trauma. Although the liver represents a central organ of innate immunity housing the generator of complement and the major arsenal (~80%) of macrophages (i.e. Kupffer cells), clinically meaningful studies to elucidate the role of complement and complement interventions in trauma remain lacking.

6.5 Kidneys

Complement activation is known to crucially contribute to acute kidney injury and organ failure during septic conditions (Hoehlig et al., 2013; Huber-Lang et al., 2001). C5a appears to be involved in damage of the glomerular filter, and therapeutic blockade of C5a could largely normalise proteinuria, urine output, and kidney function (Huber-Lang et al., 2001). However, less is known in the context of trauma, and most interactions of the kidney with complement components were discovered, again, in ischaemia–reperfusion models. For example, a recent study indicated that prolonged but not short-term ischaemia resulted in up-regulation of renal inducible haem-degrading enzyme haem oxygenase-1, which resulted in a renal inflammatory response associated with up-regulation of renal C5a receptor (Wang et al., 2019). To what extent ischaemia and reperfusion injury reflect acute kidney injury development after trauma, in which...
condition low-flow phenomena and disturbed perfusion are predominant rather than no-flow phenomena, remains a matter for debate.

In the clinical world, haemorrhagic shock is a major driver of acute kidney injury development in polytrauma patients. This is reflected by the fact of increased concentrations of neutrophil gelatinase-associated lipocalin (NGAL) and creatinine in the case of additional shock when trauma groups of an approximately similar injury severity score were compared over the first 3 days after injury (Halßgebauer et al., 2018). Similar effects were found as early as 4 h after polytrauma plus haemorrhagic shock in a mouse model (Denk et al., 2018). In pigs, traumatic haemorrhagic shock with subsequent resuscitation resulted in activation of renal complement, reflected by reduced CH50 values in renal venous blood between 12 and 22 h after shock in comparison to central blood and also by findings of C3c deposition of renal tissue (Ehrnthaller et al., 2019). Blocking C3 by a compstatin analogue in non-human primates with haemorrhagic shock led to an improved urine output and slight reduction of urine NGAL, suggesting some reno-protective effects (van Griensven et al., 2019). In porcine haemorrhagic shock, there was a time-dependent development of renal injury reflected by increased levels of both blood urea nitrogen and creatinine as early as 30 min after shock. Of note, these renal functional parameters could be almost normalised when a C1-inhibitor was applied 20 min after attaining the targeted shock level (Dalle Lucca et al., 2012), indicating complement as a major contributor to renal dysfunction during haemorrhagic shock-induced acute kidney injury. Indirect kidney injury by intensive renal cross-talking with other organs can only be speculated on. There is, for example, evidence that closed traumatic brain injury results in significant expression of key complement factors in the kidneys (C3d and C9) and induction of proapoptotic events, which were ameliorated by i.v. application of induced neuronal stem cells (Gao et al., 2017). Here, further research needs to address the exact role of complement activation products in the kidneys after trauma.

7 | THERAPEUTIC OUTLOOK: SURGERY PLUS COMPLEMENT-MODULATORY THERAPEUTIC APPROACHES AFTER SEVERE TISSUE TRAUMA

Surgical treatment concepts of traumatised patients, including damage control surgery or definite early total care, address trauma-induced tissue damage and aim in the patient to achieve a condition of haemodynamic and coagulatory stability and balanced organ function, including the maintenance or recovery of a sufficient immune system. Whereas multiple organ functions are monitored at the bedside, including the heart rate, oxygenation and urine output, the immune function, including the complement response post trauma, is very difficult to monitor, particularly in real time. Nevertheless, it appears mandatory to determine the complement activation status so as to target complement pathways in trauma and also in other conditions accordingly (Huber-Lang et al., 2016; Karasu, Nilsson, Köhl, Lambris, & Huber-Lang, 2019). Measurement of absolute concentrations of anaphylatoxins appears less ideal in the setting of trauma because the differences between healthy volunteers and severely injured patients may not be sufficiently discriminative. For example, in the case for C5a, a vast amount of the C5a receptors needs to be saturated before an excess of C5a could be detected in the blood. Therefore, not only the sole generation of C5a determines the systemic C5a concentrations and subsequent overall effects but also the numbers of leukocytes and their shedded microvesicles, as well as the corresponding content of surface-bound C5a1 and C5a2 receptors which in principle can rapidly clear the anaphylatoxin C5a from the circulation (Amara, Kalbitz, et al., 2010; Karasu et al., 2018). However, the ratio of the complement activation product and its consumption, for example the C3a/C3 ratio, might help to monitor the post-traumatic complement response and predict complications (Hecke et al., 1997). Furthermore, flowcytometric determination of the anaphylatoxin receptor profiles on leukocytes, which is accomplished within ~1 h after drawing blood, may represent a reasonable tool to indirectly assess the extent of complement activation (Amara, Kalbitz, et al., 2010). This has already been accomplished for patients in the intensive care unit, among them also patients after severe trauma, where the C5a1 receptor status on neutrophils has been proposed as a prognostic tool to predict infectious complications or sepsis outcome (Amara, Kalbitz, et al., 2010; Huber-Lang et al., 2005; Morris et al., 2011). Nevertheless, further scientific efforts are necessary to realise bedside immune and complement monitoring.

Regarding complement-modulatory therapies in the context of trauma, to date, there has only been one clinical trial. In this prospective study, a C1q inhibitor was applied in polytraumatised patients as early as upon arrival of the trauma patient in the emergency room. The study was powered for alterations in the systemic inflammatory response reflected by changes in systemic IL-6 levels but was closed based on recruitment problems (see clinical trials NCT01275976). However, in a porcine model of combined soft tissue injury, femur fracture and spleen injury, treatment with a recombinant human C1 esterase inhibitor (rhC1INH; conestat alfa) improved organ injury of the heart, lungs and intestine and, of note, also the survival rate (Campbell et al., 2016).

A preclinical study modelling traumatic haemorrhagic shock in non-human primates using a compstatin analogue (on the level of C3) revealed some protective effects on haemodynamics, cytokine profiles and organ function (van Griensven et al., 2019). When inhibiting C3 by decay accelerating factor, a recent study in rats with blast-induced blunt chest trauma displayed a decrease of the systemic pro- and anti-inflammatory cytokine profiles and an inhibition of the traumatic lung response by modulating the C3α–C3α receptor-high-mobility-group-protein-B1 transcriptional axis (Li et al., 2018).

Further downstream, C5a inhibition by an anti-C5a antibody injected in the above-mentioned rodent model of blunt chest trauma resulted in an inhibition of pulmonary and systemic neutrophil recruitment and amelioration of the cytokine response (Flierl et al., 2008). In a similar blunt thorax trauma plus femur fracture model, the application of the small peptide C5a1 antagonist PMX53 resulted in an improvement of trauma-induced impaired bone regeneration
(Recknagel et al., 2012). In this context, it is important to mention that most complement inhibitory strategies seem to be beneficial during the early inflammatory phase after trauma or hemorrhagic shock (Flierl et al., 2008; van Griensven et al., 2019), whereas long-term consequences of inhibiting complement activation products are less well known in regard to regeneration mechanisms. For example, treatment with a C5α antagonist helped to overcome the acute inflammatory impact of thorax trauma on fracture healing (Recknagel et al., 2012), but in contrast, fracture repair alone seems to be compromised in the genetic absence of C5 for weeks (Ehrnthaller et al., 2013), suggesting a putative time-dependent differential role of C5a after trauma.

Regarding neurotrauma, in a rat model of intracerebral haematoma, both complement inhibitors, N-acetyl-heparin (inhibition on the C3 level) and aurin tricarboxylic acid (membrane attack complex inhibitor) reduced early erythrolysis, brain iron deposition and brain injury (Wang et al., 2019). However, the translation into the traumatic brain injury setting is planned. In experimental traumatic brain injury, inhibition on the C3 level appears overall to be protective (Roselli et al., 2018), particularly when accomplished locally at the injury site, for example by the complement receptor 2-conjugated inhibitor (mTT30) (Rich et al., 2016). In the case of experimental spinal cord injury, different effects for the inhibition of the C3a/C3a receptor interaction have been reported: C3a receptor activation appears protective in spinal cord injury by the inhibition of chemotactic recruitment of neutrophils to the injury site (Brennan et al., 2019). Mechanistically, C3a is proposed to be a negative regulator of the PI3K/AKT pathway and thereby to restrain post-traumatic neutrophil mobilisation from the bone marrow. A relatively novel therapeutic approach may be various forms of microvesicles, which appear to be crucial in complement communication and remote effects of complement (Karasu et al., 2018). In the context of traumatic brain injury, years after trauma, astrocyte-derived exosomes with enhanced levels of central complement factors, for example C4b, factor D, Bb, MBL, C3b and C5b-9, were found in military veterans (Goetzl et al., 2020). In experimental spinal cord injury, exosomes derived from mesenchymal stem cells accumulated at the injury site, mainly bound to microglial cells, and could inhibit local complement activation (Zhao et al., 2019).

Other treatment strategies such as haemoadsorbance of inflammatory cytokines may also adsorb complement (activation) products (Datzmann & Träger, 2018) and thus alter the functionality of the complement cascade (Figure 4).

Currently, a wide range of complement inhibitors targeting specific components of the complement cascade are available and ready for use.
for clinical investigation. However, to integrate complement-modulatory treatment strategies, clinically relevant research in the field of trauma, shock and ischaemic conditions is needed in the future.

7.1 Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in the IUPHAR/BPS Guide to PHARMACOLOGY http://www.guidetopharmacology.org and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20 (Alexander et al., 2019).

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ORCID

Jörg Köhn https://orcid.org/0000-0003-1121-3178

REFERENCES

Alawieh, A., Langley, E. F., Weber, S., Adkins, D., & Tomlinson, S. (2018). Identifying the role of complement in triggering neuroinflammation after traumatic brain injury. Journal of Neuroscience, 38(10), 2519–2532. https://doi.org/10.1523/JNEUROSCI.2197-17.2018

Alexander, S. P. H., Kelly, E., Mathie, A., Peters, J. A., Veale, E. L., Armstrong, J. F., ... Wong, S. S. (2019). The concise guide to pharmacology 2019/20: Introduction and other protein targets. British Journal of Pharmacology, 176(S1). https://doi.org/10.1111/bph.14747

Amara, U., Flierl, M. A., Rittirsch, D., Klos, A., Chen, H., Acker, B., ... Huber-Lang, M. (2010). Molecular intercommunication between the complement and coagulation systems. Journal of Immunology (Baltimore, Md.: 1950), 185(9), 5626–5636. https://doi.org/10.4049/jimmunol.0903678

Amara, U., Kalbitz, M., Perl, M., Flierl, M. A., Rittirsch, D., Weiss, M., ... Huber-Lang, M. (2010). Early expression changes of complement regulatory proteins and C5a receptor (CD88) on leukocytes after multiple injury in humans. Shock (Augusta, Ga.), 33(6), 568–575. https://doi.org/10.1097/SHK.0b013e3181c999d4

Amara, U., Rittirsch, D., Flierl, M., Bruckner, U., Klos, A., Gebhard, F., & Huber-Lang, M. (2008). Interaction between the coagulation and complement system. Advances in Experimental Medicine and Biology, 632, 71–79. https://doi.org/10.1007/978-0-387-78952-1_6

Arumugam, T. V., Shiels, I. A., Woodruff, T. M., Granger, D. N., & Taylor, S. M. (2004). The role of the complement system in ischemia-reperfusion injury. Shock (Augusta, Ga.), 21(5), 401–409. https://doi.org/10.1197/0000243282004050000002

Atif, G., Aisiku, O., Shapiro, N., Hauser, C., Dalle Lucca, J., Flamenhaft, R., & Tsokos, G. C. (2016). Complement activation in trauma patients alters platelet function. Shock (Augusta, Ga.), 46(3 Suppl 1), 83–88. https://doi.org/10.1097/SHK.0000000000000675

Banerjee, A., Stillman, C. C., Moore, E. E., Dzieciatkowa, M., Kelher, M., Savaia, A., ... Hansen, K. (2018). Systemic hyperfibrinolysis after trauma: A pilot study of targeted proteomic analysis of superposed mechanisms in patient plasma. The Journal of Trauma and Acute Care Surgery, 84(6), 929–938. https://doi.org/10.1097/TA.0000000000001878

Bao, W., He, F., Yu, L., Gao, J., Meng, F., Ding, Y., ... Luo, B. (2018). Complement cascade on severe traumatic brain injury patients at the chronic unconscious stage: Implication for pathogenesis. Expert Review of Molecular Diagnostics, 18(8), 761–766. https://doi.org/10.1080/14773159.2018.1471985

Barrett, C. D., Hsu, A. T., Elson, C. D., Miyazawa, B., Kong, Y.-W., Greenwood, J. D., ... Yaffe, M. B. (2018). Blood clotting and traumatic injury with shock mediates complement-dependent neutrophil priming for extracellular ROS, ROS-dependent organ injury and coagulopathy. Clinical and Experimental Immunology, 194(1), 103–117. https://doi.org/10.1111/cei.13166

Barrett, C. D., Moore, H. B., Kong, Y.-W., Chapman, M. P., Sriman, G., Lim, D., ... Yaffe, M. B. (2019). Tranexamic acid mediates proinflammatory and anti-inflammatory signaling via complement C5a regulation in a plasminogen activator-dependent manner. The Journal of Trauma and Acute Care Surgery, 86(1), 101–107. https://doi.org/10.1097/TA.0000000000002092

Barrett, C. D., & Yaffe, M. B. (2020). Influence of tranexamic acid on the complement system in trauma. ANZ Journal of Surgery, 90(4), 418–420. https://doi.org/10.1111/ans.15538

Bekeschus, S., Lackmann, J.-W., Gimbérl, D., Napp, M., Schmidt, A., & Wende, K. (2018). A neutrophil proteomic signature in surgical trauma wounds. International Journal of Molecular Sciences, 19(3). https://doi.org/10.3390/ijms19030761

Biggins, P. J. C., Brennan, F. H., Taylor, S. M., Woodruff, T. M., & Ruitenbergen, M. J. (2017). The alternative receptor for complement component 5a, C5aR2, conveys neuroprotection in traumatic spinal cord injury. Journal of Neurotrauma, 34(12), 2075–2085. https://doi.org/10.1089/neu.2016.4701

Boone, D. R., Weisz, H. A., Willey, H. E., Torres, K. E. O., Falduto, M. T., Sinha, M., ... Hellmich, H. L. (2019). Traumatic brain injury induces long-lasting changes in immune and regenerative signaling. PLoS ONE, 14(4), e0214741. https://doi.org/10.1371/journal.pone.0214741

Braun, C. K., Kalbitz, M., Halbgewehr, R., Eisele, P., Messerer, D. A. C., Weckbach, S., ... Huber-Lang, M. S. (2017). Early structural changes of the heart after experimental polytrauma and hemorrhagic shock. PLoS ONE, 12(10), e0187327. https://doi.org/10.1371/journal.pone.0187327

Brennan, F. H., Jogia, T., Gillespie, E. R., Blomser, L. V., Li, X. X., Nowlan, B., ... Ruitenbergen, M. J. (2019). Complement receptor C3aR1 controls neutrophil mobilization following spinal cord injury through physiological antagonism of CXCR2. JCI Insight, 4(9). https://doi.org/10.1172/jci.insight.98254

Brinkmann, C. R., Jensen, L., Dagnæs-Hansen, F., Holm, I. E., Endo, Y., Fujita, T., ... Degn, S. E. (2013). Mitochondria and the lectin pathway of complement. The Journal of Biological Chemistry, 288(12), 8016–8027. https://doi.org/10.1074/jbc.M112.430204

Brohi, K., Singh, J., Heron, M., & Coats, T. (2003). Acute traumatic coagulopathy. The Journal of Trauma, 54(6), 1127–1130. https://doi.org/10.1097/01.TA.0000069184.82147.06

Burk, A. M., Martin, M., Flierl, M. A., Rittirsch, D., Helm, M., Lampl, L., ... Huber-Lang, M. (2012). Early complementopathy after multiple injuries in humans. Shock (Augusta, Ga.), 37(4), 348–354. https://doi.org/10.1097/SHK.0b013e3182471795

Cai, C., Gill, R., Eum, H.-A., Loughran, P. A., Darwiche, S., ... Billiar, T. R. (2010). Complement factor 3 deficiency attenuates hemorrhagic shock-related hepatic injury and systemic inflammatory response syndrome. American Journal of Physiology. Regulatory, Integrative and Comparative Physiology, 299(5), R1175–R1182. https://doi.org/10.1152/ajpregu.00282.2010

Campbell, J. C., Li, Y., van Amersfoort, E., Relan, A., Dubick, M., Sheppard, F., ... Dalle Lucca, J. J. (2016). C1 inhibitor limits organ injury and prolongs survival in swine subjected to battlefield simulated injury,
activation in mouse closed head injury models. Scientific Reports, 7, 45989. https://doi.org/10.1038/srep45989

Goetzl, E. J., Yaffe, K., Peltz, C. B., Ledreux, A., Gorgens, K., Davidson, B., ... Greig, N. H. (2020). Traumatic brain injury increases plasma astrocyte-derived exosome levels of neurotoxic complement proteins. FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology, 34(2), 3359–3366. https://doi.org/10.1096/fj.201902842R

Gu, H., Fisher, A. J., Mickler, E. A., Duerson, F., Cummings, O. W., Peters-Golden, M., ... Vittal, R. (2016). Contribution of the anaphylatoxin receptors, C3aR and C5aR, to the pathogenesis of pulmonary fibrosis. FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology, 30(6), 2336–2350. https://doi.org/10.1096/fj.201500044

Gulla, K. C., Gupta, K., Karup, A., Gal, P., Schwaebel, W. J., Sim, R. B., ... Hajela, K. (2010). Activation of mannann-binding lectin-associated serine proteinases leads to generation of a fibrin clot: MASPs generate a fibrin clot. Immunology, 129(4), 482–495. https://doi.org/10.1111/j.1365-2567.2009.03200.x

Hajishengallis, G., Reis, E. S., Mastellos, D. C., Ricklin, D., & Lambris, J. D. (2017). Novel mechanisms and functions of complement. Nature Immunology, 18(12), 1288–1298. https://doi.org/10.1038/ni.3858

Halbgbeauer, R., Braun, C. K., Denk, S., Mayer, B., Cinelli, P., Rademacher, P., ... Huber-Lang, M. (2018). Hemorrhagic shock drives glycoalyx barrier and organ dysfunction early after polytrauma. Journal of Critical Care, 44, 229–237. https://doi.org/10.1016/j.jcc.2017.11.025

Hammad, A., Westcott, L., & Zaben, M. (2018). The role of the complement system in traumatic brain injury: A review. Journal of Neuroinflammation, 15(1), 24. https://doi.org/10.1186/s12974-018-1066-z

Hammerschmidt, D. E., Weaver, L. J., Hudson, L. D., Craddock, P. R., & Jacob, H. S. (1980). Association of complement activation and inflammation in mouse closed head injury models. The Journal of the American Society for Experimental Biology, 21(12), 2236–2246. https://doi.org/10.1038/mt.2013.178

Hoesel, L. M., Niederbichler, A. D., Schafer, J., Ipkachti, K. R., Gao, H., Rittirsch, D., ... Ward, P. A. (2007). C5a-blockade improves burn-induced cardiac dysfunction. Journal of Immunology (Baltimore, Md.: 1950), 176(12), 7902–7910. https://doi.org/10.4049/jimmunol.176.12.7902

Hoth, J. J., Wells, J. D., Jones, S. E., Yozu, B. K., & McCall, C. E. (2014). Complement mediates a primed inflammatory response after traumatic lung injury. The Journal of Trauma and Acute Care Surgery, 76(3), 601–609. https://doi.org/10.1097/TA.0000000000001259

Huber-Lang, M., Denk, S., Fulda, S., Erler, E., Kalbitz, M., Weckbach, S., ... Perl, M. (2012). Cathespisin D is released after severe tissue trauma in vivo and is capable of generating C5a in vitro. Molecular Immunology, 50(1–2), 60–65. https://doi.org/10.1016/j.molimm.2011.12.005

Huber-Lang, M., Gebhard, F., Schmidt, C. Q., Palmer, A., Denk, S., & Wiegener, R. (2016). Complement therapeutic strategies in trauma, hemorrhagic shock and systemic inflammation—Closing Pandora’s box? Seminars in Immunology, 28(3), 278–284. https://doi.org/10.1016/j.smim.2016.04.005

Huber-Lang, M., Lambris, J. D., & Ward, P. A. (2018). Innate immune responses to trauma. Nature Immunology, 19(4), 327–341. https://doi.org/10.1038/s41590-018-0064-8

Huber-Lang, M., Sarma, J. V., Rittirsch, D., Schreiber, H., Weiss, M., Flierm, M., ... Ward, P. A. (2005). Changes in the novel orphan, C5a receptor (C5L2), during experimental sepsis and sepsis in humans. The Journal of Immunology, 174(2), 1104–1110. https://doi.org/10.4049/jimmunol.174.2.1104

Huber-Lang, M., Sarma, V. J., Lu, K. T., McGuire, S. R., Padgaonkar, V. A., Guo, R. F., ... Ward, P. A. (2001). Role of C5a in multiorgan failure during sepsis. Journal of Immunology (Baltimore, Md.), 166(2), 1193–1199. https://doi.org/10.4049/jimmunol.166.2.1193

Irmscher, S., Döring, N., Halder, L. D., Jo, E. A. H., Kopka, I., Dunker, C., ... Skerka, C. (2018). Kallikrein cleaves C3 and activates complement. Journal of Innate Immunity, 10(2), 94–105. https://doi.org/10.1159/000484257

James, S. L., Abate, D., Abate, K. H., Abay, S. M., Abbafati, C., Abbasi, N., ... Murray, C. J. L. (2018). Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries in 195 countries and territories, 1990–2017: A systematic analysis for the Global Burden of Disease Study 2017. Lancet (London, England), 392(10159), 1789–1858. https://doi.org/10.1016/S0140-6736(18)32279-7

Jenny, L., Dobó, J., Gál, P., & Schroeder, V. (2015). MASP-1 of the complement system promotes clotting via prothrombin activation. Molecular Immunology, 65(2), 398–405. https://doi.org/10.1016/j.molimm.2015.02.014

Jokiranta, T. S., Cheng, Z.-Z., Seeberger, H., Jäisi, M., Heinen, S., Noris, M., ... Zipfel, P. F. (2005). Binding of complement factor H to endothelial cells is mediated by the carboxy-terminal glycosaminoglycan binding site. The American Journal of Pathology, 167(4), 1173–1181. https://doi.org/10.1016/S0002-9440(04)61205-9

Kalbitz, M., Amann, E. M., Bosch, B., Palmer, A., Schultze, A., Pressmar, J., ... Huber-Lang, M. (2017). Experimental blunt chest trauma-induced myocardial inflammation and alteration of gap-junction protein connexin 43. PLoS ONE, 12(11), e0187270. https://doi.org/10.1371/journal.pone.0187270

Kalbitz, M., Fattahi, F., Grailler, J. J., Jajou, L., Malan, E. A., Zetouné, F. S., ... Ward, P. A. (2016). Complement-induced activation of the cardiac NRNP1 inflammasome in sepsis. FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology, 30(12), 3997–4006. https://doi.org/10.1096/fj.201600728R

Kalbitz, M., Fattahi, F., Herron, T. J., Grailler, J. J., Jajou, L., Lu, H., ... Ward, P. A. (2016). Complement destabilizes cardiomyocyte function in vivo after polymicrobial sepsis and in vitro. Journal of Immunology (Baltimore, Md.), 190(2), 2353–2361. https://doi.org/10.4049/jimmunol.1600091

Kalbitz, M., Schwarz, S., Weber, B., Bosch, B., Pressmar, J., Hoenes, F. M., ... Hildebrand, F. (2017). Cardiac depression in pigs after multiple trauma—Characterization of posttraumatic structural and functional alterations. Scientific Reports, 7(1), 17861. https://doi.org/10.1038/s41598-017-18088-1

Kanse, S. M., Gallemueller, A., Zeerleder, S., Stephan, F., Rannou, O., Denk, S., ... Huber-Lang, M. (2012). Factor VII-activating protease is activated in multiple trauma patients and generates anaphylatoxin C5a. Journal of Immunology (Baltimore, Md.), 190(6), 2858–2865. https://doi.org/10.4049/jimmunol.1103029

Karasu, E., Eisenhardt, S. U., Harant, J., & Huber-Lang, M. (2018). Extracellular vesicles: Packages sent with complement. Frontiers in Immunology, 9. https://doi.org/10.3389/fimmu.2018.00721

Karasu, E., Nilsson, B., Köhl, J., Lambris, J. D., & Huber-Lang, M. (2019). Targeting complement pathways in polytrauma- and sepsis-induced multiple-organ dysfunction. Frontiers in Immunology, 10. https://doi.org/10.3389/fimmu.2019.00543
Kenawy, H. I., Boral, I., & Bevington, A. (2015). Complement–coagulation cross-talk: A potential mediator of the physiological activation of complement by low pH. *Frontiers in Immunology*, 6(215). https://doi.org/10.3389/fimmu.2015.00215

Keragala, C. B., Draxler, D. F., McQuilten, Z. K., & Medcalf, R. L. (2018). Haemostasis and innate immunity—A complementary relationship? A review of the intricate relationship between coagulation and complement pathways. *British Journal of Haematology*, 180(6), 782–798. https://doi.org/10.1111/bjh.15062

Keshari, R. S., Silasi, R., Lupu, C., Taylor, F. B., & Lupu, F. (2017). In vivo-generated thrombin and plasmin do not activate the complement system in baboons. *Blood*, 130(24), 2678–2681. https://doi.org/10.1182/blood-2017-06-788216

Khan, M. A., Shamma, T., Kazmi, S., Altuhami, A., Ahmed, H. A., Assiri, A. M., & Broering, D. C. (2020). Hypoxia-induced complement dysregulation is associated with microvascular impairments in mouse tracheal transplant. *Journal of Translational Medicine*, 18(1), 147. https://doi.org/10.1186/s12976-020-02305-z

Kios, A., Tenner, A. J., Jothswh, K.-O., Ager, R. R., Reis, E. S., & Köhl, J. (2009). The role of the anaphylatoxins in health and disease. *Molecular Immunology*, 46(14), 2753–2766. https://doi.org/10.1016/j.molimm.2009.04.027

Kozarcin, H., Lood, C., Munthe-Fog, L., Sandholm, K., Hamad, O. A., Bengtsson, A. A., & Nilsson, B. (2016). The lectin complement pathway of Thrombosis and Haemostasis: JTH. *Histochemistry and Cell Biology*, 143(3), 351–545. https://doi.org/10.1007/-11111-135208

Krarup, A., Wallis, R., Presanis, J. S., Gál, P., & Sim, R. B. (2007). Complement analysis method and the roles of glycosaminoglycans in community. 2681. https://doi.org/10.1182/blood-2012-02-412080

Kucchesi, B. R. (1993). Complement activation, neutrophils, and oxygen radicals in reperfusion injury. *Stroke*, 24(12 Suppl), I41–H7; discussion I38–40. https://doi.org/10.1016/0228-2829(92)90127-l

Markiewski, M. M., DeAngelis, R. A., Strey, C. W., Foukas, P. G., Gerard, C., Gerard, N., ... Lambris, J. D. (2009). The regulation of liver cell survival by complement. *Journal of Immunology* (Baltimore, Md. : 1950), 182(9), 5412–5418. https://doi.org/10.4049/jimmunol.0804179

Marshall, K. M., He, S., Zhong, Z., Atkinson, C., & Tomlinson, S. (2014). Dissecting the complement pathway in hepatic injury and regeneration with a novel protective strategy. *The Journal of Experimental Medicine*, 211(9), 1793–1805. https://doi.org/10.1087/jem.20131902

Martel, C., Cointe, S., Maurice, P., Matar, S., Ghiteuc, M., Théroux, P., & Bonnefoy, A. (2011). Requirements for membrane attack complex formation and anaphylatoxins binding to collagen-activated platelets. *PLoS ONE*, 6(4), e18812. https://doi.org/10.1371/journal.pone.0018812

McNamee, A. P., Tansley, G. D., & Simmonds, M. J. (2018). Sublethal mechanical trauma alters the electrochemical properties and increases aggregation of erythrocytes. *Microvascular Research*, 120, 1–7. https://doi.org/10.1016/j.mvr.2018.05.008

Meri, S. (2016). Self-nonself discrimination by the complement system. *FEBS Letters*, 590(15), 2418–2434. https://doi.org/10.1002/1873-6468.12284

Messerer, D. A. C., Denk, S., Führ, K. J., Halgebeuer, R., Braun, C. K., Hänès, F., ... Huber-Lang, M. S. (2018). Complement C5a alters the membrane potential of neutrophils during hemorrhagic shock. *Mediators of Inflammation*, 2018(2052356). https://doi.org/10.1155/2018/2052356

Millar, J. E., Fanning, J. P., McDonald, C. I., McAuley, D. F., & Fraser, J. F. (2016). The inflammatory response to extracorporeal membrane oxygenation (ECMO): A review of the pathophysiology. *Critical Care* (London, England), 21(1), 387. https://doi.org/10.1186/s13054-016-1570-4

Mödinger, Y., Teixeira, G. Q., Neidlinger-Wilke, C., & Ignatius, A. (2018). Role of the complement system in the response to orthopedic biomaterials. *International Journal of Molecular Sciences*, 19(11). https://doi.org/10.3390/ijms19113367

Mollnes, T. E. (1998). Complement and biocompatibility. *Vox Sanguinis*, 74 (Suppl 2), 303–307. https://doi.org/10.1111/j.1423-0410.1998.tb05435.x

Morris, A. C., Brittan, M., Wilkinson, T. S., McAuley, D. F., Antonelli, J., McColloch, C., ... Simpson, A. J. (2011). C5a-mediated neutrophil dysfunction is RhoA-dependent and predicts infection in critically ill patients. *Blood*, 117(9), 5178–5188. https://doi.org/10.1182/blood-2010-08-304667

Narang, A., Qiao, F., Atkinson, C., Zhu, H., Yang, X., Kulik, L., ... Tomlinson, S. (2017). Natural IgM antibodies that bind neopeptopes exposed as a result of spinal cord injury, drive secondary injury by activating complement. *Journal of Neuroinflammation*, 14(1), 120. https://doi.org/10.1186/s12974-017-0894-6

Niederbichler, A. D., Hoesel, L. M., Westfall, M. V., Gao, H., Ipaekchi, K. R., Sun, L., ... Ward, P. A. (2006). An essential role for complement C5a in the pathogenesis of septic cardiac dysfunction. *The Journal of Experimental Medicine*, 203(1), 53–61. https://doi.org/10.1084/jem.20051207

Nordling, H., Giesser, A., Patzelt, J., Sauter, R., Emschermann, F., Stellos, K., ... Langer, H. F. (2016). Platelet bound oxLDL shows an inverse
von Zabern, V. W., Hesse, D., Nolte, R., & Haller, Y. (1987). Generation of an activated form of human C5 (C5b-like C5) by oxygen radicals. *Immunology Letters*, 14(3), 209–215. https://doi.org/10.1016/0165-2478(87)90103-9

Wang, B., Xu, H., Li, J., Gao, H.-M., Xing, Y.-H., Lin, Z., ... Cao, S.-H. (2018). Complement depletion with cobra venom factor alleviates acute hepatic injury induced by ischemia–reperfusion. *Molecular Medicine Reports*, 18(5), 4523–4529. https://doi.org/10.3892/mmr.2018.9484

Wang, H., Ricklin, D., & Lambris, J. D. (2017). Complement-activation fragment C5a mediates effector functions by binding as un tethered agonist to protease-activated receptors 1 and 4. *Proceedings of the National Academy of Sciences of the United States of America*, 114(41), 10948–10953. https://doi.org/10.1073/pnas.1707364114

Wang, L., Vijayan, V., Jang, M.-S., Thorenz, A., Greite, R., Rong, S., ... Gueler, F. (2019). Labile heme aggravates renal inflammation and complement activation after ischemia reperfusion injury. *Frontiers in Immunology*, 10. https://doi.org/10.3389/fimmu.2019.02975

Wang, M., Hua, Y., Keep, R. F., Wan, S., Novakovic, N., & Xi, G. (2019). Complement inhibition attenuates early erythrolysis in the hematoma and brain injury in aged rats. *Stroke*, 50(7), 1859–1868. https://doi.org/10.1161/STROKEAHA.119.025170

Wingrove, J. A., DiScipio, R. G., Chen, Z., Potempa, J., Travis, J., & Hugl, T. E. (1992). Activation of complement components C3 and C5 by a cysteine proteinase (gingipain-1) from *Porphyromonas gingivalis* (Bacteroides) *gingivalis*. *The Journal of Biological Chemistry*, 267(26), 18902–18907.

Wu, M. C. L., Brennan, F. H., Lynch, J. P. L., Mantovani, S., Phipps, S., Wetsel, R. A., ... Woodruff, T. M. (2013). The receptor for complement component C3a mediates protection from intestinal ischemia–reperfusion injuries by inhibiting neutrophil mobilization. *Proceedings of the National Academy of Sciences*, 110(23), 9439–9444. https://doi.org/10.1073/pnas.1218815110

Wu, X., Dubick, M. A., Schwacha, M. G., Cap, A. P., & Darlington, D. N. (2017). Tranexamic acid attenuates the loss of lung barrier function in a rat model of polytrauma and hemorrhage with resuscitation. *Shock* (Augusta, Ga.), 47(4), 500–505. https://doi.org/10.1097/SHK.0000000000001510

Xie, C. B., Jane-Wit, D., & Pober, J. S. (2020). Complement membrane attack complex: New roles, mechanisms of action and therapeutic targets. *The American Journal of Pathology*, 190(6), 1138–1150. https://doi.org/10.1016/j.ajpath.2020.02.006

Xu, Y., Tian, Z., & Xie, P. (2014). Targeting complement anaphylatoxin C5a receptor in hyperoxic lung injury in mice. *Molecular Medicine Reports*, 10(4), 1786–1792. https://doi.org/10.3892/mmr.2014.2394

Yang, Z., Aderemi, O. A., Zhao, Q., Edsall, P. R., Simovic, M. O., Lund, B. J., ... Cancio, L. C. (2019). Early complement and fibrinolytic activation in a rat model of blast-induced multi-organ damage. *Military Medicine*, 184(Suppl 1), 282–290. https://doi.org/10.1093/milmed/usy412

Ye, J., Yuan, K., Dai, W., Sun, K., Li, G., Tan, M., ... Yuan, Y. (2019). The mTORC1 signaling modulated by intracellular C3 activation in Paneth cells promotes intestinal epithelial regeneration during acute injury. *International Immunopharmacology*, 67, 54–61. https://doi.org/10.1016/j.intimp.2018.12.002

Zhang, C., Wang, C., Li, Y., Miwa, T., Liu, C., Cui, W., ... Du, J. (2017). Complement C3a signaling facilitates skeletal muscle regeneration by regulating monocyte function and trafficking. *Nature Communications*, 8(1), 2078. https://doi.org/10.1038/s41467-017-01526-z

Zhang, Q., Raoof, M., Chen, Y., Sunli, Y., Sursal, T., Junger, W., ... Hauser, C. J. (2010). Circulating mitochondrial DAMPs cause inflammatory responses to injury. *Nature*, 464(7285), 104–107. https://doi.org/10.1038/nature08780

Zhao, C., Zhou, X., Qiu, J., Xin, D., Li, T., Chu, X., ... Wang, D. (2019). Exosomes derived from bone marrow mesenchymal stem cells inhibit complement activation in rats with spinal cord injury. *Drug Design, Development and Therapy*, 13, 3693–3704. https://doi.org/10.2147/DDDT.S209636

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