

Time to Develop Therapeutic Antibodies Against Harmless Proteins Colluding with Sepsis Mediators?

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Abstract: Sepsis refers to a systemic inflammatory response syndrome resulting from microbial infections, and is partly attributable to dysregulated inflammation and associated immunosuppression. A ubiquitous nuclear protein, HMGB1, is secreted by activated leukocytes to orchestrate inflammatory responses during early stages of sepsis. When it is released by injured somatic cells at overwhelmingly higher quantities, HMGB1 may induce macrophage pyroptosis and immunosuppression, thereby impairing the host's ability to eradicate microbial infections. A number of endogenous proteins have been shown to bind HMGB1 to modulate its extracellular functions. Here, we discuss an emerging possibility to develop therapeutic antibodies against harmless proteins that collude with pathogenic mediators for the clinical management of human sepsis and other inflammatory diseases.

Keywords: antibody, HMGB1, immunosuppression, inflammation, innate immune cells, pyroptosis, sepsis

Introduction

Cohabiting with microbes, mammals employ epithelial barriers as the first layer of defense to limit the access of many pathogens. If they are breached, the host mounts an immediate immune response termed "inflammation" ("set on fire" in Greek) to eliminate these invading pathogens.¹ For instance, circulating monocytes are ceaselessly patrolling the body to search for invading pathogens, and immediately infiltrate into the infected tissues upon detecting microbial products.² Once reaching extravascular tissues, these monocytes are terminally differentiated into tissue-specific resident macrophages, which ingest and eradicate pathogens together with neutrophils and other phagocytes.³

Meanwhile, macrophages/monocytes are also equipped with Pattern Recognition Receptors [PRR, such as the Toll-like Receptor 2 (TLR2), TLR3, TLR4 and TLR9] that can bind distinct Pathogen-Associated Molecular Patterns molecules (PAMPs, such as bacterial peptidoglycan, double-stranded RNA, endotoxin and CpG-DNA).^{4,5} The engagement of PAMPs with respective PRRs triggers the immediate release of tumor necrosis factor (TNF),⁶ interleukin (IL)-1,⁷ and interferon (IFN)- α ,⁸ which collectively facilitate pathogen elimination. If unsuccessful, invading pathogens can leak into the bloodstream to trigger a systemic inflammatory response and life-threatening organ dysfunction termed "sepsis".⁹ The pathogenesis of sepsis is complex but attributable to dysregulated inflammatory

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responses and immunosuppression.^{10–12} For instance, neutralizing antibodies against TNF, the first cytokine elaborated in the inflammatory cascade, were protective in animal models of endotoxemic/bacteremic shock.⁶ However, the early release of TNF makes it difficult to target in clinical settings,¹³ prompting the search for other late mediators with wider therapeutic windows.

High Mobility Group Box 1 (HMGB1)

High mobility group 1 (HMG-1) was initially identified as a 30-kDa protein with a high mobility on electrophoresis gels,¹⁴ and recently renamed as the high mobility group box-1 (HMGB1).¹⁵ It contains a continuous stretch of negatively charged residues in the C-terminus, and two internal repeats of positively charged domains (“HMG boxes” known as “A box” and “B box”) in the N-terminus (Figure 1).¹⁶ These HMG boxes enable HMGB1 to bind chromosomal DNA to fulfill its nuclear functions in stabilizing nucleosomal structure

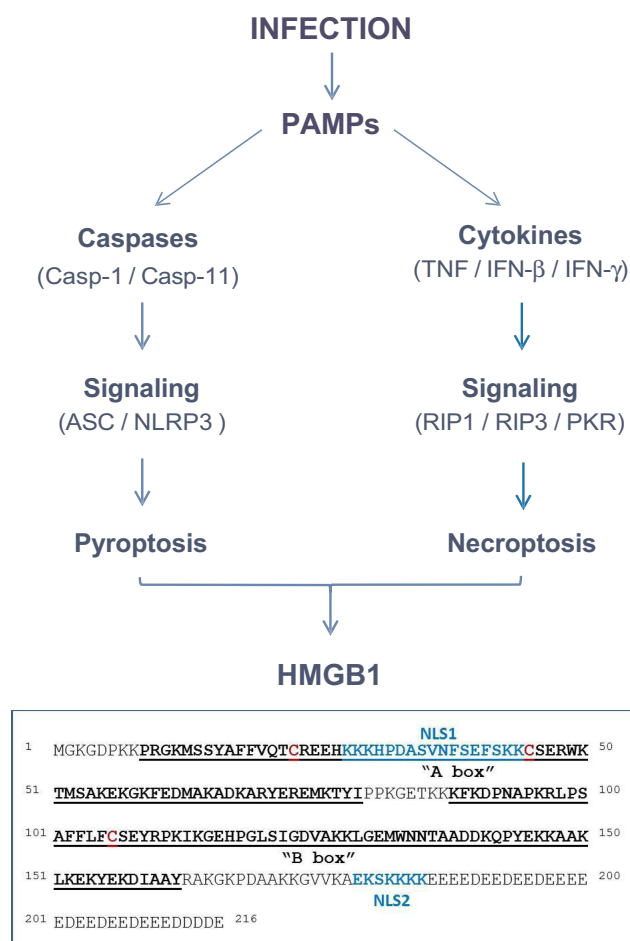


Figure 1 Pathogen-Associated Molecular Pattern molecules (PAMPs) trigger HMGB1 release through inducing pyroptosis or necroptosis.

and stability, and facilitating the binding of transcription factors to their cognate DNA sequences during gene expression.^{16,17} Conditional knockout of HMGB1 expression renders animals more susceptible to both infectious¹⁸ and injurious insults,^{19,20} supporting a beneficial role of intracellular HMGB1 in health.

Secretion by Activated Macrophages/Monocytes

Two decades ago, we initiated an effort to search for late mediators that could contribute to the pathogenesis of lethal sepsis. Specifically, we stimulated macrophage cultures with an early cytokine (eg, TNF) and screened the cell-conditioned medium for proteins that were released relatively late. This effort led to the identification of 30-kDa protein with an N-terminal amino acid sequence identical to HMG-1 (HMGB1).^{15,21} Subsequently, we and others demonstrated that many exogenous PAMPs (eg, ds-RNA, CpG-DNA and endotoxins)^{21,22} and endogenous cytokines [eg, interferon (IFN)- γ , IFN- β , serum amyloid A (SAA), and Cold-inducible RNA-binding protein (CIRP)]^{23–26} similarly induced HMGB1 translocation to cytoplasmic vesicles.^{23,27–30} Consequently, these activated macrophages/monocytes secrete cytoplasmic HMGB1 vesicles via non-classical endoplasmic reticulum-Golgi exocytotic pathways.^{21,23,27–30}

Release by Injured Somatic Cells

In addition, HMGB1 can be passively released by somatic cells undergoing cytoplasmic membrane destruction due to accidental (mechanical or chemical) events or regulated processes governed by specific caspases or kinases. For instance, many PAMPs induce a form of programmed necrosis, pyroptosis (Figure 1),³¹ that is characterized by the oligomerization of the apoptosis-associated speck-like protein containing a C-terminal caspase recruitment domain (ASC) and its integration with pro-caspase-1 and a NOD-Like Receptor (eg, NLRP3) to form a large inflammasome complex (pyroptosome) that eventually disrupts cytoplasmic membranes.^{32,33} Similarly, many proinflammatory cytokines (eg, TNF and IFN- γ) induce another form of programmed necrosis (necroptosis) via activating protein kinase receptor-interacting protein 3 (RIP3) and the interferon-induced double-stranded RNA-activated protein kinase R (PKR) (Figure 1).^{34–36} Collectively, pyroptosis^{33,37} and necroptosis³⁸ allow passive HMGB1 release following ischemia/reperfusion,^{39,40} non-penetrating trauma,^{41,42} chemical toxemia,⁴³ or radiation,⁴⁴ leading to massive HMGB1 release during lethal infections and injuries.

Extracellular HMGB1 and Innate Immunity

Extracellular HMGB1 binds many cell surface receptors such as the TLR4^{45–47} and the receptor for advanced glycation end products (RAGE) (Figure 2).^{48–51} Due to its dramatically (4–30-fold) different affinities to TLR4/MD2 ($K_D = 22.0$ nM)⁴⁷ and RAGE ($K_D = 97.7–710$ nM),^{48,49} HMGB1 may first bind TLR4/MD2 when it is actively secreted by innate immune cells at relatively lower amount.⁵² However, when it is passively released by somatic cells at relatively higher levels, HMGB1 may also bind RAGE^{48,50,53} and other low-affinity receptors. Like TLR4,^{4,45–47} RAGE also recognizes many other ligands including the advanced glycation end-products (AGEs), complement component (eg, C1q, $K_D = 5.6$ μ M) or endotoxins ($K_D = 2–35$ nM).⁵¹ Thus, HMGB1 may orchestrate divergent inflammatory responses through activating different PRRs interacting with a wide array of inflammatory ligands.

Extracellular HMGB1 Amplifies Inflammation

First, as a highly charged molecule, HMGB1 binds and facilitates the cellular uptake of negatively charged PAMPS (eg, CpG-DNA and LPS) via RAGE-receptor-mediated endocytosis.⁵³ Upon reaching acidic endosomal and lysosomal compartments near HMGB1's isoelectric pH, HMGB1

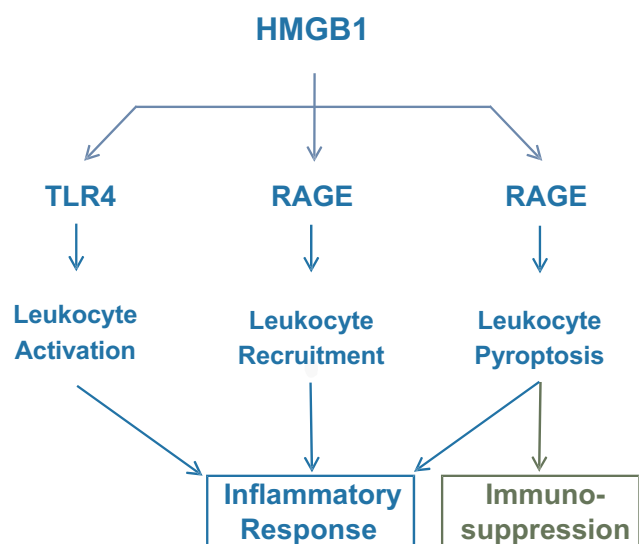


Figure 2 Extracellular HMGB1 induces divergent inflammatory responses through different receptors. Note that RAGE is involved in HMGB1 endocytosis and induction of leukocyte pyroptosis and possible immunosuppression due to immune cell depletion.

becomes neutrally charged and sets free its cargos,⁵³ thereby facilitating their recognition by respective receptors such as TLR9⁵⁴ or caspase-11⁵³. Second, the engagement of RAGE with HMGB1 also induces chemotaxis⁵⁵ and the migration of monocytes, dendritic cells^{56,57} and neutrophils,⁵⁸ thereby facilitating the recruitment of innate immune cells to the sites of infection and injury (Figure 2).⁵⁵ Third, HMGB1 can even directly activate macrophages⁵⁹ and endothelial cells⁶⁰ to produce various cytokines and chemokines,^{45,46,60–63} thereby sustaining a dysregulated inflammatory responses during infections (Figure 2).⁶⁴ Thus, extracellular HMGB1 functions as an alarmin signal to alert, recruit and activate immune cells, thereby amplifying inflammatory responses.

Following traumatic injury, HMGB1 is detected in the circulation within a few hours,^{41,42,65} and its systemic levels correlated with post-traumatic inflammatory responses^{41,66} and worsening clinical scores.⁶⁷ Accordingly, HMGB1-neutralizing antibodies have been proven protective in animal models of ischemia/reperfusion,^{39,68,69} trauma,^{70,71} chemical toxemia,^{72–74} atherosclerosis,⁷⁵ gastric ulcer,⁷⁶ and hyperoxia,⁷⁷ supporting a pathogenic role of HMGB1 in injury-elicited inflammatory diseases.

Extracellular HMGB1 Induces Immunosuppression

It is well known that antecedent traumatic injury often dampens subsequent innate immunity against secondary infections, suggesting a possible pathogenic role of DAMP in immune tolerance or immunosuppression. As aforementioned, when HMGB1 is passively released by damaged tissues at overwhelmingly high levels, it can bind RAGE^{48–50,78} to induce TLR4 internalization and desensitization to subsequent stimulation with inflammatory ligands (eg, endotoxin). Furthermore, at relatively higher doses (eg, 10 μ g/mL), HMGB1 could also binds RAGE to trigger macrophage pyroptosis,^{53,79} apoptosis⁸⁰ and necrosis,⁸⁰ resulting in possible depletion of innate immune cells and immunosuppression (Figure 2). Therefore, excessive HMGB1 accumulation may induce immune tolerance^{81,82} as well as immunosuppression⁸³ that compromises the host's ability to eradicate microbial infections during lethal injuries and infections.^{84,85}

HMGB1 as a Late Mediator of Lethal Sepsis

In preclinical settings, sepsis is routinely induced by the infusion of bacterial endotoxins (endotoxemia) or the

disruption of host epithelial barrier to induce microbial translocation by a surgical procedure termed cecal ligation and puncture (CLP).⁸⁶ In murine models of endotoxemia and CLP-sepsis, HMGB1 is first detected in the circulation 8 hours after the disease onset, and subsequently increased to plateau levels from 16 to 32 hours,^{21,87} distinguishing HMGB1 from TNF and other early proinflammatory cytokines.¹³ The pathogenesis of HMGB1 in endotoxemia was inferred from studies using HMGB1-neutralizing antibodies, which conferred a dose-dependent protection against endotoxin-induced tissue injury and lethality.^{21,88} Intriguingly, anti-HMGB1 antibodies did not affect endotoxin-induced cytokine production in the lung inflammation model, suggesting that HMGB1 may contribute to lung injury through additional inflammation-independent mechanisms.⁸⁸ Indeed, it has been shown that excessive HMGB1 accumulation in the bronchoalveolar space adversely compromised bacteria-killing capacities of alveolar macrophages,⁷⁷ which were similarly reversed by HMGB1-neutralizing antibodies.⁸⁹

In a more clinically relevant animal model of sepsis (induced by CLP), delayed administration of HMGB1-specific neutralizing antibodies, beginning 24 h after CLP, dose-dependently rescued rodents from lethal sepsis.^{87,90,91} Moreover, targeted inhibition of HMGB1 expression in macrophages and dendritic cells reduced systemic HMGB1 accumulation, and similarly rescued mice from sepsis.⁹² Taken together, these experimental data establish extracellular HMGB1 as a critical late mediator of experimental sepsis, which can be therapeutically targeted with wider therapeutic windows than other early cytokines.^{1,13,93,94}

Endogenous HMGB1-Binding Proteins

To prevent potentially harmful inflammatory responses, mammals have also developed many strategies to counter-regulate HMGB1-mediated cytokine productions. For instance, an endothelial anticoagulant cofactor, thrombomodulin (TM), could bind HMGB1 to prevent its interaction with macrophage cell surface receptors,⁹⁵ thereby preventing HMGB1-induced inflammatory response.^{96,97} Similarly, a liver-derived acute-phase protein, haptoglobin (Hp), could capture HMGB1 to trigger CD163-dependent endocytosis of HMGB1/Hp complexes, and instead induced the production of anti-inflammatory enzymes (heme oxygenase-1) and cytokines (eg, IL-10).⁹⁸

Moreover, a complement factor C1q also interacted with HMGB1 ($K_D = 200$ nM) and formed a tetramolecular complex with RAGE and LAIR-1, resulting in the production of anti-inflammatory cytokines (eg, IL-10) and pro-resolution lipid mediators.^{99,100} Thus, in a sharp contrast to exogenous PAMPs (eg, CpG-DNA and LPS), many endogenous proteins can bind HMGB1 to tilt the balance towards anti-inflammatory responses via distinct signaling pathways.^{95,98–100}

Development of Antibodies Against an Endogenous Protein (Tetranectin, TN) Colluding with HMGB1

Tetranectin (TN) was initially characterized as an oligomeric plasminogen-binding protein¹⁰¹ exhibiting >75% amino acid sequence identity between humans and rodents.¹⁰² It is expressed abundantly in the lung¹⁰³ but also present at relatively high levels (10–12 $\mu\text{g/mL}$) in the bloodstream of healthy humans¹⁰⁴. In rodents, enhanced expression or genetic depletion of TN led to abnormal osteogenesis¹⁰⁵, excessive curvature of the thoracic spine-spinal deformity,¹⁰⁶ deficient motor function (such as limb rigidity),¹⁰⁷ or impaired wound healing,^{108,109} suggesting a generally beneficial role of TN in health.

TN Depletion in Sepsis

While searching for endogenous proteins modulating HMGB1 release, we noticed that the blood level of a 20-kDa protein was almost completely depleted in a patient who died of sepsis. This 20-kDa protein was identified as human TN by mass spectrometry and immunoblotting assays.¹¹⁰ Further analysis of a cohort of 44–45 age-matched healthy controls and critically ill patients revealed a 60–70% reduction of plasma TN levels in patients with sepsis or septic shock. In accordance with these clinical findings, circulating TN levels were similarly decreased in experimental sepsis, with a >70% reduction at 24 h after disease onset—a time point when some septic animals started to lose survival.¹¹⁰

Surprising Discovery of TN-Specific Protective Antibodies

To understand the role of TN in sepsis, we would normally perform three sets of experiments to find out what would happen if we: 1) genetically knocked out its expression; 2) pharmacologically supplemented septic animals with

recombinant TN protein; and 3) treated septic animals with TN-specific antibodies? First, genetic disruption of TN expression rendered animals more susceptible to lethal sepsis with exacerbated lung inflammation and injury, suggesting a protective role of TN in sepsis.¹¹⁰ Conversely, supplementation of sub-physiological dose of TN at 2 and 24 h after the onset of lethal sepsis conferred a dose-dependent protection, further confirming its protective role in disease. Surprisingly, when we treated septic animals with polyclonal antibodies (pAbs) generated in four rabbits, we found that total IgGs purified from two rabbits reproducibly reduced septic lethality even when the first dose was given 22 h after CLP.¹¹⁰

Screening a library of peptides spanning the entire sequence of human TN revealed that these two protective pAbs uniquely recognized a peptide (P5) harboring an epitope sequence (NDALYEYLRQ, “P5-5”) exhibiting 60–70% identity between humans and rodents, but a 100% identity between humans and many other mammalian species (ranging from pigs to monkeys). We thus strategically immunized mice with human TN antigen and generated several hybridoma clones producing P5-5-reactive monoclonal antibodies (mAbs). When administered to septic mice 24 h after CLP, three P5-5-reacting mAbs similarly and significantly rescued mice from lethal sepsis by attenuating sepsis-induced TN depletion, tissue injury, as well as bacteremia.¹¹⁰ It suggests a possibility that TN domain-specific mAbs conferred protection against lethal sepsis partly by facilitating pathogen elimination.

TN Interacts with HMGB1 to Facilitate HMGB1 Endocytosis and Macrophage Pyroptosis

Intriguingly, highly purified TN protein selectively inhibited the LPS- and SAA-induced HMGB1 release without affecting the parallel release of other cytokines and chemokines. This selective inhibition of HMGB1 release was attributable to TN's capacity in capturing HMGB1 and facilitating the endocytosis of TN/HMGB1 complexes by macrophage cultures (Figure 3).¹¹⁰ Consistent with previous findings that HMGB1 endocytosis triggered macrophage pyroptosis,^{53,79} we found that TN enhanced HMGB1-induced translocation of nuclear ASC to cytoplasmic regions, where ASC either aggregated into minute puncta that appeared to be secreted through microvesicle shedding, or aggregated into a larger focus or speck

(pyroptosome) that would trigger pyroptosis.¹¹⁰ Consequently, TN significantly enhanced HMGB1-induced uptake of trypan blue dye and parallel release of LDH and ASC, a marker for macrophage pyroptosis.¹¹¹ Taken together, these findings suggest that TN could capture HMGB1 released into the circulation during sepsis, thereby promoting HMGB1 endocytosis and macrophage pyroptosis, leading to possible immunosuppression that may compromise effective pathogen elimination (Figure 3).

TN-Specific mAbs Prevent Harmful TN/HMGB1 Interaction and Macrophage Pyroptosis

To understand the protective mechanism of TN domain-specific mAbs, we tested their possibility in disrupting TN/HMGB1 interaction using the Surface Plasmon Resonance technique. When the TN-conjugated sensor chip was pre-treated with mAb, the SPR response signal for subsequent HMGB1 application was reduced by >85%, which was paralleled by an almost 6-fold increase of K_D , indicating that these TN domain-specific protective mAbs effectively interrupted TN/HMGB1 interaction (Figure 3).¹¹⁰ Furthermore, these protective mAb markedly prevented the reciprocal enhancement of cellular uptake of HMGB1 and TN, and prevented the TN/HMGB1-induced cytoplasmic ASC translocation or aggregation into large ASC specks in macrophage cultures. It suggests a possibility that TN domain-specific mAbs may confer protection against lethal sepsis partly by preventing harmful TN/HMGB1 interaction that may adversely trigger macrophage pyroptosis and immunosuppression (Figure 3).

Conclusion

Sepsis remains a major clinical problem that accounts for approximately 20% of total deaths worldwide,¹¹² and annually costs more than \$62 billion in the US alone.¹¹³ Despite a robust increase in the understanding of the pathophysiology of sepsis, many antibody-based strategies targeting early pro-inflammatory cytokines (such as TNF or IL-1) failed in clinical settings. Currently, there is still no effective therapy¹¹⁴ other than adjunctive use of antibiotics, fluid resuscitation, and supportive care.¹¹³ By using a bedside to bench approach, we have identified additional unexpected biological targets with potential translational promise. The interaction of a harmless protein (TN) with a pathogenic mediator (HMGB1) released into the circulation during sepsis adversely promoted HMGB1 endocytosis and

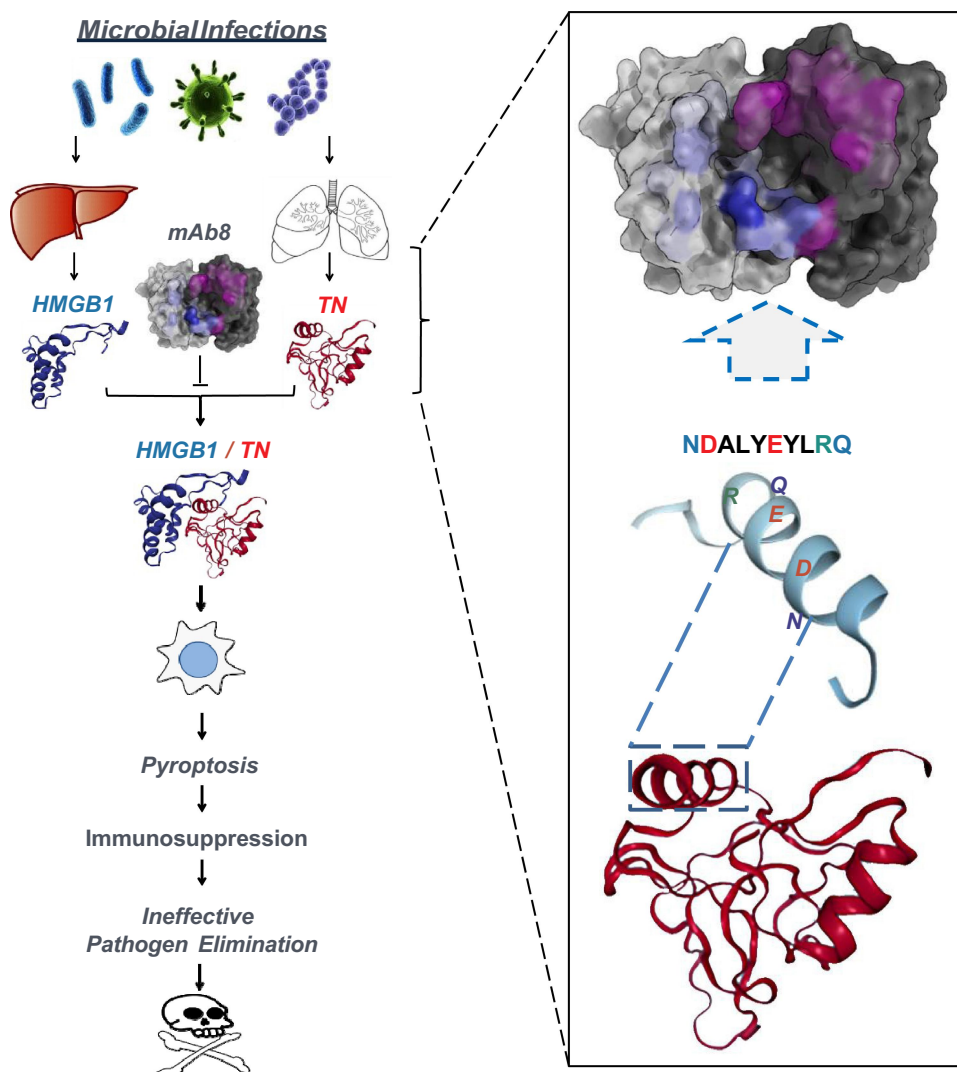


Figure 3 Proposed model for tetranectin domain-specific monoclonal antibody (mAb)-mediated protection against lethal sepsis. Severe microbial infections cause systemic accumulation of HMGB1 and concurrent depletion of TN, partly because circulating HMGB1 binds to TN to facilitate the endocytosis and degradation of TN/HMGB1 complexes by innate immune cells. The endocytosis of TN/HMGB1 complex also adversely triggers macrophage pyroptosis and immunosuppression that may compromise effective pathogen elimination and animal survival. Some TN-reactive mAbs, such as mAb8, could bind to specific epitope sequence (NDALYEYLRQ) of TN to interrupt its interaction with HMGB1, thereby impairing HMGB1 endocytosis and macrophage pyroptosis, and consequently reversing the sepsis-induced immunosuppression and animal lethality.

macrophage pyroptosis (Figure 3), which triggers both excessive inflammation and ineffective pathogen elimination in a feed-forward mechanism ultimately leading to host lethality.¹¹⁴ Although pyroptosis normally serves as a host defense mechanism against infection,¹¹⁵ it could also allow the excessive release of HMGB1 and other proinflammatory cytokines (eg, IL-1 β) that adversely drive a life-threatening inflammatory response.¹¹⁴ Meanwhile, excessive pyroptosis also depletes the number of innate immune cells necessary for pathogen clearance, resulting in a possible immunosuppression (Figure 3).

An antibody that interferes with TN/HMGB1 interaction thus represents a rational therapeutic approach to

prevent macrophage cell death and resultant sequelae. Our recent discovery of several TN-specific mAbs capable of recognizing a highly conserved epitope sequence (NDALYEYLRQ) in humans and many mammalian species (including baboon, bovine, cougar, elephant, monkey, pig and tiger) has suggested a promising therapy for sepsis in clinical settings. At present, it remains elusive whether these TN-specific mAbs also attenuate HMGB1-induced apoptosis or necrosis that are similarly associated with poor outcomes in preclinical settings. It is also not yet known whether TN-specific mAbs similarly affect TN interaction with other proteins (for example, plasminogen) that may affect sepsis-induced dysregulated coagulopathy.

Finally, given the pathogenic role of HMGB1 in injury-elicited inflammatory diseases, the role of TN in other inflammatory diseases should also be explored.¹¹⁴

Thus, it would be exciting to translate these pre-clinical findings into clinical applications through the use of humanized TN-specific mAbs capable of preventing its undesired interaction with pathogenic mediators that could cause macrophage pyroptosis and immunosuppression during lethal infections or injuries.¹¹⁰ Moreover, the discovery of mAbs capable of disrupting TN/HMGB1 interaction and endocytosis and rescuing animals from lethal sepsis has suggested an exciting possibility to develop therapeutic antibodies against harmless proteins colluding with disease mediators.

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Author Contributions

All authors have made a significant contribution to the work reported, including the conception and interpretation of relevant published literature. J.L. and G.B. generated the first draft, and H.W. made significant revisions and finalized the manuscript. All authors have agreed on the journal to which the article was submitted. All authors have reviewed and agreed on all versions of the article before submission. All authors have agreed to take responsibility and be accountable for the contents of this review article.

Disclosure

H.W. and J L are co-inventor of two provisional patent applications entitled "Use of tetranectin and peptide agonists to treat inflammatory diseases" and "Tetranectin-targeting monoclonal antibodies to fight against lethal sepsis and other pathologies". The authors report no other conflicts of interest in this work.

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