We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



15

Role of Fetuin-A in Injury and Infection

Haichao Wang, Wei Li, Shu Zhu, Ping Wang and Andrew E. Sama
Departments of Emergency Medicine and Surgery, North Shore University Hospital, Hofstra North Shore – LIJ School of Medicine at the Hofstra University
Laboratories of Emergency Medicine and Surgical Research, The Feinstein Institute for Medical Research, NY
USA

1. Introduction

Injury and infection, seemingly unrelated conditions, converge on a common process - inflammation, which is mediated partly by innate immune cells including macrophages and monocytes. These innate immune cells are equipped with pattern recognition receptors (such as TLR2, TLR4, and TLR9) (Brightbill *et al.* 1999; Poltorak *et al.* 1998; Hemmi *et al.* 2000), and can recognize both damage- and pathogen-associated molecular patterns (DAMPs, such as HMGB1; and PAMPs, such as endotoxin) (Andersson *et al.* 2000; Chen *et al.* 2009;Krieg 2002;Wang *et al.* 1999;Ivanov *et al.* 2007). In response to various PAMPs or DAMPs, innate immune cells release proinflammatory cytokines (such as TNF, IL-1, IFN-γ or HMGB1) to mount inflammatory responses. If dysregulated, an uncontrolled inflammation may adversely lead to detrimental consequences. To orchestrate the inflammatory response to infection and injury, the liver strategically re-prioritizes the synthesis and systemic release of a group of proteins collectively termed "acute phase proteins" (APPs). For instance, fetuin-A, also called the alpha-2-HS-glycoprotein for the human homologue (Christie *et al.* 1987), has been implicated as an anti-inflammatory protein during injury or infections. In this book chapter, we summarize emerging evidence to support fetuin-A as an acute phase protein capable of attenuating injury- or infection-elicited inflammatory responses.

2. Fetuin-A as a negative or positive APP

Fetuin-A was first isolated by Pederson more than sixty years ago as a major plasma protein in the fetus (Pedersen 1944). During fetal development, it is expressed in most organs including the liver, kidney, gastrointestinal tract, skin and brain (Terkelsen *et al.* 1998; Kitchener *et al.* 1997; Dziegielewska *et al.* 2000; Kitchener *et al.* 1999). In adults however, fetuin-A is produced primarily by the liver, and its synthesis is divergently regulated during injury or infection, classifying it as a negative or positive APP.

2.1 Regulators of hepatic Fetuin-A expression

Although fetuin-A is constitutively expressed in hepatocytes, its expression is negatively regulated by several proinflammatory cytokines. For instance, the fetuin-A expression levels in human HepG2 hepatoma cells were reduced by proinflammatory cytokines such as TNF, IL-1, IL-6, and IFN-γ (Daveau *et al.* 1988;Li *et al.* 2011a). IFN-γ, at concentrations as low as 10-50

ng/ml, reduced fetuin-A expression levels by as much as 50-70% (Li *et al.* 2011a). In contrast, HMGB1 (1 μg/ml), a late proinflammatory mediator of lethal systemic inflammation (Wang *et al.* 1999; Yang *et al.* 2004; Wang *et al.* 2008), elevated fetuin-A expression levels by 2-3 folds in HepG2 cells, suggesting that different cytokines divergently regulate hepatic fetuin-A expression.

2.2 Elevation of Fetuin-A Levels during ischemia

In patients with cerebral ischemic injury (stroke), plasma fetuin-A levels were paradoxically elevated (Weikert *et al.* 2008;Tuttolomondo *et al.* 2010). The elevation of circulating fetuin-A levels correlated with an increase not only in LDL-cholesterol levels (Tuttolomondo *et al.* 2010) but also in risk of cardiovascular disorders (Weikert *et al.* 2008). Similarly, serum fetuin-A levels were increased up to 10-fold in cattle following traumatic injury (Dziegielewska *et al.* 1992), suggesting fetuin-A as a positive APP during ischemic or traumatic injury. Notably, HMGB1 can be passively leaked from injured cells (Peltz *et al.* 2009), and functions as an early mediator of traumatic or ischemic injury (Zhu *et al.* 2010; Wu *et al.* 2007; Liu *et al.* 2007b; Tsung *et al.* 2005; Tsung *et al.* 2007; Watanabe *et al.* 2005). It is thus plausible that HMGB1 participates in the up-regulation of hepatic fetuin-A expression during injury.

In an animal model of focal cerebral ischemia (i.e., permanent middle cerebral artery occlusion, MCAo), fetuin-A levels in the ischemic brain tissue were also elevated in a time-dependent manner, starting between 2-6 h, peaking around 24-48 h, and returning towards base-line at 72 h post MCAo (Wang *et al.* 2010). This time-dependent increase in cerebral fetuin-A levels parallels with the transient elevation of the blood-brain barrier (BBB) permeability (Belayev *et al.* 1996), suggesting that circulating fetuin-A can gain entry across the BBB into the ischemic brain tissue. This possibility was supported by the observation that peripherally (intravenously) administered FITC-labeled fetuin-A was found in the ischemic brain region at 24 h after MCAo (Wang *et al.* 2010).

2.3 Reduction of circulating Fetuin-A levels during infection

In animal models of endotoxemia and sepsis (induced by cecal ligation and puncture, CLP), circulating fetuin-A levels were decreased in a time-dependent fashion, starting between 2-6 h, reaching a nadir (with maximal reduction by 50-60%) around 24-48 h. Afterwards, fetuin-A levels started to increase, returning towards basal levels approximately 72 h post endotoxemia or sepsis, supporting fetuin-A as a negative APP in animal models of lethal endotoxemia and sepsis (Li *et al.* 2011a). Interestingly, disruption of expression of early proinflammatory cytokines (such as IFN-γ) impaired bacterial endotoxin-mediated down-regulation of fetuin-A expression (Li *et al.* 2011a). It thus appears that early proinflammatory cytokines (such as TNF and IFN-γ) function as negative regulators to reduce circulating fetuin-A levels during an early stage of endotoxemia or sepsis; whereas late-acting proinflammatory mediators (e.g., HMGB1) stimulate fetuin-A expression to restore its circulating levels at a late stage.

In patients with other inflammatory diseases such as pancreatitis (Kusnierz-Cabala *et al.* 2010), chronic kidney diseases (Metry *et al.* 2008), and rheumatoid arthritis (Sato *et al.* 2007), serum fetuin A levels were also decreased by 20-30%. In these patients, circulating fetuin-A levels were not only inversely correlated with levels of inflammatory cytokines (such as IL-6) (Kusnierz-Cabala *et al.* 2010), but also associated with increased mortality rates (Metry *et al.* 2008). Collectively, these observations classify fetuin-A as a negative APP during infection or other inflammatory illness.

3. Biological functions of Fetuin-A

Despite its abundance, the functions of fetuin-A remain poorly understood. A wide range of biological functions have been proposed for fetuin-A based on its structural similarities to other proteins or physical interactions with biogenic molecules.

3.1 Inhibitor of insulin or TGF-β Signalling

Fetuin-A shares sequence similarity to type II TGF-β receptors (Demetriou *et al.* 1996) and insulin receptor tyrosine kinases (Mathews *et al.* 1997;Haasemann *et al.* 1991), and has thus been proposed as an inhibitor of the TGF-β or insulin signaling pathways. After binding to to TGF-β1, fetuin-A prevents TGF-β1 from binding to its receptors, thereby antagonizing TGF-β1-mediated antiproliferative effects (Demetriou *et al.* 1996). Similarly, fetuin-A can also bind to the insulin receptor, and consequently inactivate (rather than activate, as in the case for insulin) the receptor tyrosine kinase (Goustin & Abou-Samra 2010). This may partly explain why higher fetuin-A levels were associated with insulin resistance in some patients with type 2 diabetes (Ix *et al.* 2008).

3.2 Inhibition of pathological calcification

As a glycoprotein, fetuin-A carries two N-linked and three O-linked oligosaccharide chains that terminate with sialic acid residues, and can bind cationic Ca^{2+} ions. Accordingly, fetuin-A has been proposed as an endogenous inhibitor of pathological mineralization or calcification in soft tissues (Jahnen-Dechent *et al.* 2001;Schinke *et al.* 1996;Szweras *et al.* 2002;Schafer *et al.* 2003;Ketteler *et al.* 2003). Specifically, fetuin-A forms protein-mineral colloids with calcium and phosphate (Heiss *et al.* 2003;Wu *et al.* 2009), thereby preventing uncontrolled mineralization that may otherwise occur under pathological conditions (Rochette *et al.* 2009).

3.3 Inhibition of inflammation

While investigating the mechanism underlying a cationic molecule spermine-mediated anti-inflammatory actions, we serendipitously discovered that macrophages lost their responsiveness to spermine when cultured under low serum conditions (Wang *et al.* 1997). That is, despite the addition of cytokine-suppressing concentrations of spermine, the bacterial lipopolysaccharide (LPS)-induced production of TNF by these serum-starved macrophages was uninhibited. Subsequently, we discovered that these serum-starved macrophages became deprived of fetuin-A that was required for spermine to inhibit TNF production (Wang *et al.* 1997). The involvement of fetuin-A in spermine-mediated immunosuppression was confirmed by adding highly purified fetuin-A or fetuin-specific antibodies, which respectively restored or impaired spermine-mediated TNF inhibition (Wang *et al.* 1997).

It is plausible that fetuin-A functions as an opsonin for cationic spermine, and its availability to immune cells may be critical in regulating the innate immune response (Wang & Tracey 1999). Indeed, levels of fetuin-A in macrophage cultures could be altered by LPS stimulation or fetuin-A supplementation (**Figure 1A**). Intriguingly, the exogenously administered fetuin-A was predominantly localized in cytoplasmic punctate structures (**Figure 1B**), which co-localized with vesicles containing an autophagy marker (LC3) - possibly autophagosomes or amphisomes - in LPS-stimulated macrophages.

When given at higher concentrations (e.g., 3.5 mg/ml), crude fetuin-A (> 98%, Sigma-Aldrich) abrogated endotoxin-induced release of IL-1 and nitric oxide (Dziegielewska *et al.* 1998). Upon purification by gel filtration and ion-exchange chromatography, the highly purified intact fetuin-A could effectively inhibit IFN-γ- or LPS-induced release of HMGB1 (Li *et al.* 2011a), a newly identified late mediator of lethal endotoxemia and sepsis (Wang *et al.* 2008;Wang *et al.* 2009). However, even at the concentrations (e.g., 100 μg/ml) that abrogated LPS-induced HMGB1 release, fetuin-A only partly inhibited LPS-induced TNF secretion, suggesting fetuin-A as an effective inhibitor of HMGB1 release.

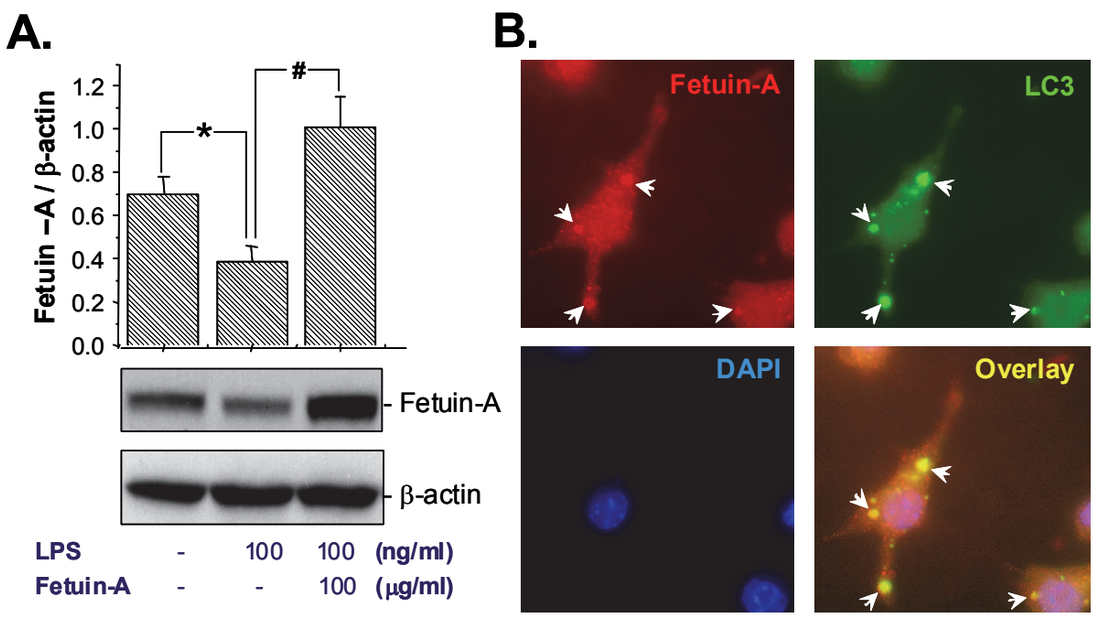


Fig. 1. **Exogenous fetuin-A was internalized into cytoplasmic vesicles in macrophage cultures**. A). Supplementation of exogenous fetuin-A prevented endotoxin-induced fetuin-A depletion**.** Murine macrophage-like RAW 264.7 cells were stimulated with LPS (100 ng/ml) in the absence or presence of fetuin-A (100 μg/ml) for 2 h, and cellular fetuin-A levels were determined by Western blotting. The relative fetuin-A levels, as a ratio to β-actin, were expressed as the mean ± SD of three independent experiments. *, $p < 0.05$ versus control ("+LPS"); #, $p < 0.01$ vs control ("+LPS"). B) Exogenous fetuin-A was internalized into LC3-containing cytoplasmic vesicles. GFP-LC3-transfected RAW 264.7 cells were stimulated with LPS (200 ng/ml) in the presence of fetuin-A (100 μg/ml) overnight, and immunostained with fetuin-A-specific antibodies.

4. Therapeutic potential of Fetuin-A in infection or injury

4.1 Carrageenan-induced paw edema

In an animal model of carrageenan-induced inflammation, intraperitoneal administration of fetuin-A (5 to 500 mg/kg) dose-dependently attenuated the development of paw edema (Ombrellino *et al.* 2001). The sialic acid moieties of fetuin-A might be required for its anti-inflammatory activities. When these sialic acid residues were removed by neuraminidase, the resultant asialofetuin-A failed to potentiate the anti-inflammatory activities of spermine (Wang *et al.* 1997) and failed to attenuate carrageenan-induced TNF production *in vivo*

(Ombrellino *et al.* 2001). In contrast, administration of anti-fetuin-A neutralizing antibodies in combination with carrageenan led to significantly increased paw edema, indicating that fetuin-A plays an important role in counter-regulating inflammatory responses.

4.2 Cerebral ischemic injury

Cerebral ischemia is frequently caused by an obstruction of a cerebral artery. Despite advances in acute and prophylactic therapies, stroke represents the leading cause of long-term disability (500,000-700,000 cases per year), and the third most common cause of death (with a mortality rate of 20-25%) in the United States.

4.2.1 Pathogenesis of cerebral ischemic injury

Cerebral ischemic injury consists of two stages: primary tissue damage in the ischemic core and secondary tissue injury in the surrounding penumbra. The primary injury in the ischemic core is primarily mediated by tissue ion (Ca^{2+} and Na^{+}) overload (Taylor & Meldrum 1995) and excitotoxicity (Lee *et al.* 1999); whereas the secondary injury in the surrounding penumbra is partly mediated by proinflammatory cytokines (**Figure 2**, Feuerstein *et al.* 1998).

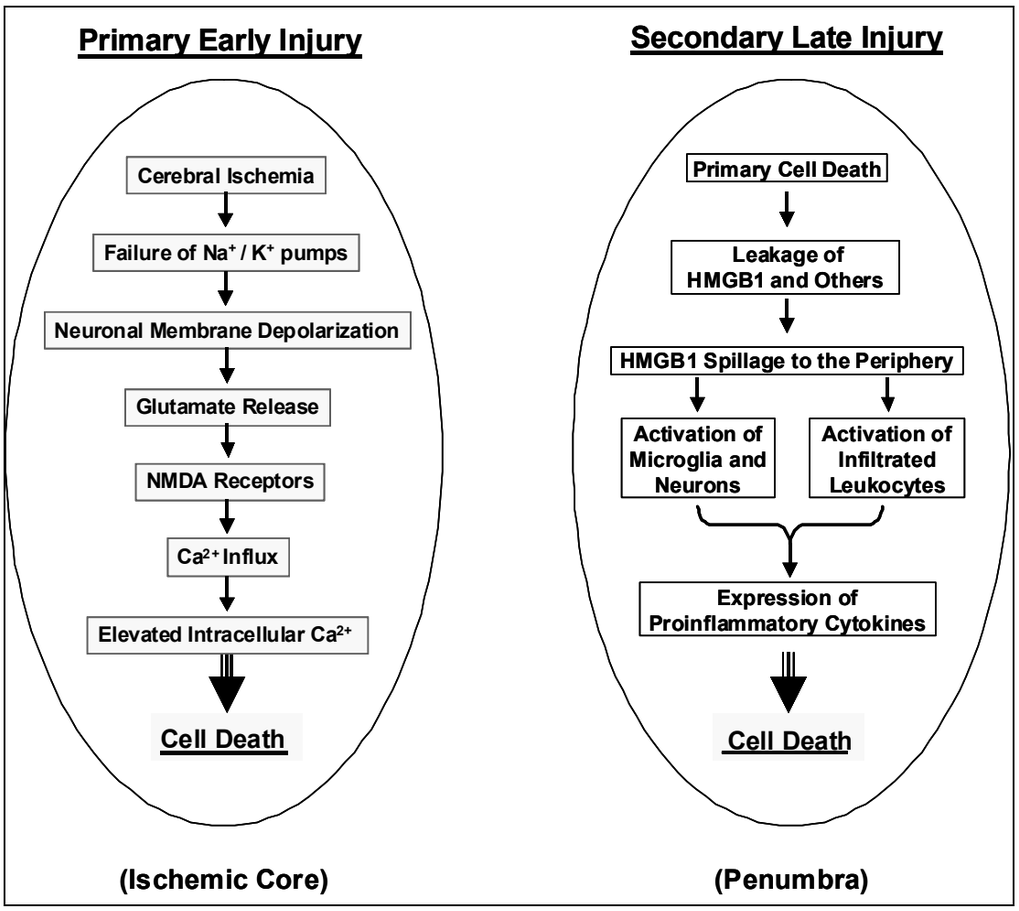


Fig. 2. **Cascade of events leading to primary injury in the ischemic core and secondary injury in the surrounding penumbra.**

4.2.1.1 Primary early injury in the core

Within seconds to minutes after cerebral ischemia, decreased ATP production leads to failure of the Na^+/K^+-ATPase pump, disruption of membrane potentials, influx of sodium and calcium, and subsequent release of excitatory amino acids (such as glutamate, **Figure 2**). Engagement of glutamate with the ionotropic N-methyl-D-aspartate receptor (NMDA) leads to Ca^{2+} influx and activation of damaging proteases (e.g., phospholipase A_2, nitric oxide synthase, endonucleases, and calpain) that compromise the functional and structural integrity of neuronal cells within 20-60 minutes (**Figure 2**). Early-stage therapeutics that block ion (Na^+ and Ca^{2+}) channels (Taylor & Meldrum 1995) and glutamate receptors (Meldrum 1990) fail in clinical trials, partly because of the impracticalities of administering such drugs at a time when those mechanisms are already activated. These failures have prompted the search for downstream targets that also mediate ischemic injury.

4.2.1.2 Secondary late injury in the penumbral zone

Outside of the ischemic core where cells are destined to die lies a penumbral zone where brain cell death continues slowly for hours and even days after the onset of ischemia (**Figure 2**). This progressive expansion of cell death in the penumbra (i.e., secondary injury) is mediated by ischemia-elicited inflammatory responses. Within a few hours, microglia and neurons become activated to produce TNF and other cytokines (Kato *et al.* 1996;Botchkina *et al.* 1997). Subsequently, polymorphonuclear cells infiltrate into the ischemic brain tissue within 12-48 hours (Akopov *et al.* 1996), followed by an influx of monocytes and macrophages over a period of one to several days. Together, these centrally- and peripherally-derived cells orchestrate a potentially injurious inflammatory response by overproducing various proinflammatory cytokines (**Figure 2**).

Many pro-inflammatory cytokines (e.g., TNF and IL-1) contribute to cerebral ischemic injury (Buttini *et al.* 1996;Zaremba & Losy 2001), because inhibition of their production (Meistrell *et al.* 1997;Bertorelli *et al.* 1998) or activity (Barone *et al.* 1997;Yang *et al.* 1999) confers protective effects. In addition, an ubiquitous nuclear protein, HMGB1, can be passively released from the ischemic core, and spilled into the surrounding periphery (Qiu *et al.* 2008). In the penumbra, it amplifies a potentially injurious inflammatory response by inducing various cytokines, chemokines, tissue factor and adhesion molecules (Andersson *et al.* 2000;Lv *et al.* 2009;Fiuza *et al.* 2003;Treutiger *et al.* 2003) (**Figure 2**). Indeed, HMGB1-specific neutralizing antibodies and antagonists (e.g., the A box) have been proven protective (Liu *et al.* 2007a;Muhammad *et al.* 2008), supporting a pathogenic role for HMGB1 in ischemic injury.

4.2.2 Divergent roles of spermine in cerebral ischemic injury

Another abundant molecule, spermine, can also be passively released by injured cells (Paschen 1992). At higher (millimolar) concentrations, spermine could be neuroprotective by binding and blocking the NMDA receptor (Araneda *et al.* 1999;Ferchmin *et al.* 2000). In addition, it counter-regulates expression of inflammatory cytokines (Zhang *et al.* 2000;Zhang *et al.* 1997;Zhang *et al.* 1999;Zhu *et al.* 2009) and scavenges free radicals (Ha *et al.* 1998;Adibhatla *et al.* 2002). However, spermine can be enzymatically converted by polyamine oxidases into cytotoxic metabolites (e.g., 3-aminopropanal) (Ivanova *et al.* 1998), which readily spreads and mediates direct cytotoxicities (Ivanova *et al.* 1998). At low (micromolar) concentrations, spermine activates the NMDA receptor (Zubrow *et al.* 2000;Ferchmin *et al.* 2000;Williams 1997), thereby augmenting glutamate-mediated neurotoxicity by overactivating Ca^{2+} fluxes and disturbances of the calcium homeostasis.

During cerebral ischemia, brain spermine levels are decreased (Paschen *et al.* 1992), owing largely to an accompanying increase in the enzymatic activity of brain polyamine oxidase (Ivanova *et al.* 1998). The loss of spermine consequently tilts the balance towards neurotoxicity through activating the NMDA receptor, and increasing susceptibility to oxidative stress as well as excessive inflammatory response.

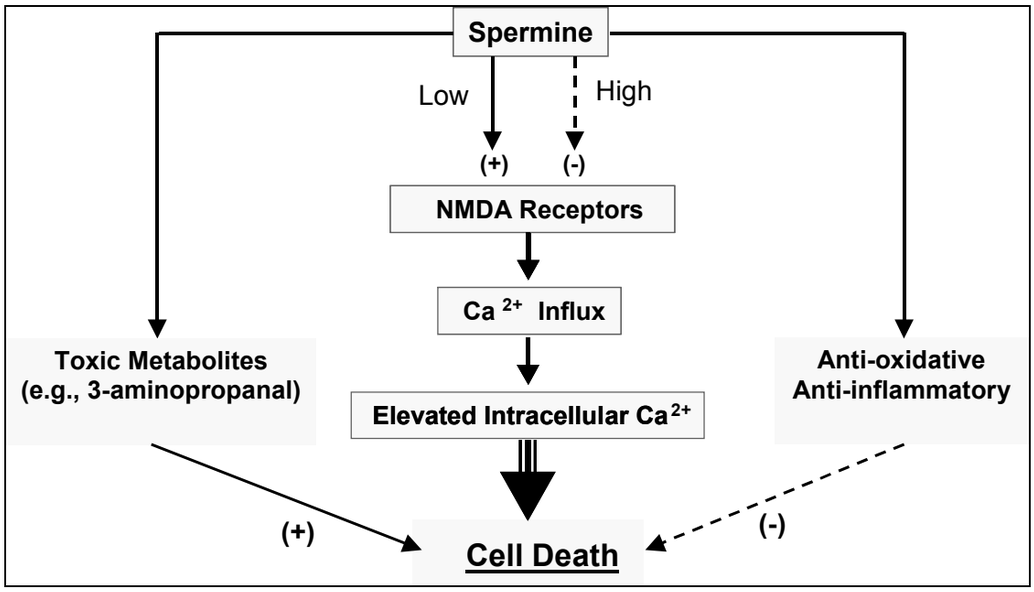


Fig. 3. **Divergent roles of spermine in cerebral ischemic injury.**

4.2.3 Peripheral administration of fetuin-A reduced cerebral ischemic injury

As mentioned earlier, when given peripherally, exogenous fetuin-A gains entry across the BBB into the ischemic brain tissue (**Figure 4**). The time-course of fetuin-A extravasation in the ischemic brain tissue parallels with the time-dependent alteration of the BBB permeability (Belayev *et al.* 1996), which was transiently elevated (5 -25 h post MCAo) followed by a return towards baseline at 72 h post MCAo (Belayev *et al.* 1996). It is possible that the temporal breakdown of the BBB is required for circulating fetuin-A to transiently gain entry into the brain. Consistently, peripheral administration of fetuin-A (50 mg/kg) promoted a dose-dependent protection against cerebral ischemic injury during an early stage of cerebral ischemia (i.e., 24 h post MCAo) (Wang *et al.* 2010). However, the fetuin-A-mediated protection was not long-lasting, and gradually diminished at a later stage (e.g., 7 days post MCAo). It is possible that the restore of BBB function at a late stage (3 days after MCAo) limits subsequent fetuin-A extravasation, thereby diminishing fetuin-A-mediated long-lasting protective effects.

Given the aforementioned pathogenic roles of Ca^{2+} and spermine in cerebral ischemia (in **section 4.2.1 and 4.2.2**), as well as the capacity of fetuin-A in binding Ca^{2+} and spermine (in **secton 3.2 and 3.3**) (Suzuki *et al.* 1994;Wang *et al.* 1997), it is plausible that fetuin-A confers protection by caging these toxic cationic molecules (Lee *et al.* 1999;Ivanova *et al.* 1998), thereby depriving them from damaging enzymes (such as Ca^{2+} -dependent proteases and polyamine oxidase). Furthermore, the fetuin-A-mediated protection is associated with a reduction of ischemia-elicited HMGB1 leakage from the ischemic core, and an inhibition of

expression of proinflammatory cytokines (e.g., TNF) in the penumbra (Wang *et al.* 2010) (**Figure 4**), suggesting that fetuin-A confers protection partly by attenuating early inflammatory responses.

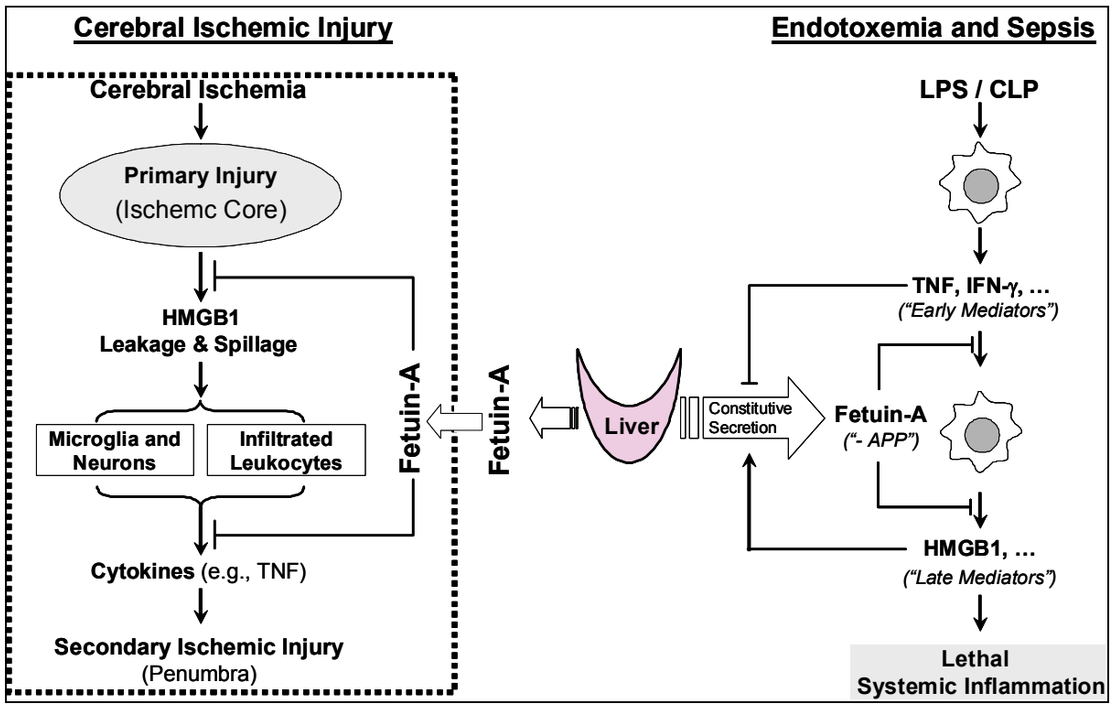


Fig. 4. **Protective roles of fetuin-A in cerebral ischemic injury and sepsis.**

4.3 Experimental sepsis

Sepsis is the most common cause of death in intensive care units, claiming approximately 225,000 victims annually in the U.S. alone. The high mortality of sepsis is in part mediated by bacterial endotoxin , which activates macrophages and monocytes to sequentially release early (e.g., TNF and IL-1) (Dinarello 1996) and late (e.g., HMGB1) proinflammatory cytokines.

4.3.1 Pathogenesis of sepsis

The pathogenesis of sepsis is partly attributable to dysregulated systemic inflammatory responses that are initiated by early proinflammatory cytokines and sustained by late-acting proinflammatory mediators. For instance, excessive accumulation of early proinflammatory cytokines, including TNF (Tracey *et al.* 1987), interleukin (IL)-1 (Dinarello & Thompson 1991), interferon (IFN)-γ (Heinzel 1990), individually or in combination, contribute to the pathogenesis of lethal systemic inflammation. Because these early cytokines are difficult to target in clinical settings, we searched for other late proinflammatory mediators that may offer a wider therapeutic window.

As aforementioned, HMGB1 is released from activated innate immune cells in response to microbial products (such as endotoxin or CpG-DNA) (Wang *et al.* 1999;Ivanov *et al.* 2007), or host cytokines (e.g., TNF or IFN-γ) (Wang *et al.* 1999;Rendon-Mitchell *et al.* 2003), and

functions as a late mediator of endotoxemia and sepsis (Wang *et al.* 1999;Yang *et al.* 2004;Wang *et al.* 2008;Wang *et al.* 2009). In murine models of endotoxemia and sepsis, HMGB1 is first detectable in the circulation eight hours after the onset of diseases, subsequently increasing to plateau levels from 16 to 32 hours (Wang *et al.* 1999;Yang *et al.* 2004) (**Figure 4**). This late appearance of circulating HMGB1 parallels with the onset of animal lethality from endotoxemia or sepsis, and distinguishes itself from TNF and other early proinflammatory cytokines (Wang *et al.* 2001). Therefore, agents capable of selectively attenuating systemic HMGB1 accumulation at a late stage may hold potential in the treatment of lethal sepsis.

4.3.2 Dual roles of spermine in experimental sepsis

In light of the anti-inflammatory activities of spermine *in vitro* (Zhang *et al.* 1997;Zhu *et al.* 2009), we evaluated the effects of spermine on animal survival in animal models of sepsis. Intraperitoneal administration of spermine (1.0 -10 mg/kg, twice daily, for three days) did not protect mice against lethal endotoxemia, but confers a dose-dependent protection against lethal sepsis. This protection was associated with a significant attenuation of systemic accumulation of HMGB1 and other cytokines (e.g., IL-6, KC, MCP-1, MIP-2, TIMP-1, sTNFRI and sTNFRII) (Zhu *et al.* 2009). At a higher dose (100 mg/kg), however, spermine decreased animal survival rate from 58% to 38% at 48 h post CLP, and further decreasing it to 0% at 72 h post CLP. It is possible that spermine is enzymatically converted by polyamine oxidases into cytotoxic metabolites (e.g., 3-aminopropanal), thereby exerting these potentially toxic effects when given at higher doses.

4.3.3 Protective role of Fetuin-A in sepsis

To understand the role of fetuin-A in systemic inflammatory diseases, we determined the influence of fetuin-A disruption on endotoxemic and septic lethality. Although fetuin-A-deficient C57BL/6J mice were not more susceptible to cerebral ischemic insult than sex- and body-matched (male, 27-29 g) wild-type C57BL/6J mice (Wang *et al.* 2010), they were more susceptible to lethal endotoxemic or septic insult (Li *et al.* 2011a). It suggests that endogenous fetuin-A occupies an integral role in host defense against lethal systemic inflammation.

The protective role of fetuin-A was further supported by the observations that supplementation with exogenous fetuin-A (20-100 mg/kg) provided a dose-dependent protection against lethal endotoxemia (Li *et al.* 2011a). In an animal model of sepsis, delayed administration of fetuin-A (20 - 100 mg/kg), beginning 24 h *after* the onset of sepsis and followed by an additional dose at 48 h post CLP, dose-dependently and significantly increased long-term animal survival rates from 45% to 90% (Li *et al.* 2011a).

4.3.4 Protective mechanisms

Supplementation of fetuin-A was associated with significant reduction of circulating HMGB1 levels, suggesting that fetuin-A confers protection by inhibiting late-acting proinflammatory mediators (Li *et al.* 2011a). The mechanisms underlying fetuin-A-mediated suppression of HMGB1 release may be complex. At the concentrations (100 μg/ml) that fetuin-A attenuated LPS-induced HMGB1 release in macrophage cultures, fetuin-A stimulated autophagy and impaired LPS-induced elevation of cytoplasmic and nuclear HMGB1 levels (Li et al. 2011a). It is presently unknown whether fetuin-A reduces

cytoplasmic HMGB1 levels by stimulating its degradation in an autophagy-dependent fashion, as what has been shown for other HMGB1 inhibitors such as EGCG, the major catechin of Green tea (*Camellia sinensis*) (Li *et al*. 2011b).

Accumulating evidence has suggested the possibility that fetuin-A functions as a negative regulator of HMGB1 release during lethal systemic inflammation (**Figure 4**). First, the time-dependent decrease of circulating fetuin-A levels was accompanied by parallel but opposite changes – a time-dependent increase - of circulating HMGB1 levels in animal models of endotoxemia (Wang *et al.* 1999) or sepsis (Yang *et al.* 2004). Second, disruption of fetuin-A expression led to elevation of serum HMGB1 levels in endotoxemia and sepsis *(Li et al. 2011a)*. Lastly, supplementation of fetuin-A resulted in significant reduction of circulating HMGB1 levels during endotoxemia and sepsis *(Li et al. 2011a)*.

Nevertheless, the current study can not exclude other alternative mechanisms by which fetuin-A confers these protective effects. For instance, fetuin-A may be capable of binding bacteria (Chmiela *et al.* 1997;Dubreuil *et al.* 2002), thereby affecting macrophage-mediated pathogen elimination. Furthermore, fetuin-A may facilitate macrophages-mediated ingestion and elimination of apoptotic neutrophils (Lord 2003;Jersmann *et al.* 2003), thereby preventing secondary necrosis and passive leakage of injurious molecules (e.g., proteases, reactive oxygen species, and HMGB1) (Bell *et al.* 2006).

5. Conclusions

A liver-derived acute phase protein, fetuin-A, appears to be distinctly regulated by different proinflammatory mediators. A previously under-appreciated protective role for fetuin-A in injury and infection has been suggested by recent studies. Fetuin-A is capable of crossing the blood-brain barrier, inhibiting early inflammatory response in animal models of cerebral ischemia, thereby conferring a short-term neuroprotection against ischemic injury. Disruption of fetuin-A expression renders mice significantly more susceptible to lethal endotoxemia or sepsis; whereas repetitive administration of fetuin-A confers a dose-dependent and long-lasting protection in animal models of lethal endotoxemia and sepsis. Thus, fetuin-A occupies protective roles against injury- or infection-elicited inflammation.

6. Acknowledgment

We thank Arvin Jundoria for critical reading of the manuscript. Work in the author's laboratory was supported by the National Institute of General Medical Sciences (R01GM063075 and R01GM070817 to HW) and the National Center of Complementary & Alternative Medicine (R01AT05076 to HW).

7. References

Adibhatla R.M., Hatcher J.F., Sailor K. & Dempsey R.J. (2002) Polyamines and central nervous system injury: spermine and spermidine decrease following transient focal cerebral ischemia in spontaneously hypertensive rats. *Brain Res* 938, 81-86

Akopov S.E., Simonian N.A. & Grigorian G.S. (1996) Dynamics of polymorphonuclear leukocyte accumulation in acute cerebral infarction and their correlation with brain tissue damage. *Stroke* 27, 1739-1743

Andersson U., Wang H., Palmblad K., Aveberger A.C., Bloom O., Erlandsson-Harris H., Janson A., Kokkola R., Zhang M., Yang H. & Tracey K.J. (2000) High Mobility Group 1 Protein (HMG-1) Stimulates Proinflammatory Cytokine Synthesis in Human Monocytes. *J Exp Med* 192, 565-570

Araneda R.C., Lan J.Y., Zheng X., Zukin R.S. & Bennett M.V. (1999) Spermine and arcaine block and permeate N-methyl-D-aspartate receptor channels. *Biophys.J* 76, 2899-2911

Barone F.C., Arvin B., White R.F., Miller A., Webb C.L., Willette R.N., Lysko P.G. & Feuerstein G.Z. (1997) Tumor necrosis factor-alpha. A mediator of focal ischemic brain injury. *Stroke* 28, 1233-1244

Belayev L., Busto R., Zhao W. & Ginsberg M.D. (1996) Quantitative evaluation of blood-brain barrier permeability following middle cerebral artery occlusion in rats. *Brain Res.* 739, 88-96

Bell C.W., Jiang W., Reich C.F. & Pisetsky D.S. (2006) The Extracellular Release of HMGB1 during Apoptotic Cell Death. *Am J Physiol Cell Physiol* 291(6), C1318-1325

Bertorelli R., Adami M., Di Santo E. & Ghezzi P. (1998) MK 801 and dexamethasone reduce both tumor necrosis factor levels and infarct volume after focal cerebral ischemia in the rat brain. *Neurosci Lett* 246, 41-44

Botchkina G.I., Meistrell M.E., Botchkina I.L. & Tracey K.J. (1997) Expression of TNF and TNF receptors (p55 and p75) in the rat brain after focal cerebral ischemia. *Mol Med* 3, 765-781

Brightbill H.D., Libraty D.H., Krutzik S.R., Yang R.B., Belisle J.T., Bleharski J.R., Maitland M., Norgard M.V., Plevy S.E., Smale S.T., Brennan P.J., Bloom B.R., Godowski P.J. & Modlin R.L. (1999) Host defense mechanisms triggered by microbial lipoproteins through toll-like receptors. *Science* 285, 732-736

Buttini M., Appel K., Sauter A., Gebicke-Haerter P.J. & Boddeke H.W. (1996) Expression of tumor necrosis factor alpha after focal cerebral ischaemia in the rat. *Neuroscience* 71, 1-16

Chmiela M., Czkwianianc E., Wadstrom T. & Rudnicka W. (1997) Role of Helicobacter pylori surface structures in bacterial interaction with macrophages. *Gut* 40, 20-24

Christie D.L., Dziegielewska K.M., Hill R.M. & Saunders N.R. (1987) Fetuin: the bovine homologue of human alpha 2HS glycoprotein. *FEBS Lett* 214, 45-49

Daveau M., Christian D., Julen N., Hiron M., Arnaud P. & Lebreton J.P. (1988) The synthesis of human alpha-2-HS glycoprotein is down-regulated by cytokines in hepatoma HepG2 cells. *FEBS Lett* 241, 191-194

Demetriou M., Binkert C., Sukhu B., Tenenbaum H.C. & Dennis J.W. (1996) Fetuin/alpha2-HS glycoprotein is a transforming growth factor-beta type II receptor mimic and cytokine antagonist. *J Biol Chem* 271, 12755-12761

Dinarello C.A. (1996) Biologic basis for interleukin-1 in disease. *Blood* 87, 2095-2147

Dinarello C.A. & Thompson R.C. (1991) Blocking IL-1: interleukin 1 receptor antagonist in vivo and in vitro. *Immunol Today* 12, 404-410

Dubreuil J.D., Giudice G.D. & Rappuoli R. (2002) Helicobacter pylori interactions with host serum and extracellular matrix proteins: potential role in the infectious process. *Microbiol Mol Biol Rev* 66, 617-29, table

Dziegielewska K.M. & Andersen N.A. (1998) The fetal glycoprotein, fetuin, counteracts ill-effects of the bacterial endotoxin, lipopolysaccharide, in pregnancy. *Biol Neonate.* 74, 372-375

Dziegielewska K.M., Andersen N.A. & Saunders N.R. (1998) Modification of macrophage response to lipopolysaccharide by fetuin. *Immunol Lett* 60, 31-35

Dziegielewska K.M., Brown W.M., Gould C.C., Matthews N., Sedgwick J.E. & Saunders N.R. (1992) Fetuin: an acute phase protein in cattle. *J Comp Physiol [B]* 162, 168-171

Dziegielewska K.M., Daikuhara Y., Ohnishi T., Waite M.P., Ek J., Habgood M.D., Lane M.A., Potter A. & Saunders N.R. (2000) Fetuin in the developing neocortex of the rat: distribution and origin. *J Comp Neurol* 423, 373-388

Ferchmin P.A., Perez D. & Biello M. (2000) Spermine is neuroprotective against anoxia and N-methyl-D-aspartate in hippocampal slices. *Brain Res* 859, 273-279

Feuerstein G.Z., Wang X. & Barone F.C. (1998) The role of cytokines in the neuropathology of stroke and neurotrauma. *Neuroimmunomodulation* 5, 143-159

Fiuza C., Bustin M., Talwar S., Tropea M., Gerstenberger E., Shelhamer J.H. & Suffredini A.F. (2003) Inflammation-promoting activity of HMGB1 on human microvascular endothelial cells. *Blood* 101, 2652-2660

Goustin A.S. & Abou-Samra A.B. (2010) The "thrifty" gene encoding Ahsg/Fetuin-A meets the insulin receptor: Insights into the mechanism of insulin resistance. *Cell Signal*

Ha H.C., Sirisoma N.S., Kuppusamy P., Zweier J.L., Woster P.M. & Casero R.A., Jr. (1998) The natural polyamine spermine functions directly as a free radical scavenger. *Proc Natl Acad Sci U S A* 95, 11140-11145

Haasemann M., Nawratil P. & Muller-Esterl W. (1991) Rat tyrosine kinase inhibitor shows sequence similarity to human alpha 2-HS glycoprotein and bovine fetuin. *Biochem J* 274, 899-902

Heinzel F.P. (1990) The role of IFN-gamma in the pathology of experimental endotoxemia. *J Immunol* 145, 2920-2924

Heiss A., DuChesne A., Denecke B., Grotzinger J., Yamamoto K., Renne T. & Jahnen-Dechent W. (2003) Structural basis of calcification inhibition by alpha 2-HS glycoprotein/fetuin-A. Formation of colloidal calciprotein particles. *J Biol Chem* 278, 13333-13341

Hemmi H., Takeuchi O., Kawai T., Kaisho T., Sato S., Sanjo H., Matsumoto M., Hoshino K., Wagner H., Takeda K. & Akira S. (2000) A Toll-like receptor recognizes bacterial DNA. *Nature* 408, 740-745

Ivanov S., Dragoi A.M., Wang X., Dallacosta C., Louten J., Musco G., Sitia G., Yap G.S., Wan Y., Biron C.A., Bianchi M.E., Wang H. & Chu W.M. (2007) A novel role for HMGB1 in TLR9-mediated inflammatory responses to CpG-DNA. *Blood.* 110, 1970-1981

Ivanova S., Botchkina G.I., Al-Abed Y., Meistrell M., Batliwalla F., Dubinsky J.M., Iadecola C., Wang H., Gregersen P.K., Eaton J.W. & Tracey K.J. (1998) Cerebral ischemia enhances polyamine oxidation: identification of enzymatically formed 3-aminopropanal as an endogenous mediator of neuronal and glial cell death. *J Exp Med* 188, 327-340

Ix J.H., Wassel C.L., Kanaya A.M., Vittinghoff E., Johnson K.C., Koster A., Cauley J.A., Harris T.B., Cummings S.R. & Shlipak M.G. (2008) Fetuin-A and incident diabetes mellitus in older persons. *JAMA* 300, 182-188

Jahnen-Dechent W., Schafer C., Heiss A. & Grotzinger J. (2001) Systemic inhibition of spontaneous calcification by the serum protein alpha 2-HS glycoprotein/fetuin. *Z Kardiol* 90 Suppl 3, 47-56

Jersmann H.P., Dransfield I. & Hart S.P. (2003) Fetuin/alpha2-HS glycoprotein enhances phagocytosis of apoptotic cells and macropinocytosis by human macrophages. *Clin Sci (Lond)* 105, 273-278

Kato H., Kogure K., Liu X.H., Araki T. & Itoyama Y. (1996) Progressive expression of immunomolecules on activated microglia and invading leukocytes following focal cerebral ischemia in the rat. *Brain Res.* 734, 203-212

Ketteler M., Bongartz P., Westenfeld R., Wildberger J.E., Mahnken A.H., Bohm R., Metzger T., Wanner C., Jahnen-Dechent W. & Floege J. (2003) Association of low fetuin-A (AHSG) concentrations in serum with cardiovascular mortality in patients on dialysis: a cross-sectional study. *Lancet* 361, 827-833

Kitchener P.D., Dziegielewska K.M., Hutton E.J., Hinrichsen C.F. & Saunders N.R. (1999) Fetuin in neurons of the retina and cerebellum during fetal and postnatal development of the rat. *Int J Dev Neurosci* 17, 21-30

Kitchener P.D., Dziegielewska K.M., Knott G.W., Miller J.M., Nawratil P., Potter A.E. & Saunders N.R. (1997) Fetuin expression in the dorsal root ganglia and trigeminal ganglia of perinatal rats. *Int J Dev Neurosci* 15, 717-727

Krieg A.M. (2002) CpG motifs in bacterial DNA and their immune effects. *Annu Rev Immunol* 20, 709-760

Kusnierz-Cabala B., Gurda-Duda A., Panek J., Fedak D., Dumnicka P., Solnica B. & Kulig J. (2010) Serum fetuin A concentrations in patients with acute pancreatitis. *Clin Lab* 56, 191-195

Lee J.M., Zipfel G.J. & Choi D.W. (1999) The changing landscape of ischaemic brain injury mechanisms. *Nature* 399 Supplement, A7-A14

Li W., Zhu S., Li J., Huang Y., Zhou R., Fan X., Yang H., Gong X., Eissa N.T., Jahnen-Dechent W., Wang P., Tracey K.J., Sama A.E. & Wang H. (2011a) A hepatic protein, fetuin-A, occupies a protective role in lethal systemic inflammation. *PLoS ONE* 6(2), e16945

Li, W., Zhu S., Li J., Assa A., Xu J., Fan S., Eissa N.T., Tracey K.T., Sama A.E., & Wang H. (2011b). EGCG induces autophagy and reduced cytoplasmic HMGB1 levels in endotoxin-stimulated macrophages. *Biochem Pharmacol* 81(9), 1152-1163.

Liu K., Mori S., Takahashi H.K., Tomono Y., Wake H., Kanke T., Sato Y., Hiraga N., Adachi N., Yoshino T. & Nishibori M. (2007a) Anti-high mobility group box 1 monoclonal antibody ameliorates brain infarction induced by transient ischemia in rats. *FASEB J* 21, 3904-3916

Liu K., Mori S., Takahashi H.K., Tomono Y., Wake H., Kanke T., Sato Y., Hiraga N., Adachi N., Yoshino T. & Nishibori M. (2007b) Anti-high mobility group box 1 monoclonal antibody ameliorates brain infarction induced by transient ischemia in rats. *FASEB J* 21, 3904-3916

Lord J.M. (2003) A physiological role for alpha2-HS glycoprotein: stimulation of macrophage uptake of apoptotic cells. *Clin Sci (Lond)* 105, 267-268

Lv B., Wang H., Tang Y., Fan Z., Xiao X. & Chen F. (2009) High-mobility group box 1 protein induces tissue factor expression in vascular endothelial cells via activation of NF-kappaB and Egr-1. *Thromb Haemost* 102, 352-359

Mathews S.T., Srinivas P.R., Leon M.A. & Grunberger G. (1997) Bovine fetuin is an inhibitor of insulin receptor tyrosine kinase. *Life Sci* 61, 1583-1592

Meistrell M.E., Botchkina G.I., Wang H., Di Santo E., Cockroft K.M., Bloom O., Vishnubhakat J.M., Ghezzi P. & Tracey K.J. (1997) Tumor necrosis factor is a brain damaging cytokine in cerebral ischemia. *Shock* 8, 341-348

Meldrum B. (1990) Protection against ischaemic neuronal damage by drugs acting on excitatory neurotransmission. *Cerebrovasc Brain Metab Rev* 2, 27-57

Metry G., Stenvinkel P., Qureshi A.R., Carrero J.J., Yilmaz M.I., Barany P., Snaedal S., Heimburger O., Lindholm B. & Suliman M.E. (2008) Low serum fetuin-A concentration predicts poor outcome only in the presence of inflammation in prevalent haemodialysis patients. *Eur J Clin Invest* 38, 804-811

Muhammad S., Barakat W., Stoyanov S., Murikinati S., Yang H., Tracey K.J., Bendszus M., Rossetti G., Nawroth P.P., Bierhaus A. & Schwaninger M. (2008) The HMGB1 receptor RAGE mediates ischemic brain damage. *J Neurosci* 28, 12023-12031

Ombrellino M., Wang H., Yang H., Zhang M., Vishnubhakat J., Frazier A., Scher L.A., Friedman S.G. & Tracey K.J. (2001) Fetuin, a negative acute phase protein, attenuates TNF synthesis and the innate inflammatory response to carrageenan. *Shock* 15, 181-185

Paschen W. (1992) Polyamine metabolism in reversible cerebral ischemia. *Cerebrovasc Brain Metab Rev* 4, 59-88

Paschen W., Csiba L., Rohn G. & Bereczki D. (1991) Polyamine metabolism in transient focal ischemia of rat brain. *Brain Res* 566, 354-357

Paschen W., Widmann R. & Weber C. (1992) Changes in regional polyamine profiles in rat brains after transient cerebral ischemia (single versus repetitive ischemia): evidence for release of polyamines from injured neurons. *Neurosci Lett* 135, 121-124

Pedersen KO. (1944) Fetuin, a new globulin isolated from serum. *Nature* 154, 575-576

Peltz E.D., Moore E.E., Eckels P.C., Damle S.S., Tsuruta Y., Johnson J.L., Sauaia A., Silliman C.C., Banerjee A. & Abraham E. (2009) HMGB1 is markedly elevated within 6 hours of mechanical trauma in humans. *Shock* 32, 17-22

Poltorak A., He X., Smirnova I., Liu M.Y., Huffel C.V., Du X., Birdwell D., Alejos E., Silva M., Galanos C., Freudenberg M., Ricciardi-Castagnoli P., Layton B. & Beutler B. (1998) Defective LPS signaling in C3H/HeJ and C57BL/10ScCr mice: mutations in Tlr4 gene. *Science* 282, 2085-2088

Qin S., Wang H., Yuan R., Li H., Ochani M., Ochani K., Rosas-Ballina M., Czura C.J., Huston J.M., Miller E., Lin X., Sherry B., Kumar A., Larosa G., Newman W., Tracey K.J. & Yang H. (2006) Role of HMGB1 in apoptosis-mediated sepsis lethality. *J Exp Med* 203, 1637-1642

Qiu J., Nishimura M., Wang Y., Sims J.R., Qiu S., Savitz S.I., Salomone S. & Moskowitz M.A. (2008) Early release of HMGB-1 from neurons after the onset of brain ischemia. *J Cereb Blood Flow Metab* 28, 927-938

Rendon-Mitchell B., Ochani M., Li J., Han J., Wang H., Yang H., Susarla S., Czura C., Mitchell R.A., Chen G., Sama A.E., Tracey K.J. & Wang H. (2003) IFN-gamma Induces High Mobility Group Box 1 Protein Release Partly Through a TNF-Dependent Mechanism. *J Immunol* 170, 3890-3897

Rochette C.N., Rosenfeldt S., Heiss A., Narayanan T., Ballauff M. & Jahnen-Dechent W. (2009) A shielding topology stabilizes the early stage protein-mineral complexes of fetuin-A and calcium phosphate: a time-resolved small-angle X-ray study. *Chembiochem* 10, 735-740

Sato H., Kazama J.J., Wada Y., Kuroda T., Narita I., Gejyo F., Gao P. & Yamashita H. (2007) Decreased levels of circulating alpha2-Heremans-Schmid glycoprotein/Fetuin-A (AHSG) in patients with rheumatoid arthritis. *Intern Med* 46, 1685-1691

Schafer C., Heiss A., Schwarz A., Westenfeld R., Ketteler M., Floege J., Muller-Esterl W., Schinke T. & Jahnen-Dechent W. (2003) The serum protein alpha 2-Heremans-Schmid glycoprotein/fetuin-A is a systemically acting inhibitor of ectopic calcification. *J Clin Invest* 112, 357-366

Schinke T., Amendt C., Trindl A., Poschke O., Muller-Esterl W. & Jahnen-Dechent W. (1996) The serum protein alpha2-HS glycoprotein/fetuin inhibits apatite formation in vitro and in mineralizing calvaria cells. A possible role in mineralization and calcium homeostasis. *J Biol Chem* 271, 20789-20796

Suzuki M., Shimokawa H., Takagi Y. & Sasaki S. (1994) Calcium-binding properties of fetuin in fetal bovine serum. *J Exp Zoology* 270, 501-507

Szweras M., Liu D., Partridge E.A., Pawling J., Sukhu B., Clokie C., Jahnen-Dechent W., Tenenbaum H.C., Swallow C.J., Grynpas M.D. & Dennis J.W. (2002) alpha 2-HS glycoprotein/fetuin, a transforming growth factor-beta/bone morphogenetic protein antagonist, regulates postnatal bone growth and remodeling. *J Biol Chem* 277, 19991-19997

Taylor C.P. & Meldrum B.S. (1995) Na+ channels as targets for neuroprotective drugs. *Trends Pharmacol Sci* 16, 309-316

Terkelsen O.B., Jahnen-Dechent W., Nielsen H., Moos T., Fink E., Nawratil P., Muller-Esterl W. & Mollgard K. (1998) Rat fetuin: distribution of protein and mRNA in embryonic and neonatal rat tissues. *Anat Ebryol (Berl)* 197, 125-133

Tracey K.J., Fong Y., Hesse D.G., Manogue K.R., Lee A.T., Kuo G.C., Lowry S.F. & Cerami A. (1987) Anti-cachectin/TNF monoclonal antibodies prevent septic shock during lethal bacteraemia. *Nature* 330, 662-664

Treutiger C.J., Mullins G.E., Johansson A.S., Rouhiainen A., Rauvala H.M., Erlandsson-Harris H., Andersson U., Yang H., Tracey K.J., Andersson J. & Palmblad J.E. (2003) High mobility group 1 B-box mediates activation of human endothelium. *J Intern Med* 254, 375-385

Tsung A., Klune J.R., Zhang X., Jeyabalan G., Cao Z., Peng X., Stolz D.B., Geller D.A., Rosengart M.R. & Billiar T.R. (2007) HMGB1 release induced by liver ischemia involves Toll-like receptor 4 dependent reactive oxygen species production and calcium-mediated signaling. *J Exp Med* 204, 2913-2923

Tsung A., Sahai R., Tanaka H., Nakao A., Fink M.P., Lotze M.T., Yang H., Li J., Tracey K.J., Geller D.A. & Billiar T.R. (2005) The nuclear factor HMGB1 mediates hepatic injury after murine liver ischemia-reperfusion. *J Exp Med* 201, 1135-1143

Tuttolomondo A., Di Raimondo D., Di Sciacca R., Casuccio A., Bivona G., Bellia C., Barreca L., Serio A., D'Aguanno G., Ciaccio M., Licata G. & Pinto A. (2010) Fetuin-A and CD40 L plasma levels in acute ischemic stroke: differences in relation to TOAST subtype and correlation with clinical and laboratory variables. *Atherosclerosis.* 208, 290-296

Wang H., Bloom O., Zhang M., Vishnubhakat J.M., Ombrellino M., Che J., Frazier A., Yang H., Ivanova S., Borovikova L., Manogue K.R., Faist E., Abraham E., Andersson J., Andersson U., Molina P.E., Abumrad N.N., Sama A. & Tracey K.J. (1999) HMG-1 as a late mediator of endotoxin lethality in mice. *Science* 285, 248-251

Wang H., Li W., Zhu S., Li J., D'Amore J., Ward M.F., Yang H., Wu R., Jahnen-Dechent W., Tracey K.J., Wang P. & Sama A.E. (2010) Peripheral administration of fetuin-A attenuates early cerebral ischemic injury in rats. J Cereb Blood Flow Metab 30, 493-504

Wang H., Liao H., Ochani M., Justiniani M., Lin X., Yang L., Al Abed Y., Wang H., Metz C., Miller E.J., Tracey K.J. & Ulloa L. (2004) Cholinergic agonists inhibit HMGB1 release and improve survival in experimental sepsis. *Nat Med* 10, 1216-1221

Wang H. & Tracey K.J. (1999) Fetuin opsonizes macrophage-deactivating cations. In: *Update in Intensive Care and Emergency Medicine: Immune Response in the Critically Ill* (eds Marshall J.C. & Cohen J.), pp. 155-163. SpringerVerlag Press.

Wang H., Ward M.F. & Sama A.E. (2009) Novel HMGB1-inhibiting therapeutic agents for experimental sepsis. *Shock.* 32, 348-357

Wang H., Yang H., Czura C.J., Sama A.E. & Tracey K.J. (2001) HMGB1 as a Late Mediator of Lethal Systemic Inflammation. *Am J Respir Crit Care Med* 164, 1768-1773

Wang H., Zhang M., Soda K., Sama A. & Tracey K.J. (1997) Fetuin protects the fetus from TNF [letter]. *Lancet* 350, 861-862

Wang H., Zhu S., Zhou R., Li W. & Sama A.E. (2008) Therapeutic potential of HMGB1-targeting agents in sepsis. *Expert Rev Mol Med* 10:e32.

Watanabe T., Kubota S., Nagaya M., Ozaki S., Nagafuchi H., Akashi K., Taira Y., Tsukikawa S., Oowada S. & Nakano S. (2005) The role of HMGB-1 on the development of necrosis during hepatic ischemia and hepatic ischemia/reperfusion injury in mice. *J Surg Res* 124, 59-66

Weikert C., Stefan N., Schulze M.B., Pischon T., Berger K., Joost H.G., Haring H.U., Boeing H. & Fritsche A. (2008) Plasma fetuin-a levels and the risk of myocardial infarction and ischemic stroke. *Circulation* 118, 2555-2562

Williams K. (1997) Modulation and block of ion channels: a new biology of polyamines. *Cell Signal* 9, 1-13

Wu C.Y., Martel J., Young D. & Young J.D. (2009) Fetuin-A/albumin-mineral complexes resembling serum calcium granules and putative nanobacteria: demonstration of a dual inhibition-seeding concept. *PLoS.One.* 4, e8058

Wu H., Chen G., Wyburn K.R., Yin J., Bertolino P., Eris J.M., Alexander S.I., Sharland A.F. & Chadban S.J. (2007) TLR4 activation mediates kidney ischemia/reperfusion injury. *J.Clin.Invest* 117, 2847-2859

Yang G.Y., Gong C., Qin Z., Liu X.H. & Lorris B.A. (1999) Tumor necrosis factor alpha expression produces increased blood-brain barrier permeability following temporary focal cerebral ischemia in mice. *Brain Res Mol Brain Res* 69, 135-143

Yang H., Ochani M., Li J., Qiang X., Tanovic M., Harris H.E., Susarla S.M., Ulloa L., Wang H., DiRaimo R., Czura C.J., Wang H., Roth J., Warren H.S., Fink M.P., Fenton M.J., Andersson U. & Tracey K.J. (2004) Reversing established sepsis with antagonists of endogenous high-mobility group box 1. *Proc Natl Acad Sci U S A* 101, 296-301

Zaremba J. & Losy J. (2001) Early TNF-alpha levels correlate with ischaemic stroke severity. *Acta Neurol Scand* 104(5), 288-295

Zhang M., Borovikova L.V., Wang H., Metz C. & Tracey K.J. (1999) Spermine inhibition of monocyte activation and inflammation. *Mol Med* 5, 595-605

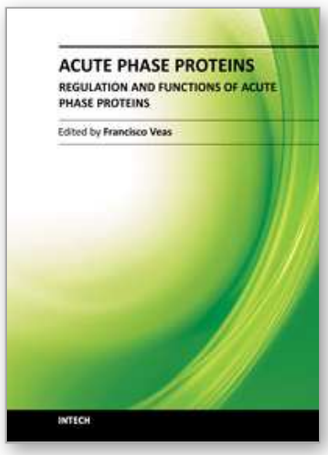
Zhang M., Caragine T., Wang H., Cohen P.S., Botchkina G., Soda K., Bianchi M., Ulrich P., Cerami A., Sherry B. & Tracey K.J. (1997) Spermine inhibits proinflammatory cytokine synthesis in human mononuclear cells: a counterregulatory mechanism that restrains the immune response. *J Exp Med* 185, 1759-1768

Zhang M., Wang H. & Tracey K.J. (2000) Regulation of macrophage activation and inflammation by spermine: a new chapter in an old story. *Crit Care Med* 28, N60-N66

Zhu S., Ashok M., Li J., Li W., Yang H., Wang P., Tracey K.J., Sama A.E. & Wang H. (2009a) Spermine protects mice against lethal sepsis partly by attenuating surrogate inflammatory markers. *Mol Med* 15, 275-282

Zhu S., Li W., Ward M.F., Sama A.E. & Wang H. (2010) High mobility group box 1 protein as a potential drug target for infection- and injury-elicited inflammation. *Inflamm.Allergy Drug Targets.* 9, 60-72

Zubrow A.B., Numagami Y., Fritz K.I., Mishra O.P. & Delivoria-Papadopoulos M. (2000) Spermine dependent activation of the N-methyl-D-aspartate receptor and the effect of nitric oxide synthase inhibition during hypoxia in the cerebral cortex of newborn piglets. *Brain Res* 854, 11-18



Acute Phase Proteins - Regulation and Functions of Acute Phase Proteins

Edited by Prof. Francisco Veas

ISBN 978-953-307-252-4
Hard cover, 368 pages
Publisher InTech
Published online 03, October, 2011
Published in print edition October, 2011

The two volumes of Acute Phase Proteins book consist of chapters that give a large panel of fundamental and applied knowledge on one of the major elements of the inflammatory process during the acute phase response, i.e., the acute phase proteins expression and functions that regulate homeostasis. We have organized this book in two volumes - the first volume, mainly containing chapters on structure, biology and functions of APP, the second volume discussing different uses of APP as diagnostic tools in human and veterinary medicine.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Haichao Wang, Wei Li, Shu Zhu, Ping Wang and Andrew E. Sama (2011). Role of Fetuin-A in Injury and Infection, Acute Phase Proteins - Regulation and Functions of Acute Phase Proteins, Prof. Francisco Veas (Ed.), ISBN: 978-953-307-252-4, InTech, Available from: http://www.intechopen.com/books/acute-phase-proteins-regulation-and-functions-of-acute-phase-proteins/role-of-fetuin-a-in-injury-and-infection

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2011 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the Creative Commons Attribution 3.0 License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen