Insights into the Apoptotic Death of Immune Cells in Sepsis

Ying-yi Luan,¹ Yong-ming Yao,¹ Xian-zhong Xiao,² and Zhi-yong Sheng¹

Sepsis with subsequent multiple-organ dysfunction is a distinct systemic inflammatory response to concealed or obvious infection, and it is a leading cause of death in intensive care units. Thus, one of the key goals in critical care medicine is to develop novel therapeutic strategies that will affect favorably on outcome of septic patients. In addition to systemic response to infection, apoptosis is implicated to be an important mechanism of the death of immune cells, including neutrophils, macrophages, T lymphocytes, and dendritic cells, and it is usually followed by the development of multiple-organ failure in sepsis. The implication of apoptosis of immune cells is now highlighted by multiple studies that demonstrate that prevention of cell apoptosis can improve survival in relevant animal models of severe sepsis. In this review, we focus on major apoptotic death pathways and molecular mechanisms that regulate apoptosis of different immune cells, and advances in these areas that may be translated into more promising therapies for the prevention and treatment of severe sepsis.

Introduction

SEPSIS REPRESENTS A COMPLEX clinical morbidity that results from a harmful or devastating host response to infection. Its treatment is as yet unsatisfactory, and its mortality is still alarmingly high despite recent advances in the development of novel treatment modalities as well as therapeutic strategies for severe sepsis or septic shock. It is generally accepted that sepsis is an inflammatory state resulting from the systemic response to infection. Over the past decade, studies in experimental models and in patients suggested that the immune response of sepsis was followed by its dysregulation, with the initial appropriate host response to an amplified infection. As a result of a concerted effort to disclose the underlying pathogenetic mechanisms, there have been accumulating evidences to suggest that profound apoptosis of immune cells that occurs in sepsis is the important factor in immunosuppression followed by death of the potential (Lang and Matute-Bello 2009).

Apoptosis of immune cells has been increasingly recognized as an important factor in the pathophysiology of septic complications. Sepsis impairs immune function by inducing defects in innate immunity in form of widespread apoptosis of lymphocytes in the spleen, thymus, and other organs (Hattori and others 2010). Other immune cells that undergo apoptotic changes include neutrophils, macrophages, dendritic cells (DCs), as well as various lymphocyte populations (Lang and Matute-Bello 2009; Alves-Filho and others 2010; Martins and others 2012; Kockara and Kayatas 2013). This article is a brief overview of our understanding concerning

the pathways of altered apoptotic cell death in various types of innate immune cells, as to highlight recent investigations on the critical role of cell apoptosis in the pathophysiology of septic response. Additionally, we will try to elucidate the pathogenesis of the apoptotic cell death to provide a promising target for the treatment of severe sepsis in the future.

Mechanisms of Apoptosis During Sepsis

Apoptosis is a genetically programmed mechanism of cell death; in contrast to necrosis, it generally does not produce inflammation and injury to the tissue. It plays an important role in normal physiology, such as homeostasis regulation, and in the pathophysiology of many diseases (Hattori and others 2010). Inducers of apoptosis include steroids, cytokines such as tumor necrosis factor (TNF)- α , high mobility group box-1 protein (HMGB1), Fas ligand (FasL), heat shock, oxygen-free radicals, nitric oxide (NO), glucocorticoids, granzymes, and TNF- α -induced protein 8 like-2 (TIPE2), which may regulate Fas-mediated apoptosis by directly modulating the activities of cysteinyl aspartate-specific protease (caspase)-8 in the death-induced signaling complex (DISC), or by altering the levels of death and survival factors that control the Fas apoptotic pathway, whereas other cytokines, such as interleukin (IL)-1, IL-6, and granulocyte colony-stimulating factor (G-CSF), often inhibit apoptosis (Wesche and others 2005; Sun and others 2008; Hattori and others 2010). During the process of sepsis, increased levels of these proinflammatory cytokines (TNF- α ,

¹Department of Microbiology and Immunology, Burns Institute, First Hospital Affiliated to the Chinese PLA General Hospital, Beijing, People's Republic of China.

²Department of Pathophysiology, Xiang-Ya School of Medicine, Central South University, Changsha, People's Republic of China.

IL-1 β , IL-6, and G-CSF) were also involved in inflammation and implicated as principal effectors of the host immune responses.

Apoptotic cell death can be initiated by a plethora of stimuli that generally feed into 1 of 3 known signaling pathways, including the extrinsic death receptor pathway, the intrinsic (mitochondrial) pathway, and the endoplasmic reticulum (ER) stress-induced pathway. They ultimately converge into a common pathway causing the activation of effector enzymes termed caspases. The extrinsic death receptor pathway transduces the signals of extracellular death ligands belonging to the TNF family. When the TNF family receptors, such as Fas, bind to their respective ligands, such as FasL, it causes trimerization and subsequent DISC formation, which includes the recruitment of the adaptor molecule Fas-associated death domain (FADD) through the homophilic interaction of their own death domain (DD) to the DD of the adaptor molecule, as well as FADD binding to these activated DDs and recruiting procaspase 8 into DISC (Hattori and others 2010). The death signal is then transduced from the DISC to a downstream caspase cascade, such as caspase-3, leading to apoptosis. Unlike the extrinsic death receptor pathway, the intrinsic pathway feeds cell death signals via the mitochondria, which are induced to release polypeptidic agent *dangereux*. This pathway is highly dependent on the stoichiometry of anti-apoptotic versus proapoptotic Bcl-2 family members. Bcl-2, Bcl-x_L, Bcl-w, Mcl-1 and Bfl-1/A1 can function as an antiapoptotic protein, whereas Bcl-x_S, as well as Bak, Bim, Bmf, Bad, and Bid protein, can promote cell death (Oberholzer and others 2001). The ER/stress-induced pathway is the least well-understood; in response to endoplasmic reticulum stress (ERS), mammalian cells trigger unfolded protein response signaling pathways to cope with stressful conditions and to monitor the protein folding capacity of the ER and transmit that information to mechanisms that can modulate the ER environment, regulate various aspects of cellular metabolism, and even influence the fate of the cell (Bravo and others 2012; Zhu and others 2012).

Neutrophil apoptosis

In the setting of sepsis, inflammation and apoptosis can be considered as dual pathogenic processes. Apoptosis is a genetically programmed mechanism of cell death, with the aim of regulating immune homeostasis and eliminating auto-

reactive lymphocytes (Fadeel and Orrenius 2005; Luan and others 2014). However, an uncontrolled apoptosis of immune cells may compromise the ability of the host to eliminate the invading pathogens. Neutrophils are inflammatory cells with potent oxidative and proteolytic potential that are usually the first line of defense against invading pathogens. There are a series of effector functions performed by neutrophils, which represent an important mechanism of immunity against infections.

A wide variety of inflammatory diseases, including acute respiratory distress syndrome, pneumonia, sepsis, acute coronary artery disease, rheumatoid arthritis, and cystic fibrosis, are associated with delayed neutrophil apoptosis in the blood, sputum, or synovial fluid (Milot and Filep, 2011). There is also an increasing evidence in these studies that show that increased apoptosis of neutrophils was correlated with the severity and/or outcome of the disease. Various molecular mechanisms have been implicated in promotion or suppression of neutrophil apoptosis. Neutrophils constitutively express the proapoptotic members of the Bcl-2 family, including Bax, Bad, Bak, Bid, and Bik (Moulding and others 2001; Milot and Filep 2011) (Table 1), which accelerate or delay apoptosis. It has been established that increased levels of the antiapoptotic protein Mcl-1 were detected in neutrophils isolated from patients with severe sepsis. Cyclin-dependent kinases, an antiapoptotic Bcl-2 family member, whose activity appears to be involved in regulating Mcl-1 expression, are a key regulator of neutrophil apoptosis and lifespan.

Mechanisms governing neutrophil apoptosis in sepsis are complex. Neutrophil apoptosis is also regulated by a complex network of intracellular death/survival signaling pathways. A study of neutrophil apoptosis in septic patients indicated that delayed cell death is preceded by activation of nuclear factor (NF)- κ B and then suppression of caspases-9 and -3. It has been demonstrated that bacterial lipoprotein ligation through Toll-like receptor (TLR) 2 and CD14 on the surface of the neutrophil might inhibit mitochondrial membrane depolarization, which expedites the degradation of active caspase-3, thus delays neutrophil death (Mica and others 2004). In other studies, constitutive neutrophil apoptosis was found to be associated with prolonged phosphorylation of p38 mitogen-activated protein kinase (MAPK), activation of which led to reduction of Mcl-1 and acceleration of apoptotic cell death (Derouet and others 2006).

TABLE 1. THE MAJOR APOPTOTIC DEATH PATHWAYS AND MOLECULES ASSOCIATED WITH IMMUNE CELLS IN SEPSIS

Effector molecules/ pathways	Different immune cell subsets			
	Neutrophil	Macrophage	DC	T cell
Cytokines	TNF- α , IL-1 β /IL-10	TNF- α , IL-6, IL-18	IL-12/IL-10	IL-2, IFN- γ , TNF- α
Signature receptor/ apoptotic molecules	TLR2/Bax, Bad, Bak, Bid, Bik, Mcl-1, CDK9	RAGE/TIPE2, HMGB1	TLR2,4, MINOR/PD-1	TCR/Bcl-2, Bcl-x _L , Bim
Primary signaling regulator	p38-MAPK, Caspase-3,9 signaling	JAK-STAT, Caspase-3 signaling	NFAT, MAPK1, CD40-CD40L, Caspase-3 signaling	NF- κ B, NFAT, Caspase-12,3 signaling

CDK9, cyclin-dependent kinase 9; DC, dendritic cell; HMGB1, high mobility group box-1 protein; IFN- γ , interferon- γ ; IL, interleukin; JAK-STAT, Janus kinase-signal transducer and activator of transcription; MAPK, mitogen-activated protein kinase; NFAT, nuclear factor of activated T cell; NF- κ B, nuclear factor- κ B; RAGE, receptor for advanced glycation end products; TIPE2, tumor necrosis factor- α induced protein 8 like-2; TLR, toll-like receptor; TNF- α , tumor necrosis factor- α .

Macrophage apoptosis

In addition to apoptosis of neutrophils, recent studies of accelerated inflammatory processes involved in septic response have implicated apoptosis of macrophages in the pathogenesis of severe sepsis. Macrophages play critical roles in initiating, maintaining, and resolving host inflammatory responses; on the other hand, excessive macrophage apoptosis can lead to immunosuppression and contribute to the risk of an occurrence of secondary, opportunistic infection, as observed in the critically injured and septic patients. Several mechanisms underlying apoptosis in macrophages have been reported.

Sepsis is a highly complicated disorder; multiple cytokine-associated signaling pathways may promote activation of apoptosis and accelerate inflammatory events during the septic syndrome. Ample evidence is provided that some cytokines, such as IL-1, IL-6, and G-CSF, can provoke inflammation but inhibit apoptosis, whereas other cytokines like TNF- α and HMGB1 can induce apoptosis in many cell populations (Kockara and Kayatas 2013; Luan and others 2014). Thus, apoptosis of macrophages can occur in the absence of some cytokines or extensive expression of other cytokines. A prospective study found that HMGB1 stimulation was able to induce apoptosis of mouse peritoneal macrophages, and its effect was dose and time dependent (Zhu and others 2009; Luan and others 2014). HMGB1 is a specific and saturable ligand for the receptor for advanced glycation end products (RAGE). HMGB1-induced intracellular signaling through RAGE can activate 2 different cascades, one of which is the Ras-MAPK pathway and subsequent NF- κ B, a transcription factor that upregulates expression of HMGB1 and other products of the activated macrophage (Zheng and others 2013; Luan and others 2014) (Fig. 1). Caspase cascade is well known for its function in triggering cell toxicity and programmed cell death, and it has been shown that apoptosis of macrophages induced by HMGB1 is reduced via blocking of RAGE and caspase-3 activation. It was also revealed that the transcriptional activity of NF- κ B/p65 in macrophages was inhibited after HMGB1 treatment, indicating that the induction

of apoptosis might be associated with RAGE and caspase-3 activation and inhibition of NF- κ B signaling pathway (Zhu and others 2009; Luan and others 2014). Further, studies by Jiang and others (2007) have shown that with lipopolysaccharide (LPS) stimulation, the extent of HMGB1 released from macrophages was correlated with the occurrence of apoptosis as measured by caspase-3 activation *in vitro*. In addition, Sun and others (2008) found that the target of TIPE2 action on the apoptotic pathway was likely downstream of caspase-8 or DISC in the RAW 264.7 macrophages. Based on these findings, blockage of caspase-8 activation with a specific caspase-8 inhibitor significantly diminished the hyper-responsiveness of TIPE2 knockdown RAW 264.7 macrophages, indicating the potential role of TIPE2 in the regulation of macrophage apoptosis (Sun and others 2008).

Apoptosis of DCs

DCs are key antigen-presenting cells, as they sense the presence of pathogens, the processes of presenting the antigens to T lymphocytes, and initiate innate and adaptive immune responses against invading pathogens. Following activation with inflammatory stimuli, conventional dendritic cells (cDCs) become particularly efficient at antigen processing, and they achieve the ability to migrate to the T-cell areas of secondary lymphoid organs, where they present antigens to naive T cells to initiate primary adaptive responses (Granucci and Zanoni 2009). Once cDCs acquire the effector ability, they undergo terminal differentiation and finally die via apoptosis.

DC apoptosis is an important event that regulates the balance between tolerance and immunity through multiple pathways, and defects in DC apoptosis can trigger autoimmunity (Kushwah and Hu 2010). In several pathological and infected conditions, it has been observed that DC apoptosis is also associated with the development of immunosuppressive state. The mechanism of DC apoptosis induced by LPS was recently elucidated, and it was shown that activation of the c2 and c3 isoforms of nuclear factor of activated T cells (NFAT) as mediated by CD14 played a key role in this process (Granucci and Zanoni 2009). Particularly, it has been

FIG. 1. Regulation of apoptosis by HMGB1 in macrophages. HMGB1 is capable of inducing apoptosis of mouse peritoneal macrophages and the effect of HMGB1 on macrophage apoptosis is in a dose- and time-dependent manner. Caspase-3 activity might contribute to HMGB1-mediated macrophage apoptosis. It is necessary for rapid apoptosis via inhibiting NF- κ B pathways in monocytes, and also inhibition of NF- κ B signaling pathway may enhance HMGB1-induced apoptosis in the macrophages. Caspase-3, cysteinyl aspartate-specific protease-3; HMGB1, high mobility group box-1 protein; NF- κ B, nuclear factor- κ B; RAGE, receptor for advanced glycation end products; TLR4, Toll-like receptor-4.

found that the exposure of DCs to LPS induces Src-family kinases and phospholipase C $\gamma 2$ activation, and an influx of extracellular Ca^{2+} and calcineurin-dependent nuclear NFAT translocation (Granucci and others 2008; Paulick and Bertozzi 2008; Granucci and Zanoni 2009). In addition, there are many other molecular mechanisms leading to DC apoptosis after activation. TNF-related apoptosis-inducing ligand (TRAIL), a transmembrane protein expressed on effector cells, induces leukemic pDC apoptosis via binding to DR4 and DR5 receptors (Blum and others 2006). TRAIL-dependent apoptosis involves the extrinsic pathway with caspase-8 and -10 acting as initiator caspases. It has now been implicated that the Nur77 family, including Nurr77, Nurr1, and MINOR receptors, regulates apoptosis of immune cells. Increased expression of MINOR could induce DC apoptosis but its suppression was noted to lead to the inhibition of DC apoptosis (Wang and others 2009; Kushwah and Hu 2010). Programmed cell death (PD)-1 is a well-established negative regulator of T cell responses by inhibiting proliferation and cytokine production of T cells via interaction with its ligand, B7-H1 (PD-L1) and B7-DC (PD-L2), which are expressed on non-T cells (Park and others 2014). Recently, PD-1 was found to be expressed in activated DCs, and treatment with anti-PD-1 antibody during DC maturation contributed to enhanced DC survival. When DCs were treated with PD-1 knockdown, it resulted in increased MAPK1 and CD40-CD40L signaling, suggesting that PD-1 appeared to be involved in the apoptosis of activated DCs (Park and others 2014). Further, DCs are sensitive to HLA-DR-induced apoptosis, which is independent of caspase activation or tyrosine kinase/phosphatases. The rapid and extensive caspase-3-mediated apoptosis of DCs can lead to immunosuppression, which is observed both in humans and mouse models of sepsis, and suppression of DC apoptosis in mice results in resistance to endotoxin-induced sepsis and immune depression, highlighting the role of DC apoptosis in mediating septic pathology (Tinsley and others 2003; Gautier and others 2008).

Apoptosis of T lymphocytes

The role of T lymphocytes in all adaptive immune responses against microorganism invasion is of great importance. Patients with severe sepsis show impaired host defenses that contribute to the lethality of the disorder. Recent work implicated that apoptosis of T lymphocytes appeared to be critically involved in the pathophysiology of sepsis. In light of recent data, apoptosis of T lymphocyte has been suggested as the potential factor in the immune dysfunction and determination of septic severity (Lang and Matute-Bello 2009; Alves-Filho and others 2010; Luan and others 2014; Liu and others 2013). Clinical findings with regard to lymphocyte apoptosis were also correlated well with the results from septic mice reproduced by cecal ligation and puncture (CLP), as demonstrated by transferase-mediated dUTP nick-end labeling (TUNEL) staining (Matsuda and others 2010; Luan and others 2014). Further, T cell apoptosis might be associated with regulatory T cell during sepsis; the underlining regulatory mechanism is complicated, including downregulation of expression of IL-2 mRNA, consumption of IL-2, resulting in a form of apoptosis dependent on cytokine deprivation, through Fas/FasL pathway as well as granzyme depended manner.

Over the past decade, apoptosis of T lymphocytes is suggested to be tightly regulated by a complex network of signaling pathways that controls expression and degradation of key molecules in experimental models (Ma and others 2008). In the study of intrinsic death receptor pathway, Weber and others (2008) found an increase in proapoptotic protein Bim and a decrease in level of antiapoptotic molecules (Bcl-2 and Bcl-xL) in the lymphocytes of patients with severe sepsis. Studies using transgenic mice that selectively overexpress Bcl-2 and Bcl-xL in T lymphocytes confirmed that both of the antiapoptotic molecules could appreciably reduce lymphocyte apoptosis and increase survival in animal models of CLP-induced sepsis (Hotchkiss and others 1999; Schwulst and others 2008). Besides being triggered from signals inside the cell, apoptosis can be activated from the extrinsic pathway by different FasL and Fas-associated receptors. It has been demonstrated that caspase-8 plays a central role in the regulation of apoptosis in an *ex vivo* model, as it is related to other executioner caspase activity and NF- κ B activity. Downregulation of caspase-8 decreased apoptosis of T lymphocyte and improved survival of mice in CLP-induced septic mice. In addition to the intrinsic and extrinsic pathways, ER stress-mediated pathway is involved in the apoptotic process of T lymphocytes via activation of numerous overlapping cascades (caspase-12) (Jimbo and others 2003; Luan and others 2014). ROS-mediated ER stress and mitochondrial dysfunction may also trigger T lymphocyte apoptosis in severe injury; however, the exact regulatory mechanism remains to be fully elucidated. It is now widely accepted that there may be crosstalk between the intrinsic pathways and the ER-mediated or extrinsic pathway (Oakes and others 2006; Dillon and others 2011; Daigneault and others 2012; Shaw and others 2012). Septic thymocyte apoptosis can be promoted by glucocorticoid, and it has been regarded as the most clinically relevant treatment for alleviating septic manifestations. Moreover, Shubin and others had shown that B and T lymphocyte attenuator (BTLA) expression contributed to apoptotic cell loss of primary and secondary lymphoid organ in experimental septic mice, suggesting that BTLA-induced apoptotic lymphocyte loss might be a mechanism for increased risk of nosocomial infection in critically ill patients (Carreno and Collins 2003; Sherwood and Hotchkiss 2013; Shubin and others 2013). Another approach showed that T cell exhaustion was mediated in part by PD-1 effects on T cells. *In vitro* blockade of the PD-1-PD-L1 signaling markedly decreased CD4⁺ T cell apoptosis and improved lymphocyte function in clinically relevant animal models of bacterial sepsis (Chang and others 2014). Though the cell death in the adaptive immune system seems to be beneficial to the host, by downregulating the inflammatory response to sepsis, the extensive loss of immune cells may contribute to the sepsis-associated multiple-organ dysfunction syndrome, increase risk of secondary opportunistic infections, and finally lead to septic death. These findings indicate that increased apoptosis in T lymphocytes might play a determining role in the outcome to septic syndrome.

Conclusions

Severe sepsis and septic shock occur with a high incidence in emergency departments and intensive care units, and they may result in both widespread activation and

dysfunction of the innate as well as adaptive responses in immune system. Over the past quarter century, there has been evolution of aggressive surgical procedures, extensive methods of supportive care, and a vast array of antimicrobial choices; mortality in severely septic patients has not been reduced in spite of these therapeutic strategies. In recent years, a great deal of evidence indicates that an unfavorable outcome of severe sepsis and septic shock is highly associated with an increased rate of apoptosis in different types of immune cells, including neutrophils, macrophages, DCs, as well as various lymphocyte populations. Therefore, inhibiting the major molecules and blocking extrinsic death receptor pathway, the intrinsic pathway, or the ER stress-induced pathway in order to modulate immune cell apoptosis through siRNA or other technique may represent a promising therapeutic strategy for the critically ill patients with severe sepsis as well as prevent the development of multiple-organ dysfunction syndrome.

Acknowledgments

This work was supported, in part, by grants from the National Natural Science Foundation (Nos. 81130035, 81372054, 81272090, and 81121004), the National Basic Research Program of China (No. 2012CB518102), and the Medical Research Foundation of Chinese PLA (Nos. AWS11J008 and BWS12J050).

Author Disclosure Statement

No competing financial interests exist.

References

- Alves-Filho JC, Spiller F, Cunha FQ. 2010. Neutrophil paralysis in sepsis. *Shock* 34 Suppl:115–121.
- Blum A, Chaperot L, Molens JP, Foissaud V, Plantaz D, Plumas J. 2006. Mechanisms of TRAIL-induced apoptosis in leukemic plasmacytoid dendritic cells. *Exp Hematol* 34(12):1655–1662.
- Bravo R, Gutierrez T, Paredes F, Gatica D, Rodriguez AE, Pedrozo Z, Chiong M, Parra V, Quest AF, Rothermel BA, Lavandero S. 2012. Endoplasmic reticulum: ER stress regulates mitochondrial bioenergetics. *Int J Biochem Cell Biol* 44(1):16–20.
- Carreno BM, Collins M. 2003. BTLA: a new inhibitory receptor with a B7-like ligand. *Trends Immunol* 24(10):524–527.
- Chang K, Svabek C, Vazquez-Guillamet C, Sato B, Rasche D, Wilson S, Robbins P, Ulbrandt N, Suzich J, Green J, Patera AC, Blair W, Krishnan S, Hotchkiss R. 2014. Targeting the programmed cell death 1: programmed cell death ligand 1 pathway reverses T cell exhaustion in patients with sepsis. *Crit Care* 18(1):R3.
- Daigneault M, De Silva TI, Bewley MA, Preston JA, Marriott HM, Mitchell AM, Mitchell TJ, Read RC, Whyte MK, Dockrell DH. 2012. Monocytes regulate the mechanism of T-cell death by inducing Fas-mediated apoptosis during bacterial infection. *PLoS Pathog* 8(7):e1002814.
- Derouet M, Thomas L, Moulding DA, Akgul C, Cross A, Moots RJ, Edwards SW. 2006. Sodium salicylate promotes neutrophil apoptosis by stimulating caspase-dependent turnover of Mcl-1. *J Immunol* 176(2):957–965.
- Dillon SM, Friedlander LJ, Rogers LM, Meditz AL, Folkvord JM, Connick E, McCarter MD, Wilson CC. 2011. Blood myeloid dendritic cells from HIV-1-infected individuals display a proapoptotic profile characterized by decreased Bcl-2 levels and by caspase-3⁺ frequencies that are associated with levels of plasma viremia and T cell activation in an exploratory study. *J Virol* 85(1):397–409.
- Fadeel B, Orrenius S. 2005. Apoptosis: a basic biological phenomenon with wide-ranging implications in human disease. *J Intern Med* 258(6):479–517.
- Gautier EL, Huby T, Saint-Charles F, Ouzilleau B, Chapman MJ, Lesnik P. 2008. Enhanced dendritic cell survival attenuates lipopolysaccharide-induced immunosuppression and increases resistance to lethal endotoxic shock. *J Immunol* 180(10):6941–6946.
- Granucci F, Zanoni I. 2009. The dendritic cell life cycle. *Cell Cycle* 8(23):3816–3821.
- Granucci F, Zanoni I, Ricciardi-Castagnoli P. 2008. Central role of dendritic cells in the regulation and deregulation of immuneresponses. *Cell Mol Life Sci* 65(11):1683–1697.
- Hattori Y, Takano K, Teramae H, Yamamoto S, Yokoo H, Matsuda N. 2010. Insights into sepsis therapeutic design based on the apoptotic death pathway. *J Pharmacol Sci* 114(4):354–365.
- Hotchkiss RS, Swanson PE, Knudson CM, Chang KC, Cobb JP, Osborne DF, Zollner KM, Buchman TG, Korsmeyer SJ, Karl IE. 1999. Overexpression of Bcl-2 in transgenic mice decreases apoptosis and improves survival in sepsis. *J Immunol* 162(7):4148–4156.
- Jiang W, Bell CW, Pisetsky DS. 2007. The relationship between apoptosis and high-mobility group protein 1 release from murine macrophages stimulated with lipopolysaccharide or polyinosinic-polycytidylic acid. *J Immunol* 178(10):6495–6503.
- Jimbo A, Fujita E, Kouroku Y, Ohnishi J, Inohara N, Kuida K, Sakamaki K, Yonehara S, Momoi T. 2003. ER stress induces caspase-8 activation, stimulating cytochrome c release and caspase-9 activation. *Exp Cell Res* 283(2):156–166.
- Kockara A, Kayatas M. 2013. Renal cell apoptosis and new treatment options in sepsis-induced acute kidney injury. *Ren Fail* 35(2):291–294.
- Kushwah R, Hu J. 2010. Dendritic cell apoptosis: regulation of tolerance versus immunity. *J Immunol* 185(2):795–802.
- Lang JD, Matute-Bello G. 2009. Lymphocytes, apoptosis and sepsis: making the jump from mice to humans. *Crit Care* 13(1):109.
- Liu ZG, Ni SY, Chen GM, Cai J, Guo ZH, Chang P, Li YS. 2013. Histones-mediated lymphocyte apoptosis during sepsis is dependent on p38 phosphorylation and mitochondrial permeability transition. *PLoS One* 8(10):e77131.
- Luan YY, Dong N, Xie M, Xiao XZ, Yao YM. 2014. The significance and regulatory mechanisms of innate immune cells in the development of sepsis. *J Interferon Cytokine Res* 34(1):2–15.
- Ma T, Han L, Gao Y, Li L, Shang X, Hu W, Xue C. 2008. The endoplasmic reticulum stress-mediated apoptosis signal pathway is involved in sepsis-induced abnormal lymphocyte apoptosis. *Eur Surg Res* 41(2):219–225.
- Martins ST, Silveira GF, Alves LR, Duarte dSCN, Bordignon J. 2012. Dendritic cell apoptosis and the pathogenesis of dengue. *Viruses* 4(11):2736–2753.
- Matsuda N, Teramae H, Futatsugi M, Takano K, Yamamoto S, Tomita K, Suzuki T, Yokoo H, Koike K, Hattori Y. 2010. Up-regulation of histamine H4 receptors contributes to splenic apoptosis in septic mice: counteraction of the anti-apoptotic action of nuclear factor-kappaB. *J Pharmacol. Exp Ther* 332(3):730–737.
- Mica L, Harter L, Trentz O, Keel M. 2004. Endotoxin reduces CD95-induced neutrophil apoptosis by cIAP-2-mediated caspase-3 degradation. *J Am Coll Surg* 199(4):595–602.

- Milot E, Filep JG. 2011. Regulation of neutrophil survival/apoptosis by Mcl-1. *Scientific World J* 11:1948–1962.
- Moulding DA, Akgul C, Derouet M, White MR, Edwards W. 2001. BCL-2 family expression in human neutrophils during delayed and accelerated apoptosis. *J Leukoc Biol* 70(5):783–792.
- Oakes SA, Lin SS, Bassik MC. 2006. The control of endoplasmic reticulum-initiated apoptosis by the BCL-2 family of proteins. *Curr Mol Med* 6(1):99–109.
- Oberholzer C, Oberholzer A, Clare-Salzler M, Moldawer LL. 2001. Apoptosis in sepsis: a new target for therapeutic exploration. *FASEB J* 15(6):879–892.
- Park SJ, Namkoong H, Doh J, Choi JC, Yang BG, Park Y, Chul SY. 2014. Negative role of inducible PD-1 on survival of activated dendritic cells. *J Leukoc Biol* 95(4):621–629.
- Paulick MG, Bertozzi CR. 2008. The glycosylphosphatidylinositol anchor: a complex membrane-anchoring structure for proteins. *Biochemistry* 47(27):6991–7000.
- Schwulst SJ, Muenzer JT, Peck-Palmer OM, Chang KC, Davis CG, McDonough JS, Osborne DF, Walton AH, Unsinger J, McDunn JE, Hotchkiss RS. 2008. Bim siRNA decreases lymphocyte apoptosis and improves survival in sepsis. *Shock* 30(2):127–134.
- Shaw SM, Critchley WR, Puchalka CM, Williams SG, Yonan N, Fildes JE. 2012. Brain natriuretic peptide induces CD8⁺ T cell death via a caspase 3 associated pathway—implications following heart transplantation. *Transpl Immunol* 26(2–3):119–122.
- Sherwood ER, Hotchkiss RS. 2013. BTLA as a biomarker and mediator of sepsis-induced immunosuppression. *Crit Care* 17(6):1022.
- Shubin NJ, Monaghan SF, Heffernan DS, Chung CS, Ayala A. 2013. B and T lymphocyte attenuator expression on CD4⁺ T-cells associates with sepsis and subsequent infections in ICU patients. *Crit Care* 17(6):R276.
- Sun H, Gong S, Carmody RJ, Hilliard A, Li L, Sun J, Kong L, Xu L, Hilliard B, Hu S, Shen H, Yang X, Chen YH. 2008. TIPE2, a negative regulator of innate and adaptive immunity that maintains immune homeostasis. *Cell* 133(3):415–426.
- Tinsley KW, Grayson MH, Swanson PE, Drewry AM, Chang KC, Karl IE, Hotchkiss RS. 2003. Sepsis induces apoptosis and profound depletion of splenic interdigitating and follicular dendritic cells. *J Immunol* 171(2):909–914.
- Wang T, Jiang Q, Chan C, Gorski KS, McCadden E, Kardian D, Pardoll D, Whartenby KA. 2009. Inhibition of activation-induced death of dendritic cells and enhancement of vaccine efficacy via blockade of MINOR. *Blood* 113(13):2906–2913.
- Weber SU, Schewe JC, Lehmann LE, Muller S, Book M, Klaschik S, Hoeft A, Stuber, F. 2008. Induction of Bim and Bid gene expression during accelerated apoptosis in severe sepsis. *Crit Care* 12(5):R128.
- Wesche DE, Lomas-Neira JL, Perl M, Chung CS, Ayala A. 2005. Leukocyte apoptosis and its significance in sepsis and shock. *J Leukoc Biol* 78(2):325–337.
- Zheng D, Sun Q, Su Z, Kong F, Shi X, Tong J, Shen P, Peng T, Wang S, Xu H. 2013. Enhancing specific-antibody production to the ragB vaccine with GITRL that expand Tfh, IFN-gamma(+) T cells and attenuates *Porphyromonas gingivalis* infection in mice. *PLoS One* 8(4):e59604.
- Zhu XM, Yao FH, Yao YM, Dong N, Yu Y, Sheng ZY. 2012. Endoplasmic reticulum stress and its regulator XBP-1 contributes to dendritic cell maturation and activation induced by high mobility group box-1 protein. *Int J Biochem Cell Biol* 44(7):1097–1105.
- Zhu XM, Yao YM, Liang HP, Liu F, Dong N, Yu Y, Sheng ZY. 2009. Effect of high mobility group box-1 protein on apoptosis of peritoneal macrophages. *Arch Biochem Biophys* 492(1–2):54–61.

Address correspondence to:

Prof. Yong-ming Yao

Department of Microbiology and Immunology

Burns Institute

First Hospital Affiliated to the Chinese

PLA General Hospital

Fucheng Road 51

Haidian District

Beijing 100048

People's Republic of China

E-mail: c_ff@sina.com

Received 28 April 2014/Accepted 3 June 2014