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Gram-positive and gram-negative bacterial toxins in sepsis

A brief review

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Bacterial sepsis is a major cause of fatality worldwide. Sepsis is a multi-step process that involves an uncontrolled inflammatory response by the host cells that may result in multi organ failure and death. Both gram-negative and gram-positive bacteria play a major role in causing sepsis. These bacteria produce a range of virulence factors that enable them to escape the immune defenses and disseminate to remote organs, and toxins that interact with host cells via specific receptors on the cell surface and trigger a dysregulated immune response. Over the past decade, our understanding of toxins has markedly improved, allowing for new therapeutic strategies to be developed. This review summarizes some of these toxins and their role in sepsis.

Introduction

Sepsis is defined as a systemic inflammatory response syndrome (SIRS) in the presence of suspected or proven infection.[1] It is the second most common cause of death in non-coronary intensive care units (ICU) and the tenth overall cause of death in high income countries.[2,3] The incidence of sepsis in the past two decades has annually increased by 9%, to reach 240 per 100 000 people in the USA by 2013.[4,5]

Initially it was thought that the major organisms that caused bacterial sepsis were gram-negative bacteria.[6] However, over the past 25 y it has been shown that gram-positive bacteria are the most common cause of sepsis.[7] Some of the most frequently isolated bacteria in sepsis are *Staphylococcus aureus* (*S. aureus*), *Streptococcus pyogenes* (*S. pyogenes*), *Klebsiella* spp., *Escherichia coli* (*E. coli*), and *Pseudomonas aeruginosa* (*P. aureginosa*).[8]

In order to cause disease, pathogens have to employ an array of factors known as virulence factors that protect them from the host innate immune system and enable them to cross mucosal barriers, disseminate, and replicate in distant organs.[9,10] Importantly, each stage of infection involves the expression of different virulence factors depending on the stage of infection. Some of the most important bacterial virulence factors are toxins. These toxins include endotoxin or lipopolysaccharide (LPS) that is present in the outer membrane of the gram-negative bacterium and several other secreted exotoxins and enterotoxins in other bacteria. Bacterial toxins are mainly divided into three types based on their mode of action. Type I toxins disrupt host cells without the need to enter the cells. These include superantigens (SAgs) produced by *S. aureus* and *S. pyogenes*.[11] Type II toxins, such as hemolysins and phospholipases destroy host cell membranes to invade and interrupt host defense processes within the cell.[12] Type III toxins, also known as A/B toxins due to their binary structure; disrupt host cell defenses to allow dissemination to remote organs. The B component of these toxins binds to the host cell surface, while the A component possess the enzymatic activity to damage the cell.[12] Several lethal toxins including Shiga toxin, cholera toxin, and anthrax lethal toxin belong to the Type III toxin family.

The host innate immune cells recognize several of the bacterial virulence factors via unique receptors called pattern-recognition receptors (PRRs).[13] PRRs recognize conserved motifs on the pathogen surface to initiate an innate immune response. Over the last decade with major research in the field of toxins and their interaction with host cells and PRRs, there has been a wealth of knowledge in understanding sepsis. This review aims to briefly focus on our current knowledge of some important toxins and their functions.

Endotoxins

Endotoxins are the glycolipid, LPS macromolecules that make up about 75% of the outer membrane of gram-negative bacteria that are capable of causing lethal shock.[14,15] The structure of LPS generally consists of a hydrophobic lipid A domain, an oligosaccharide core, and the outermost O-antigen polysaccharide.[16] Lipid A is a di-glucosamine-based lipid that serves as a hydrophobic anchor of LPS to the microbial membrane. *E. coli* is known to harbor approximately 10^6 lipid A residues on the surface.[17,18] Lipid A is a highly diverse molecule and the diversity is manifested in part in the number of fatty-acid side chains and the presence of terminal phosphate residues. Lipid A of *E. coli* that is hexa-acylated with side chains of 12–14 carbons has enhanced stimulatory effect of human cells compared with lipid A where the length of the side chains or the charge has been altered.[19-21] The lipid A of some human pathogens like *Francisella* spp., *Yersinia pestis*, and

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Helicobacter pylori contain typically only 4 or 5 acyl chains of 16–18 carbons in length and are poorly recognized by human LPS receptor known as Toll-like receptor 4 (TLR4).[22-24]

Lipid A is the single region of LPS that is recognized by the innate immune system. Picomolar concentrations of lipid A are sufficient to trigger a macrophage to produce proinflammatory cytokines like TNF-α and IL1β.[25-27] To trigger an innate immune response, the lipid A portion of LPS alone is sufficient, yet the adaptive immune response during infection is usually directed toward the O-antigen.[28] The key pattern recognition receptor for LPS recognition is Toll-like receptor 4 (TLR4).[29] LPS in circulation is solubilized by LPS-binding protein (LBP) in the serum.[30] The endotoxin is then transferred to an extrinsic glycosylphosphatidylinositol-anchored membrane protein on leukocytes called CD14.[31] CD14 can also be present in the soluble form. CD14 transfers LPS to MD2, which then binds to TLR4 to form the TLR4-MD2 receptor complex and triggers LPS recognition.[31] Soluble MD2 non-covalently associates with TLR4, however it binds to LPS directly even in the absence of TLR4.[32-34] Once the LPS-MD2-TLR4 complex forms, the entire complex dimerizes[35] and recruits cytoplasmic adaptor molecules, through the interaction with Toll-interleukin-1 receptor (TIR) domains.[36]

When TLR4 is activated upon its recognition of LPS, it signals through either a MyD88 (myeloid differentiation primary response gene 88)-dependent or a MyD88-independent pathway. The MyD88-dependent pathway induces the activation of NFκB and mitogen-activated protein kinase genes leading to the release of proinflammatory cytokines, whereas the MyD88 independent pathway (also known as the TRIF pathway-Toll-interleukin-1 receptor domain-containing, adaptor-inducing interferon β) activates the Type-1 interferon-inducible genes followed by NFκB production.[37]

The lipid A component of LPS is sufficient to cause endothelial cell injury by promoting the expression of tissue factor and proinflammatory cytokines, leading to apoptosis of these cells.[38-40] In a blood stream infection, presence of lipid A can lead to endotoxin shock. In murine TLR4, an 82-amino acids long hypervariable region is responsible for recognition of lipid A.[27] The structure-length and the number of acyl chains are critically important in human TLR4 signaling.

Several gram-negative bacteria have developed ways to modify lipid A structure depending on the environment and host cells leading to greater resistance to host cationic antimicrobial peptides (CAMPs) and altering TLR4 recognition.[41] CAMPs are a group of peptides produced by eukaryotes that are an important component of the innate immune responses against pathogens. Due to their cationic nature, CAMPs disrupt bacterial surface by inserting into the anionic cell wall and phospholipid membrane, thereby killing the pathogen.[42] Studies report that an extremely low concentration of CAMPs is sufficient to modify lipid A.[43] Modifications of lipid A are regulated by a two component system that is an environmental sensor-kinase regulator called PhoP-PhoQ in several gram-negative bacteria including *S.* Typhimurium. This two component system promotes the resistance of *S.* Typhimurium to CAMPs and also enables the pathogen to survive within human and murine macrophages.[41] PhoP–PhoQ regulated lipid A modifications involves the deacylation of several fatty acids and also the addition of palmitate, aminoarabinose, and phosphoethanolamine to the lipid A structure. Compared with non-regulated lipid A, PhoP–PhoQ regulated lipid A modifications leads them to be less recognized and stimulatory to the TLR4 complex, a phenomenon that could lead to the persistence of infection.[43,44] Acylation of lipid A is regulated by three enzymes, PagP, PagL, and LpxO in *Salmonella*, which catalyze the acylation, deacylation, and hydroxylation of lipid A respectively.[45-48] PagP enables the addition of C_{16}:0 fatty acid by transferring the fatty acids from the inner membrane portion of lipid A to the outer membrane region of the molecule.[45] PagL causes deacylation of the lipid A structure and decreases the recognition of lipid A when the pathogen colonizes host cells.[44] Both PagP and PagL modify the recognition of lipid A by the TLR4 complex. Addition of aminoarabinose decreases the negative charge of lipid A, making it more resistant to CAMPs.[49] Similarly, clinical isolates of *P. aeruginosa* that colonize the airways of cystic fibrosis patients synthesize unique lipid A molecules with an highly modified aminoarabinose and fatty-acid chains has been identified.[50]

LPS induces inflammatory cells to express a number of proinflammatory cytokines including IL-8, IL-6, IL-1β, IL-1, IL-12, and IFNγ;[51,52] however, TNFα seems to be of critical importance during endotoxic shock[53-55] and causes tissue damage.[56] In some clinical studies and animal models of sepsis, anti-TNF antibodies have shown to help in the treatment of septic shock.[57] Mice lacking the TNF receptor have an attenuated response to endotoxins.[58,59] During LPS-induced shock, TNFα, in addition to inducing anti-inflammatory cytokines such as IL-10 and IL-4,[60] also triggers the expression of proinflammatory cytokines, IL-1, IL-6, and IL-8 among others.[61] Apart from cytokine induction, TNFα also induces nitric oxide synthase (iNOS) and cyclooxygenase (COX-2) that catalyze the production of nitric oxide (NO) and prostaglandin E2 (PGE2).[62,63] Both NO and PGE2 are vasodilators that may cause the reduction in the migration of neutrophils to the site of infection by inhibiting the endothelium–leukocyte binding.[62-64] LPS in combination with TNFα induces apoptosis of the endothelium layer in several tissues including intestine, lungs, and thymus.[65] Several strategies to ameliorate endotoxin shock have been tested in both preclinical and in clinical trials. Despite the compelling evidence that LPS is a major factor in the pathophysiology of septic shock, recent trial targeting lipid-A portion of LPS with a drug called eritoran was unable to improve outcome in a large phase 3 clinical trial.[66]

Superantigens

Superantigens (SAg) are one of the most potent toxins produced by bacteria, namely, *S. aureus* and *S. pyogenes*. They are non-glycosylated proteins that have a relatively low molecular weight.[67] SAgs produced by *S. aureus* include staphylococcal enterotoxins SE (A–E) and toxic shock syndrome toxin-1 (TSST-1), while the toxins produced by *S. pyogenes* include streptococcus pyrogenic exotoxin A and C (SPEA and SPEC)[68,69] and the streptococcal mitogenic exotoxin Z (SMEZ).[67] These toxins are

capable of producing a massive cellular immune response that could lead to a fatal toxic shock.[70] Unlike conventional antigens that are processed by antigen presenting cells and presented to T cells through the MHC-II molecules, SAgs bind directly to the outer leaflet of MHC-II molecules[71-73] specific domains of the variable portion of β-chain (Vβ) of the T-cell receptor.[70,74-77] This allows for bypassing the processing by antigen presenting cells and stimulates most T cells. In addition to binding to MHC-II and the Vβ-chain, it has been recently shown that SAgs also engage a third receptor, CD28, which is a costimulatory molecule on T cells.[78-81] SAg bind directly at the homodimer interface of CD28 to cause toxicity by inducting a cytokine storm.[81] Unlike conventional antigens that normally activate <0.01% of T cells, SAgs activate >20% of T cells by binding to the MHC-II and T-cell receptor directly.[82-84] This leads to a massive induction of proinflammatory T-helper 1 (Th1) cytokines including tumor necrosis factor (TNF), interferon γ (IFN γ), and interleukin-2 (IL-2).[82,83,85,86] Further details on superantigens can be found in the paper by Reglinski and Sriskandan in this issue of *Virulence*.[87]

P. aeruginosa and Exotoxin A

In ICUs *P. aeruginosa*, a gram-negative bacterium is among the top five organisms causing pulmonary, urinary tract, soft-tissue, and bloodstream infections.[88] *P. aeruginosa* express several virulence factors such as flagella, pili, and LPS that play an important role in their pathogenesis. However, the toxins of *P. aeruginosa* are some of the most potent factors these organisms express and secrete.[89] Apart from the toxins they secrete, *P. aeruginosa* also inject one set of toxins directly into host cells through a macromolecular syringe called Type III secretion system.[90]

On the basis of weight, exotoxin A of this organism is the most toxic compound it produces.[91] Exotoxin A is part of an enzyme family called mono-ADP-ribosyltransferase.[91] The toxin affects the protein synthesis in host cells by catalyzing the ADP ribosylation of eukaryotic elongation factor 2, much like the mechanism of diphtheria toxin.[91] It is released by *P. aeruginosa* as a proenzyme that is toxic to animals and cultured cells but has very low enzymatic activity.[92] This toxin undergoes partial proteolysis by the serine endoprotease called furin, and then enters host cells through receptor mediated endocytosis. Exotoxin A is internalized into clatherin coated vesicles and moves into the endosomes.[93] The LD50 of exotoxin A was shown to be 0.2 μg in a 20 g mouse by the intraperitoneal route of administration. Between 80% and 90% of all clinical isolates of *P. aeruginosa* have demonstrated exotoxin A production in vitro.[94,95] It is presumed to escape into the cytosol through a translocation event. Studies have demonstrated that domain la of exotoxin A is the primary region of the toxin involved in cellular binding. In vivo studies with mice injected with purified exotoxin A lacking the la domain showed attenuation of toxicity compared with mice injected with native exotoxin A.[91] Administration of IVIG that are enriched in neutralizing antibodies to exotoxin A, however, led to no clinical improvement in patients with established *Pseudomonas* bacteremia.

Bacillus anthracis and Toxins

Bacillus anthracis (*B. anthracis*), the causative agent of the disease anthrax is a gram-positive bacteria that is able to survive in the environment in the spore form.[96] The disease is generally contracted mainly through three routes, namely, cutaneous, gastrointestinal, and the inhalation routes.[97-99] In spite of appropriate therapy, all the three routes of infection can lead to fatal disease as a result of sepsis and shock-like symptoms.[100] The inhalation route generally leads to the highest fatality and is a serious bioterrorism threat today.[101] The toxins of *B. anthracis* play a vital role in the pathogenesis of the disease. The toxins are made up of three secreted proteins working in binary combinations, namely protective antigen (PA), lethal factor (LF), and edema factor (EF).[102,103] The PA combines with EF to form the edema toxin (ET) and with LF to form the lethal toxin (LT).[104]

LF, a 90-kD zinc protease consisting of 4-folding domains,[105] is known to recognize six out of the seven mitogen-activated protein kinases, 1–4, 6, and 7. These are bound by domains II and III and cleaved at the N-terminus by domain IV.[106-108] The cleavage, results in the possible disruption of downstream signaling, mainly the inactivation of ERK1/2 (extracellular-signal-regulated-kinases), p38, and SAPK (stress-activated protein kinases)/JNK (Jun N-terminal kinases) pathways that are important for the activation of immune responses.[109] LT induces apoptosis in different cell types including Human umbilical vein endothelial cells by disrupting the ERK, p38, and JNK/SAPK pathways, with the ERK pathway being of upmost importance.[110] LT affects the translocation of tight junction proteins and alters the cytoskeleton reorganization by reducing levels of F-actin and blocking localization of vascular endothelial cadherin.[111] In human endothelial cells that are TNF-induced, LT amplifies expression of vascular cell adhesion molecule-1 that results in vasculitis and barrier disruption of cells.[112-114] Lymphocytic processes like T-cells activation, proliferation, and cytokine production are shown to be suppressed by both LT and ET.[115-117] The mechanism of T-cell suppression is the direct effect of LT cleaving MAPKKs, whereas ET suppresses T-cell processes by elevating the level of cAMP activity.[118] Both LT and ET prevent chemotaxis of T cells and macrophages by reducing the activation of MAPK to different chemokines.[119] While EF plays a greater role in disrupting the neutrophil migration and cytokine production, LF is directly lethal to macrophages and prevents dendritic cell maturation.[120,121] These deleterious effects of LF and EF on the immune cells impair phagocytosis of inhaled spores and vegetative forms of *B. anthracis*, allowing them to be transported to lymph nodes. A hemorrhagic and septic medistinitis develops accompanied by high-grade bacteremia, septic shock, and death. The toxic nature of both LT and ET results in bacterial dissemination to remote organs resulting in widespread tissue necrosis and death. A number of therapeutic strategies have been developed in an attempt to block the effects of anthrax toxins and improve outcomes.[122]

Conclusion

Treatment of sepsis still remains a serious concern and challenge in hospitals. Bacterial toxins from both gram-positive and gram-negative bacteria allow the pathogen to modulate host defenses through their interaction with cells enabling the bacteria to escape the innate immune system to remote organs. The type of toxin plays a major role in the outcome of disease. Over the last decade our understanding of the mechanisms by which these toxins modulate host defense has tremendously improved. This could enable a more efficient way of targeting the toxins and better clinical outcomes.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References

1. LaRosa SP, Opal SM. Sepsis strategies in development. Clin Chest Med 2008; 29:735-47, x-xi; PMID:18954707; http://dx.doi.org/10.1016/j.ccm.2008.06.007
2. Visintin A, Halmen KA, Latz E, Monks BG, Golenbock DT. Pharmacological inhibition of endotoxin responses is achieved by targeting the TLR4 coreceptor, MD-2. J Immunol 2005; 175:6465-72; PMID:16272300
3. Kim HM, Park BS, Kim JI, Kim SE, Lee J, Oh SC, Enkhbayar P, Matsushima N, Lee H, Yoo OJ, et al. Crystal structure of the TLR4-MD-2 complex with bound endotoxin antagonist Eritoran. Cell 2007; 130:906-17; PMID:17803912; http://dx.doi.org/10.1016/j.cell.2007.08.002
4. Solomon SB, Cui X, Gerstenberger E, Danner RL, Fitz Y, Banks SM, Natanson C, Eichacker PQ. Effective dosing of lipid A analogue E5564 in rats depends on the timing of treatment and the route of Escherichia coli infection. J Infect Dis 2006; 193:634-44; PMID:16453258; http://dx.doi.org/10.1086/500147
5. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med 2001; 29:1303-10; PMID:11445675; http://dx.doi.org/10.1097/00003246-200107000-00002
6. Parrillo JE, Parker MM, Natanson C, Suffredini AF, Danner RL, Cunnion RE, Ognibene FP. Septic shock in humans. Advances in the understanding of pathogenesis, cardiovascular dysfunction, and therapy. Ann Intern Med 1990; 113:227-42; PMID:2197912; http://dx.doi.org/10.7326/0003-4819-113-3-227
7. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med 2003; 348:1546-54; PMID:12700374; http://dx.doi.org/10.1056/NEJMoa022139
8. Opal SM, Garber GE, LaRosa SP, Maki DG, Freebairn RC, Kinasewitz GT, Dhainaut JF, Yan SB, Williams MD, Graham DE, et al. Systemic host responses in severe sepsis analyzed by causative microorganism and treatment effects of drotrecogin alfa (activated). Clin Infect Dis 2003; 37:50-8; PMID:12830408; http://dx.doi.org/10.1086/375593
9. Bergsten G, Samuelsson M, Wullt B, Leijonhufvud I, Fischer H, Svanborg C. PapG-dependent adherence breaks mucosal inertia and triggers the innate host response. J Infect Dis 2004; 189:1734-42; PMID:15116313; http://dx.doi.org/10.1086/383278
10. Merrell DS, Falkow S. Frontal and stealth attack strategies in microbial pathogenesis. Nature 2004; 430:250-6; PMID:15241423; http://dx.doi.org/10.1038/nature02760
11. Proft T, Sriskandan S, Yang L, Fraser JD. Superantigens and streptococcal toxic shock syndrome. Emerg Infect Dis 2003; 9:1211-8; PMID:14609454; http://dx.doi.org/10.3201/eid0910.030042
12. van der Poll T, Opal SM. Host-pathogen interactions in sepsis. Lancet Infect Dis 2008; 8:32-43; PMID:18063412; http://dx.doi.org/10.1016/S1473-3099(07)70265-7
13. Akira S, Uematsu S, Takeuchi O. Pathogen recognition and innate immunity. Cell 2006; 124:783-801; PMID:16497588; http://dx.doi.org/10.1016/j.cell.2006.02.015
14. Morrison DC, Ryan JL. Endotoxins and disease mechanisms. Annu Rev Med 1987; 38:417-32; PMID:3555304; http://dx.doi.org/10.1146/annurev.med.38.1.417
15. Bone RC. Sepsis, the sepsis syndrome, multi-organ failure: a plea for comparable definitions. Ann Intern Med 1991; 114:332-3; PMID:1987879; http://dx.doi.org/10.7326/0003-4819-114-4-332
16. Raetz CR, Whitfield C. Lipopolysaccharide endotoxins. Annu Rev Biochem 2002; 71:635-700; PMID:12045108; http://dx.doi.org/10.1146/annurev.biochem.71.110601.135414
17. Galloway SM, Raetz CR. A mutant of Escherichia coli defective in the first step of endotoxin biosynthesis. J Biol Chem 1990; 265:6394-402; PMID:2180947
18. Guan Z, Breazeale SD, Raetz CR. Extraction and identification by mass spectrometry of undecaprenyl diphosphate-MurNAc-pentapeptide-GlcNAc from Escherichia coli. Anal Biochem 2005; 345:336-9; PMID:16118008; http://dx.doi.org/10.1016/j.ab.2005.07.002
19. Schromm AB, Brandenburg K, Loppnow H, Zähringer U, Rietschel ET, Carroll SF, Koch MH, Kusumoto S, Seydel U. The charge of endotoxin molecules influences their conformation and IL-6-inducing capacity. J Immunol 1998; 161:5464-71; PMID:9820522
20. Schromm AB, Brandenburg K, Loppnow H, Moran AP, Koch MH, Rietschel ET, Seydel U. Biological activities of lipopolysaccharides are determined by the shape of their lipid A portion. Eur J Biochem 2000; 267:2008-13; PMID:10727940; http://dx.doi.org/10.1046/j.1432-1327.2000.01204.x
21. Somerville JE Jr., Cassiano L, Darveau RP. Escherichia coli msbB gene as a virulence factor and a therapeutic target. Infect Immun 1999; 67:6583-90; PMID:10569778
22. Girard R, Pedron T, Uematsu S, Balloy V, Chignard M, Akira S, Chaby R. Lipopolysaccharides from Legionella and Rhizobium stimulate mouse bone marrow granulocytes via Toll-like receptor 2. J Cell Sci 2003; 116:293-302; PMID:12482915; http://dx.doi.org/10.1242/jcs.00212
23. Moran AP, Lindner B, Walsh EJ. Structural characterization of the lipid A component of Helicobacter pylori rough- and smooth-form lipopolysaccharides. J Bacteriol 1997; 179:6453-63; PMID:9335296
24. Smith MF Jr., Mitchell A, Li G, Ding S, Fitzmaurice AM, Ryan K, Crowe S, Goldberg JB. Toll-like receptor (TLR) 2 and TLR5, but not TLR4, are required for Helicobacter pylori-induced NF-kappa B activation and chemokine expression by epithelial cells. J Biol Chem 2003; 278:32552-60; PMID:12807870; http://dx.doi.org/10.1074/jbc.M305536200
25. Beutler B, Cerami A. Tumor necrosis, cachexia, shock, and inflammation: a common mediator. Annu Rev Biochem 1988; 57:505-18; PMID:3052281; http://dx.doi.org/10.1146/annurev.bi.57.070188.002445
26. Dinarello CA. Interleukin-1 and interleukin-1 antagonism. Blood 1991; 77:1627-52; PMID:1826616
27. Miller SI, Ernst RK, Bader MW. LPS, TLR4 and infectious disease diversity. Nat Rev Microbiol 2005; 3:36-46; PMID:15608698; http://dx.doi.org/10.1038/nrmicro1068
28. Bryant CE, Spring DR, Gangloff M, Gay NJ. The molecular basis of the host response to lipopolysaccharide. Nat Rev Microbiol 2010; 8:8-14; PMID:19946286
29. Medzhitov R, Preston-Hurlburt P, Janeway CA Jr. A human homologue of the Drosophila Toll protein signals activation of adaptive immunity. Nature 1997; 388:394-7; PMID:9237759; http://dx.doi.org/10.1038/41131
30. Schumann RR, Leong SR, Flaggs GW, Gray PW, Wright SD, Mathison JC, Tobias PS, Ulevitch RJ. Structure and function of lipopolysaccharide binding protein. Science 1990; 249:1429-31; PMID:2402637; http://dx.doi.org/10.1126/science.2402637
31. Wright SD, Ramos RA, Tobias PS, Ulevitch RJ, Mathison JC. CD14, a receptor for complexes of lipopolysaccharide (LPS) and LPS binding protein. Science 1990; 249:1431-3; PMID:1698311; http://dx.doi.org/10.1126/science.1698311
32. Shimazu R, Akashi S, Ogata H, Nagai Y, Fukudome K, Miyake K, Kimoto M. MD-2, a molecule that confers lipopolysaccharide responsiveness on Toll-like receptor 4. J Exp Med 1999; 189:1777-82; PMID:10359581; http://dx.doi.org/10.1084/jem.189.11.1777
33. Nagai Y, Akashi S, Nagafuku M, Ogata M, Iwakura Y, Akira S, Kitamura T, Kosugi A, Kimoto M, Miyake K. Essential role of MD-2 in LPS responsiveness and TLR4 distribution. Nat Immunol 2002; 3:667-72; PMID:12055629
34. Gioannini TL, Teghanemt A, Zhang D, Coussens NP, Dockstader W, Ramaswamy S, Weiss JP. Isolation of an endotoxin-MD-2 complex that produces Toll-like receptor 4-dependent cell activation at picomolar concentrations. Proc Natl Acad Sci U S A 2004; 101:4186-91; PMID:15010525; http://dx.doi.org/10.1073/pnas.0306906101
35. Feng C, Stamatos NM, Dragan AI, Medvedev A, Whitford M, Zhang L, Song C, Rallabhandi P, Cole L, Nhu QM, et al. Sialyl residues modulate LPS-mediated signaling through the Toll-like receptor 4 complex. PLoS One 2012; 7:e32359; PMID:22496731; http://dx.doi.org/10.1371/journal.pone.0032359
36. Poltorak A, He X, Smirnova I, Liu MY, Van Huffel C, Du X, Birdwell D, Alejos E, Silva M, Galanos C, et al. Defective LPS signaling in C3H/HeJ and C57BL/10ScCr mice: mutations in Tlr4 gene. Science 1998; 282:2085-8; PMID:9851930; http://dx.doi.org/10.1126/science.282.5396.2085
37. Lu YC, Yeh WC, Ohashi PS. LPS/TLR4 signal transduction pathway. Cytokine 2008; 42:145-51; PMID:18304834; http://dx.doi.org/10.1016/j.cyto.2008.01.006
38. Bannerman DD, Erwert RD, Winn RK, Harlan JM. TIRAP mediates endotoxin-induced NF-kappaB activation and apoptosis in endothelial cells. Biochem Biophys Res Commun 2002; 295:157-62; PMID:12083783; http://dx.doi.org/10.1016/S0006-291X(02)00638-1

39. Delvos U, Janssen B, Müller-Berghaus G. Effect of lipopolysaccharides on cultured human endothelial cells. Relationship between tissue factor activity and prostacyclin release. Blut 1987; 55:101-8; PMID:3111564; http://dx.doi.org/10.1007/BF00631779
40. Suttorp N, Galanos C, Neuhof H. Endotoxin alters arachidonate metabolism in pulmonary endothelial cells. Am J Physiol 1987; 253:C384-90; PMID:3115111
41. Ernst RK, Guina T, Miller SI. Salmonella typhimurium outer membrane remodeling: role in resistance to host innate immunity. Microbes Infect 2001; 3:1327-34; PMID:11755422; http://dx.doi.org/10.1016/S1286-4579(01)01494-0
42. Pinheiro da Silva F, Machado MC. Antimicrobial peptides: clinical relevance and therapeutic implications. Peptides 2012; 36:308-14; PMID:22659161; http://dx.doi.org/10.1016/j.peptides.2012.05.014
43. Guo L, Lim KB, Gunn JS, Bainbridge B, Darveau RP, Hackett M, Miller SI. Regulation of lipid A modifications by Salmonella typhimurium virulence genes phoP-phoQ. Science 1997; 276:250-3; PMID:9092473; http://dx.doi.org/10.1126/science.276.5310.250
44. Kawasaki K, Ernst RK, Miller SI. 3-O-deacylation of lipid A by PagL, a PhoP/PhoQ-regulated deacylase of Salmonella typhimurium, modulates signaling through Toll-like receptor 4. J Biol Chem 2004; 279:20044-8; PMID:15014080; http://dx.doi.org/10.1074/jbc.M401275200
45. Guo L, Lim KB, Poduje CM, Daniel M, Gunn JS, Hackett M, Miller SI. Lipid A acylation and bacterial resistance against vertebrate antimicrobial peptides. Cell 1998; 95:189-98; PMID:9790526; http://dx.doi.org/10.1016/S0092-8674(00)81750-X
46. Trent MS, Pabich W, Raetz CR, Miller SI. A PhoP/PhoQ-induced Lipase (PagL) that catalyzes 3-O-deacylation of lipid A precursors in membranes of Salmonella typhimurium. J Biol Chem 2001; 276:9083-92; PMID:11108722; http://dx.doi.org/10.1074/jbc.M010730200
47. Bishop RE, Gibbons HS, Guina T, Trent MS, Miller SI, Raetz CR. Transfer of palmitate from phospholipids to lipid A in outer membranes of gram-negative bacteria. EMBO J 2000; 19:5071-80; PMID:11013210; http://dx.doi.org/10.1093/emboj/19.19.5071
48. Gibbons HS, Lin S, Cotter RJ, Raetz CR. Oxygen requirement for the biosynthesis of the S-2-hydroxymyristate moiety in Salmonella typhimurium lipid A. Function of LpxO, A new Fe2+/alpha-ketoglutarate-dependent dioxygenase homologue. J Biol Chem 2000; 275:32940-9; PMID:10903325; http://dx.doi.org/10.1074/jbc.M005779200
49. Gunn JS, Ryan SS, Van Velkinburgh JC, Ernst RK, Miller SI. Genetic and functional analysis of a PmrA-PmrB-regulated locus necessary for lipopolysaccharide modification, antimicrobial peptide resistance, and oral virulence of Salmonella enterica serovar typhimurium. Infect Immun 2000; 68:6139-46; PMID:11035717; http://dx.doi.org/10.1128/IAI.68.11.6139-6146.2000
50. Ernst RK, Yi EC, Guo L, Lim KB, Burns JL, Hackett M, Miller SI. Specific lipopolysaccharide found in cystic fibrosis airway Pseudomonas aeruginosa. Science 1999; 286:1561-5; PMID:10567263; http://dx.doi.org/10.1126/science.286.5444.1561
51. Tracey KJ, Lowry SF. The role of cytokine mediators in septic shock. Adv Surg 1990; 23:21-56; PMID:2403458
52. Beutler B. Endotoxin, tumor necrosis factor, and related mediators: new approaches to shock. New Horiz 1993; 1:3-12; PMID:7922391
53. Beutler B, Milsark IW, Cerami AC. Passive immunization against cachectin/tumor necrosis factor protects mice from lethal effect of endotoxin. Science 1985; 229:869-71; PMID:3895437; http://dx.doi.org/10.1126/science.3895437
54. Tracey KJ, Beutler B, Lowry SF, Merryweather J, Wolpe S, Milsark IW, Hariri RJ, Fahey TJ 3rd, Zentella A, Albert JD, et al. Shock and tissue injury induced by recombinant human cachectin. Science 1986; 234:470-4; PMID:3764421; http://dx.doi.org/10.1126/science.3764421
55. Tobias PS, Mathison JC, Ulevitch RJ. A family of lipopolysaccharide binding proteins involved in responses to gram-negative sepsis. J Biol Chem 1988; 263:13479-81; PMID:3138236
56. Tracey KJ, Fong Y, Hesse DG, Manogue KR, Lee AT, Kuo GC, Lowry SF, Cerami A. Anti-cachectin/TNF monoclonal antibodies prevent septic shock during lethal bacteraemia. Nature 1987; 330:662-4; PMID:3317066; http://dx.doi.org/10.1038/330662a0
57. van der Poll T, Lowry SF. Tumor necrosis factor in sepsis: mediator of multiple organ failure or essential part of host defense? Shock 1995; 3:1-12; PMID:7850574
58. Rothe J, Lesslauer W, Lötscher H, Lang Y, Koebel P, Köntgen F, Althage A, Zinkernagel R, Steinmetz M, Bluethmann H. Mice lacking the tumour necrosis factor receptor 1 are resistant to TNF-mediated toxicity but highly susceptible to infection by Listeria monocytogenes. Nature 1993; 364:798-802; PMID:8395024; http://dx.doi.org/10.1038/364798a0
59. Pfeffer K, Matsuyama T, Kündig TM, Wakeham A, Kishihara K, Shahinian A, Wiegmann K, Ohashi PS, Krönke M, Mak TW. Mice deficient for the 55 kd tumor necrosis factor receptor are resistant to endotoxic shock, yet succumb to L. monocytogenes infection. Cell 1993; 73:457-67; PMID:8387893; http://dx.doi.org/10.1016/0092-8674(93)90134-C
60. Dinarello CA. The role of interleukin-1 in host responses to infectious diseases. Infect Agents Dis 1992; 1:227-36; PMID:1344662
61. Wang R, Fang Q, Zhang L, Radvany L, Sharma A, Noben-Trauth N, Mills GB, Shi Y. CD28 ligation prevents bacterial toxin-induced septic shock in mice by inducing IL-10 expression. J Immunol 1997; 158:2856-61; PMID:9058822
62. Kilbourn RG, Gross SS, Jubran A, Adams J, Griffith OW, Levi R, Lodato RF. NG-methyl-L-arginine inhibits tumor necrosis factor-induced hypotension: implications for the involvement of nitric oxide. Proc Natl Acad Sci U S A 1990; 87:3629-32; PMID:2333306; http://dx.doi.org/10.1073/pnas.87.9.3629
63. Kettelhut IC, Fiers W, Goldberg AL. The toxic effects of tumor necrosis factor in vivo and their prevention by cyclooxygenase inhibitors. Proc Natl Acad Sci U S A 1987; 84:4273-7; PMID:3108890; http://dx.doi.org/10.1073/pnas.84.12.4273
64. Benjamim CF, Silva JS, Fortes ZB, Oliveira MA, Ferreira SH, Cunha FQ. Inhibition of leukocyte rolling by nitric oxide during sepsis leads to reduced migration of active microbicidal neutrophils. Infect Immun 2002; 70:3602-10; PMID:12065501; http://dx.doi.org/10.1128/IAI.70.7.3602-3610.2002
65. Haimovitz-Friedman A, Cordon-Cardo C, Bayoumy S, Garzotto M, McLoughlin M, Gallily R, Edwards CK 3rd, Schuchman EH, Fuks Z, Kolesnick R. Lipopolysaccharide induces disseminated endothelial apoptosis requiring ceramide generation. J Exp Med 1997; 186:1831-41; PMID:9382882; http://dx.doi.org/10.1084/jem.186.11.1831
66. Opal SM, Laterre PF, Francois B, LaRosa SP, Angus DC, Mira JP, Wittebole X, Dugernier T, Perrotin D, Tidswell M, et al.; ACCESS Study Group. Effect of eritoran, an antagonist of MD2-TLR4, on mortality in patients with severe sepsis: the ACCESS randomized trial. JAMA 2013; 309:1154-62; PMID:23512062; http://dx.doi.org/10.1001/jama.2013.2194
67. Brosnahan AJ, Schlievert PM. Gram-positive bacterial superantigen outside-in signaling causes toxic shock syndrome. FEBS J 2011; 278:4649-67; PMID:21535475; http://dx.doi.org/10.1111/j.1742-4658.2011.08151.x
68. Bohach GA, Fast DJ, Nelson RD, Schlievert PM. Staphylococcal and streptococcal pyrogenic toxins involved in toxic shock syndrome and related illnesses. Crit Rev Microbiol 1990; 17:251-72; PMID:2206394; http://dx.doi.org/10.3109/10408419009105728
69. Marrack P, Kappler J. The staphylococcal enterotoxins and their relatives. Science 1990; 248:1066; PMID:2343314
70. Herman A, Kappler JW, Marrack P, Pullen AM. Superantigens: mechanism of T-cell stimulation and role in immune responses. Annu Rev Immunol 1991; 9:745-72; PMID:1832875; http://dx.doi.org/10.1146/annurev.iy.09.040191.003525
71. Mourad W, Scholl P, Diaz A, Geha R, Chatila T. The staphylococcal toxic shock syndrome toxin 1 triggers B cell proliferation and differentiation via major histocompatibility complex-unrestricted cognate T/B cell interaction. J Exp Med 1989; 170:2011-22; PMID:2584933; http://dx.doi.org/10.1084/jem.170.6.2011
72. Scholl PR, Diez A, Geha RS. Staphylococcal enterotoxin B and toxic shock syndrome toxin-1 bind to distinct sites on HLA-DR and HLA-DQ molecules. J Immunol 1989; 143:2583-8; PMID:2551962
73. Scholl P, Diez A, Mourad W, Parsonnet J, Geha RS, Chatila T. Toxic shock syndrome toxin 1 binds to major histocompatibility complex class II molecules. Proc Natl Acad Sci U S A 1989; 86:4210-4; PMID:2542966; http://dx.doi.org/10.1073/pnas.86.11.4210
74. Fraser JD. High-affinity binding of staphylococcal enterotoxins A and B to HLA-DR. Nature 1989; 339:221-3; PMID:2785644; http://dx.doi.org/10.1038/339221a0
75. Choi YW, Herman A, DiGiusto D, Wade T, Marrack P, Kappler J. Residues of the variable region of the T-cell-receptor beta-chain that interact with S. aureus toxin superantigens. Nature 1990; 346:471-3; PMID:2377208; http://dx.doi.org/10.1038/346471a0
76. Kappler J, Kotzin B, Herron L, Gelfand EW, Bigler RD, Boylston A, Carrel S, Posnett DN, Choi Y, Marrack P. V beta-specific stimulation of human T cells by staphylococcal toxins. Science 1989; 244:811-3; PMID:2524876; http://dx.doi.org/10.1126/science.2524876
77. Janeway CA Jr., Yagi J, Conrad PJ, Katz ME, Jones B, Vroegop S, Buxser S. T-cell responses to Mls and to bacterial proteins that mimic its behavior. Immunol Rev 1989; 107:61-88; PMID:2522086; http://dx.doi.org/10.1111/j.1600-065X.1989.tb00003.x
78. Muraille E, De Smedt T, Urbain J, Moser M, Leo O. B7.2 provides co-stimulatory functions in vivo in response to staphylococcal enterotoxin B. Eur J Immunol 1995; 25:2111-4; PMID:7542606; http://dx.doi.org/10.1002/eji.1830250747
79. Saha B, Harlan DM, Lee KP, June CH, Abe R. Protection against lethal toxic shock by targeted disruption of the CD28 gene. J Exp Med 1996; 183:2675-80; PMID:8676089; http://dx.doi.org/10.1084/jem.183.6.2675
80. Mittrücker HW, Shahinian A, Bouchard D, Kündig TM, Mak TW. Induction of unresponsiveness and impaired T cell expansion by staphylococcal enterotoxin B in CD28-deficient mice. J Exp Med 1996; 183:2481-8; PMID:8676068; http://dx.doi.org/10.1084/jem.183.6.2481
81. Arad G, Levy R, Nasie I, Hillman D, Rotfogel Z, Barash U, Supper E, Shpilka T, Minis A, Kaempfer R. Binding of superantigen toxins into the CD28 homodimer interface is essential for induction of cytokine genes that mediate lethal shock. PLoS Biol 2011; 9:e1001149; PMID:21931534; http://dx.doi.org/10.1371/journal.pbio.1001149

82. Marrack P, Blackman M, Kushnir E, Kappler J. The toxicity of staphylococcal enterotoxin B in mice is mediated by T cells. J Exp Med 1990; 171:455-64; PMID:2303780; http://dx.doi.org/10.1084/jem.171.2.455
83. Miethke T, Wahl C, Heeg K, Echtenacher B, Krammer PH, Wagner H. T cell-mediated lethal shock triggered in mice by the superantigen staphylococcal enterotoxin B: critical role of tumor necrosis factor. J Exp Med 1992; 175:91-8; PMID:1730929; http://dx.doi.org/10.1084/jem.175.1.91
84. Leder L, Llera A, Lavoie PM, Lebedeva MI, Li H, Sékaly RP, Bohach GA, Gahr PJ, Schlievert PM, Karjalainen K, et al. A mutational analysis of the binding of staphylococcal enterotoxins B and C3 to the T cell receptor beta chain and major histocompatibility complex class II. J Exp Med 1998; 187:823-33; PMID:9500785; http://dx.doi.org/10.1084/jem.187.6.823
85. Arad G, Levy R, Hillman D, Kaempfer R. Superantigen antagonist protects against lethal shock and defines a new domain for T-cell activation. Nat Med 2000; 6:414-21; PMID:10742148; http://dx.doi.org/10.1038/74672
86. Hackett SP, Stevens DL. Superantigens associated with staphylococcal and streptococcal toxic shock syndrome are potent inducers of tumor necrosis factor-beta synthesis. J Infect Dis 1993; 168:232-5; PMID:8515117; http://dx.doi.org/10.1093/infdis/168.1.232
87. Reglinski M, Sriskandan S. The contribution of group A streptococcal virulence determinants to the pathogenesis of sepsis. Virulence 2013; 5:5; PMID:24157731
88. Trautmann M, Lepper PM, Haller M. Ecology of Pseudomonas aeruginosa in the intensive care unit and the evolving role of water outlets as a reservoir of the organism. Am J Infect Control 2005; 33(Suppl 1):S41-9; PMID:15940115; http://dx.doi.org/10.1016/j.ajic.2005.03.006
89. Veesenmeyer JL, Hauser AR, Lisboa T, Rello J. Pseudomonas aeruginosa virulence and therapy: evolving translational strategies. Crit Care Med 2009; 37:1777-86; PMID:19325463; http://dx.doi.org/10.1097/CCM.0b013e31819ff137
90. Frank DW. The exoenzyme S regulon of Pseudomonas aeruginosa. Mol Microbiol 1997; 26:621-9; PMID:9427393; http://dx.doi.org/10.1046/j.1365-2958.1997.6251991.x
91. Wolf P, Elsässer-Beile U. Pseudomonas exotoxin A: from virulence factor to anti-cancer agent. Int J Med Microbiol 2009; 299:161-76; PMID:18948059; http://dx.doi.org/10.1016/j.ijmm.2008.08.003
92. Woods DE, Iglewski BH. Toxins of Pseudomonas aeruginosa: new perspectives. Rev Infect Dis 1983; 5(Suppl 4):S715-22; PMID:6415785; http://dx.doi.org/10.1093/clinids/5.Supplement_4.S715
93. Saelinger CB, Morris RE. Intracellular trafficking of Pseudomonas exotoxin A. Antibiot Chemother (1971) 1987; 39:149-59; PMID:3118781
94. Bjorn MJ, Vasil ML, Sadoff JC, Iglewski BH. Incidence of exotoxin production by Pseudomonas species. Infect Immun 1977; 16:362-6; PMID:68931
95. Pollack M, Taylor NS, Callahan LT 3rd. Exotoxin production by clinical isolates of pseudomonas aeruginosa. Infect Immun 1977; 15:776-80; PMID:404244
96. Weiner ZP, Glomski IJ. Updating perspectives on the initiation of Bacillus anthracis growth and dissemination through its host. Infect Immun 2012; 80:1626-33; PMID:22354031; http://dx.doi.org/10.1128/IAI.06061-11
97. Abramova FA, Grinberg LM, Yampolskaya OV, Walker DH. Pathology of inhalational anthrax in 42 cases from the Sverdlovsk outbreak of 1979. Proc Natl Acad Sci U S A 1993; 90:2291-4; PMID:8460135; http://dx.doi.org/10.1073/pnas.90.6.2291
98. Inglesby TV, O'Toole T, Henderson DA, Bartlett JG, Ascher MS, Eitzen E, Friedlander AM, Gerberding J, Hauer J, Hughes J, et al.; Working Group on Civilian Biodefense. Anthrax as a biological weapon, 2002: updated recommendations for management. JAMA 2002; 287:2236-52; PMID:11980524; http://dx.doi.org/10.1001/jama.287.17.2236
99. Mock M, Fouet A. Anthrax. Annu Rev Microbiol 2001; 55:647-71; PMID:11544370; http://dx.doi.org/10.1146/annurev.micro.55.1.647
100. Turnbull PC. Anthrax vaccines: past, present and future. Vaccine 1991; 9:533-9; PMID:1771966; http://dx.doi.org/10.1016/0264-410X(91)90237-Z
101. Holty JE, Bravata DM, Liu H, Olshen RA, McDonald KM, Owens DK. Systematic review: a century of inhalational anthrax cases from 1900 to 2005. Ann Intern Med 2006; 144:270-80; PMID:16490913; http://dx.doi.org/10.7326/0003-4819-144-4-200602210-00009
102. Collier RJ, Young JA. Anthrax toxin. Annu Rev Cell Dev Biol 2003; 19:45-70; PMID:14570563; http://dx.doi.org/10.1146/annurev.cellbio.19.111301.140655
103. Brossier F, Mock M. Toxins of Bacillus anthracis. Toxicon 2001; 39:1747-55; PMID:11595637; http://dx.doi.org/10.1016/S0041-0101(01)00161-1
104. Pezard C, Berche P, Mock M. Contribution of individual toxin components to virulence of Bacillus anthracis. Infect Immun 1991; 59:3472-7; PMID:1910002
105. Pannifer AD, Wong TY, Schwarzenbacher R, Renatus M, Petosa C, Bienkowska J, Lacy DB, Collier RJ, Park S, Leppla SH, et al. Crystal structure of the anthrax lethal factor. Nature 2001; 414:229-33; PMID:11700563; http://dx.doi.org/10.1038/n35101998
106. Rainey GJ, Young JA. Antitoxins: novel strategies to target agents of bioterrorism. Nat Rev Microbiol 2004; 2:721-6; PMID:15372082; http://dx.doi.org/10.1038/nrmicro977
107. Duesbery NS, Webb CP, Leppla SH, Gordon VM, Klimpel KR, Copeland TD, Ahn NG, Oskarsson MK, Fukasawa K, Paull KD, et al. Proteolytic inactivation of MAP-kinase-kinase by anthrax lethal factor. Science 1998; 280:734-7; PMID:9563949; http://dx.doi.org/10.1126/science.280.5364.734
108. Vitale G, Pellizzari R, Recchi C, Napolitani G, Mock M, Montecucco C. Anthrax lethal factor cleaves the N-terminus of MAPKKs and induces tyrosine/threonine phosphorylation of MAPKs in cultured macrophages. Biochem Biophys Res Commun 1998; 248:706-11; PMID:9703991; http://dx.doi.org/10.1006/bbrc.1998.9040
109. Park JM, Greten FR, Li ZW, Karin M. Macrophage apoptosis by anthrax lethal factor through p38 MAP kinase inhibition. Science 2002; 297:2048-51; PMID:12202685; http://dx.doi.org/10.1126/science.1073163
110. Xie T, Auth RD, Frucht DM. The effects of anthrax lethal toxin on host barrier function. Toxins (Basel) 2011; 3:591-607; PMID:22069727; http://dx.doi.org/10.3390/toxins3060591
111. During RL, Li W, Hao B, Koenig JM, Stephens DS, Quinn CP, Southwick FS. Anthrax lethal toxin paralyzes neutrophil actin-based motility. J Infect Dis 2005; 192:837-45; PMID:16088833; http://dx.doi.org/10.1086/432516
112. Warfel JM, D'Agnillo F. Anthrax lethal toxin enhances TNF-induced endothelial VCAM-1 expression via an IFN regulatory factor-1-dependent mechanism. J Immunol 2008; 180:7516-24; PMID:18490752
113. Steele AD, Warfel JM, D'Agnillo F. Anthrax lethal toxin enhances cytokine-induced VCAM-1 expression on human endothelial cells. Biochem Biophys Res Commun 2005; 337:1249-56; PMID:16242117; http://dx.doi.org/10.1016/j.bbrc.2005.09.180
114. Warfel JM, Steele AD, D'Agnillo F. Anthrax lethal toxin induces endothelial barrier dysfunction. Am J Pathol 2005; 166:1871-81; PMID:15920171; http://dx.doi.org/10.1016/S0002-9440(10)62496-0
115. Paccani SR, Tonello F, Ghittoni R, Natale M, Muraro L, D'Elios MM, Tang WJ, Montecucco C, Baldari CT. Anthrax toxins suppress T lymphocyte activation by disrupting antigen receptor signaling. J Exp Med 2005; 201:325-31; PMID:15699068; http://dx.doi.org/10.1084/jem.20041557
116. Fang H, Cordoba-Rodriguez R, Lankford CS, Frucht DM. Anthrax lethal toxin blocks MAPK kinase-dependent IL-2 production in CD4+ T cells. J Immunol 2005; 174:4966-71; PMID:15814725
117. Comer JE, Chopra AK, Peterson JW, König R. Direct inhibition of T-lymphocyte activation by anthrax toxins in vivo. Infect Immun 2005; 73:8275-81; PMID:16299324; http://dx.doi.org/10.1128/IAI.73.12.8275-8281.2005
118. Paccani SR, Baldari CT. T cell targeting by anthrax toxins: two faces of the same coin. Toxins (Basel) 2011; 3:660-71; PMID:22069732; http://dx.doi.org/10.3390/toxins3060660
119. Rossi Paccani S, Tonello F, Patrussi L, Capitani N, Simonato M, Montecucco C, Baldari CT. Anthrax toxins inhibit immune cell chemotaxis by perturbing chemokine receptor signalling. Cell Microbiol 2007; 9:924-9; PMID:17087730; http://dx.doi.org/10.1111/j.1462-5822.2006.00840.x
120. Moayeri M, Leppla SH. Cellular and systemic effects of anthrax lethal toxin and edema toxin. Mol Aspects Med 2009; 30:439-55; PMID:19638283; http://dx.doi.org/10.1016/j.mam.2009.07.003
121. Tournier JN, Rossi Paccani S, Quesnel-Hellmann A, Baldari CT. Anthrax toxins: a weapon to systematically dismantle the host immune defenses. Mol Aspects Med 2009; 30:456-66; PMID:19560486; http://dx.doi.org/10.1016/j.mam.2009.06.002
122. Artenstein AW, Opal SM. Novel approaches to the treatment of systemic anthrax. Clin Infect Dis 2012; 54:1148-61; PMID:22438345; http://dx.doi.org/10.1093/cid/cis017