Journal of
Microbial & Biochemical Technology

Gola et al., J Microbial Biochem Technol 2014, R1
DOI: 10.4172/1948-5948.R1-007

Review Article Open Access

Apoptosis is a Major Pathogenic Event for Several Important Viral and Bacterial Pathogens

Vikas Gola[1], Kapil Gaur[1]*, Jaya Juneja[1], Richa Gupta[2], Kshitija Iyer[3], Rashi Nigam[3], Eluri Bhavya[4], Lincy Jessica[5] and Sakshi Behal[1]

[1]*Deenbandhu Chhotu Ram University of Science and Technology, Murthal, Sonepat, Haryana, India*
[2]*IMS Engineering College, Ghaziabad, India*
[3]*VIT University, Vellore, Tamil Nadu, India*
[4]*Osmania University, Hyderabad, India*
[5]*Chaithanya Bharathi Institute of Technology, Hyderabad, India*

Abstract

The development of post exposure medical specialty for a good kind of high-consequence pathogens are of important importance to counteract mortality and morbidity related to these pathogens and to enhance biological security. Any broad-spectrum medicine intervention that could mitigate the results of multiple potential bio-threat agents would represent a big breakthrough in each the understanding and treatment of the infections caused by rising infectious diseases and bio-threat agents. Necrobiosis has repeatedly been shown as a standard pathological feature of a good kind of various high-consequence pathogens that cover both infectious agent and microorganism bio-threat agents. During this abstract, we tend to examine the proof establishing this unhealthful commonality and discuss potential implications that this shared feature would possibly suggest for therapeutic intervention.

Keywords: Necrobiosis; Viruses; Apoptosis; Bacterial pathogens; Infectious diseases; Deoxyribonucleic acid; *F. tularensis; B. anthracis*

Introduction

The actuating agents of the many exotic or rising infectious diseases also are thought-about top-priority bio-threat agents, and therefore the development of effective post exposure medicine to combat the severe mortality of those agents is crucial. A number of the top-priority bio-threat viruses include the eradicated pox virus and infectious agent harm of forty five ever (VHF) viruses. The viruses causing VHFs with relevancy as bio-threat agents represent many infectious agent families and embody arena viruses, bunya viruses, and therefore the filo viruses. [1]. Top-priority microorganism bio-threat agents include Bacillus, the actuating agent of anthrax, and bacteria species, and the causative agent of rabbit fever. The US government has prioritized the event of 50 effective medical countermeasures for these potential agents of act of terrorism [2]. These microbes exhibit a various array of unhealthful mechanisms that lead to overwhelming infection, system deregulating, and infrequently death. The large loss of lymphocytes, nerve fiber cells, and alternative cell varieties through the mechanism of necrobiosis is an often-overlooked common unhealthful event shared by this various set of severe infections.

55 necrobiosis, or programmed necrobiosis, involves a series of organic chemistry events that cause a characteristic cell morphology and necrobiosis. The variability of cell morphological changes embrace blebbing; changes to the cyto-membrane, like loss of membrane spatial property and attachment; cell shrinkage; nuclear fragmentation; body substance condensation; and body deoxyribonucleic acid fragmentation. These changes is known histologically and ultra-structurally by cell 60 morphology and victimization the terminal deoxynucleotidyl enzyme dUTP nick-end labeling (TUNEL) assay, that detects deoxyribonucleic acid fragmentation by labeling the terminal finish of nucleic acids. Immunostaining for protease three, an apoptosis-related amino-alkanoic acid proteinase, is another technique that can be accustomed determines apoptotic cells though not all apoptotic pathways are protease dependent. Necrobiosis leads to the orderly disposal of cellular rubble, thereby avoiding harm to the organism that is in distinction to crosis. Mortification may be a style of traumatic necrobiosis that results from acute cellular injury and is pro-inflammatory. Necrobiosis of lymphocytes might prevent the event of a practical adjustive reaction to the foresaid severe infections, causative to the mortality of those choose pathogens.Animal models mimicking human illness square measure usually won't to study the pathological process 70 of those high-consequence pathogens Parrino et al. antecedently summarized proof from some of these animal models and mentioned however anti-apoptotic interventions might be wont to improve outcome for severe human infections [3]. Herein, we have a tendency to expand upon this idea and summarize further proof from animal models and what's identified concerning the pathology of human infections parenthetically that huge apoptotic loss of lymphocytes takes place in an exceedingly various set of 75 severe infections caused by high-consequence pathogens. Recognizing that several high consequence pathogens converge on this singular pathophysiological mechanism, we discuss how this common mechanism might be targeted for the event of potential nonspecific therapeutics for severe infections caused by rising pathogens and choose bio-threat agents.

The Poxviruses: Smallpox and Monkeypox

Variola virus (VARV) could be a member of the Ortho-poxvirus genus within the Poxviridae family, and is that the r agent of variola major. VARV, extremely infectious via aerosol and micro-droplet transmission, caused large epidemics within the past and remains a vital concern for biodefense despite its wipeout in 1979. Monkeypox virus (MPXV), a connected ortho-poxvirus, is associate degree rising

***Corresponding author:** Kapil Gaur, B.tech Biotechnology, Deenbandhu Chhotu Ram University of Science and Technology, Murthal, Sonepat, Haryana-131039, India, Tel: 8376837633; E-mail: djgaur007@gmail.com

Received December 08, 2014; **Accepted** December 09, 2014; **Published** December 30, 2014

Citation: Gola V, Gaur K, Juneja J, Gupta R, Iyer K (2014) Apoptosis is a Major Pathogenic Event for Several Important Viral and Bacterial Pathogens. J Microb Biochem Technol R1: 007. doi:10.4172/1948-5948.R1-007

animal disease endemic in central and western continent. MPXV will manufacture similar symptoms as VARV, however is sometimes milder in humans [4]. Each VARV and MPXV are classified as class a bio-threat agents, and therefore the occurrence of monkeypox within the U.S. in 2003 underscores the importance of developing effective medical specialty for these viruses.Vaccinia virus (VACV), the virus used for the variola major immunogen, is commonly used as a model for learning poxviruses. VACV has been shown to each block and promote cell death of various populations of immune cells. VACV-induced cell death of macrophages and nerve fiber cells in vitro, presumptively through the action of early immediate cistron transcription resulting in a decrease in the levels of Bcl-x(L), AN anti-apoptotic macromolecule of the Bcl-2 family [5]. Apparently, in a contrasting anti-apoptotic mechanism, VACV F11L macromolecule interferes with the mitochondrial part of the intrinsic cell death pathway, and serpin SP1-2 protects infected cells from the Fas-mediated apoptotic pathway [6]. Little is thought regarding the role of caspase-mediated cell death of lymphocytes in human animal virus sickness, but mechanical primate (NHP) studies examining the pathophysiology of VARV have shed lightweight on the potential pathological role of large immune death. Once cynomolgus macaques were inoculated with many VARV strains, animals that succumbed to infection displayed marked T-cell depletion in humortissues that the authors attribute to infected macrophageinitiated apoptotic communication [7]. Leukocyte depletion and degeneration of the liver and spleen were a homogenous microscopic finding of this study additionally to the observation of virus infected monocyte/macrophages and epithelium cells [7]. Our cluster has confirmed these previous histo-pathological findings in VARV infections and extended similar observations to a lethal NHP model of MPXV infection. Once cynomolgus macaques were infected with MPXV, apoptosis within the spleen was evident in terminally infected animals wherever focally in depth necrotizing inflammation poignant white pulp follicles was often determined. Strong TUNEL staining was determined in the follicles and to a lesser degree caspase-3 staining, that suggests either that the temporal order of protease activation is transient or that caspase-mediated cell death could occur through protease freelance pathways. These results highlight the vital role of leukocyte caspase-mediated cell death throughout deadly MPXV viral infection of NHPs.

The Filoviruses: Ebola and Marburg

Ebola Hemorrhagic Fever (EHF) and Marburg Hemorrhagic Fever (MHF) are rising infective agent diseases that cause severe hemorrhagic fever in humans and NHP. These harm fevers are caused by Ebola-Virus (EBOV) and Marburg-Virus (MARV), members of the family. There are 5 species of EBOV and one species of MARV [8]. Outbreaks occur primarily in Africa, and mortality rates vary from 50-90% for EHF and 20%-80% for MHF [9-11]. Development of vaccines and also therapeutics is significant thanks to progressively frequent outbreaks and the classification of EBOV and MARV as potential bio-threat agents. Currently, there aren't any FDA-approved countermeasures to treat these deadly Ebola viral diseases.Although lymphocytes aren't fruitfully infected by EBOV or MARV, bystander lymphocyte cell death has been systematically discovered in each the mouse [12,13] and NHP models [14] and is recommended to occur in human animal virus illness [10]. In human infections, vital loss of T lymphocytes related a lot of powerfully with fatal outcome than with survivors in associate degree outbreak of EBOV Sudan in 2000 [6]. This loss of lymphocytes is hypothesized to contribute to the lack of associate degree reconciling immune reaction against EBOV and MARV infection, leading to increased severity of illness and death [14]. Filoviruses are shown to induce cell death of CD4+ T cells, CD8+ T cells, and NK cells [13,15,16]. NHP infection associate degreed mouse infection with an adapted Zaire EBOV (ZEBOV) is characterized by huge cell death of each T and NK lymphocytes, primarily through classical cell death [17]. Almost like EBOV infection, MARV infected NHPs conjointly show huge lymph cell death [6] that corresponds with many clinically documented MARV human infections [18]. Strong TUNEL staining and caspase-3 immuno-staining confirms the presence of numerous apoptotic lymphocytes and cellular debris in the spleens of a terminally infected NHP. These results underscore the significant role that apoptosis plays in terminally filovirus infected NHPs.

The Arenaviruses: Lassa, Machupo, and Junin

Arenaviruses area unit a number of the causal agents of VHF, they're endemic in each continent and South America, and area unit comprised of previous World and New World viruses, severally. The foremost high-consequence arenaviral infective agent is that the previous World Lassa virus (LASV), that is assessed as a class A infective agent. LASV is that the causal agent of hemorrhagic fever, that contains a death rate between 15 August 1945 and 2 hundredth for hospitalized patients [19]. LASV remains endemic in regions of western continent, wherever there is area unit close to 3,000 infections annually [20]. There's no approved LASV immunogen, and medical care is restricted to treatment with antiviral drug, that is effective if administered sharply early in infection. New World animal viruses, like arenavirus (MACV) and arenavirus (JUNV), have emerged in recent decades because the causal agents of severe microorganism hemorrhagic fevers in South America. LASV infection is characterized by epithelium involvement, whereas tube deregulating and hemorrhages area unit additional pronounced within the New World arena viruses.

Macrophages area unit associate early target cell for infection, and later within the illness course epithelial cells area unit infected along-side important blood disorder. However, programmed cell death in arenaviral infections isn't well-characterized and careful studies area unit restricted. Associate in vitro study of JUNV infection incontestable that JUNV doesn't induce programmed cell death of glial cells however that JUNV infection will promote astrocyte production of gas [21]. Pirital virus, a New World arenavirus, infection of adult Syrian hamsters resulted in apoptotic proof within the liver of infected animals [22]. Recent NHP studies of chorio-meningitis virus (LCMV) as a model for human infection with LASV incontestable marked lymphocyte [23]. Marmoset animal studies of LASV infection reveal bodily fluid depletion within the spleen and body fluid nodes, confirming previous human observations of LASV pathology [24,25]. Therefore, the significant role of lymphocyte apoptosis in arenavirus disease is an important area of future research.

B. anthracis

Anthrax is Associate in nursing acute infection caused by the gram-positive microorganism *B. anthracis*. The bacteria occur naturally throughout the planet, primarily infecting herbivores and different life 175 that ingest the sturdy, dormant spores of *B. anthracis*. Human's square measure accidental hosts of *B. anthracis* and human infection are understood to lead to 3 differing types of disease: body covering, channel, and anthrax [26]. Untreated anthrax infection mortality rates approach 100 percent, as critical 100 percent to twenty for the body covering type [27]. *B. anthracis* is taken into account a class A infectious agent and its ability to be used as a bio-arm is highlighted by the anthrax attacks against the U.S in Oct 2001 [28]. There's associate

FDA-approved immunogen for anthrax, and antibiotic prevention has established effective if administered early when infection. *B. anthracis* produces 2 potent exotoxins, puffiness poison (ET) and deadly poison (LT) [29]. The anthrax LT promotes caspase-mediated cell death in some cell varieties, most notably macrophages, and deregulates the host innate and adaptation immune responses by meddlesome with a range of communication pathways as well as the mitogen-activated super molecule enzyme pathway (MAPK) [30]. Once within the cell, LT by selection induces caspase-mediated cell death in activated macrophages in vitro through the inhibition of p38 MAP enzyme [31]. Mutant macrophages that don't specific associate anthrax poison receptor don't seem to be prone to intoxication and subsequent caspase-mediated cell death [32]. To boot, mice receiving a bolus of toxin-resistant macrophages square measure considerably additional probably to survive associate anthrax infection [33]. Epithelium cells of the system have conjointly been ascertained to undergo classic caspase-mediated cell death when exposure to LT [34], though alternative reports ail direct cytotoxicity of epithelium cells by LT [35]. We've of times ascertained lymphocytolysis within the spleen of macaque macaques that succumbed to *B. anthracis*. Lymphocytolysis with tingible body scavenger cell infiltration may be a frequent finding within the white pulp of the spleen. These cells were TUNEL positive and therefore the presence of caspase-3 positive cells and cellular scrap confirms lymphatic tissue caspase-mediated cell death and supports the findings ascertained histologically and with TUNEL. White blood cell caspase-mediated cell death maybe plays a crucial role within the pathogenesis of *B. anthracis* in NHPs.

F. tularensis

The inducive agent of rabbit fever is that the extremely infectious, gram-negative, animate thing bacteria *Francisella tularensis*. *F. tularensis* could be a class A microorganism, incorporates a terribly low infectious dose, and might cause a "plague-like" malady [36]. Preferentially replicating within the cytoplasm of host macrophages and monocytes, the bacterium can even be found in hepatocytes and extra-cellular within the blood of infected mice [37]. *F. tularensis* infection is characterized by depletion of scavenger cell populations owing to pro-apoptopic kind I antiviral drug (IFN) communication. Typically, the host cell recognition of cytosolic bacterium that on the loose bodily process triggers innate kind I IFN communication, ultimately leading to the activation of caspase-1 and also the inflamesome with the discharge of IL-1B and IL-18 [38,39]. Whereas host macrophages answer infection by activating cleavage of the amino acid enzyme, caspase-1, and concomitant activation of the multi-protein inflamesome advanced, the animate thing bacterium free the host innate reaction by promoting necrobiosis of macrophages through the capsase-3 dependent pathway.

Apoptosis induced by *F. tularensis* infection has been noted to occur at a later stage of infection as compared to other gram-negative bacteria [40]. This delay in apoptosis allows *F. tularensis* to replicate intracellular. Both caspase-1 and caspase-3 pathways have been documented to be triggered during *F. tularensis* infection [41,42]. Interestingly, the caspase pathways are triggered early during infection, but there is also a simultaneous activation of NF- κB (potent regulator of anti-apoptotic genes) which correlates with the delay of apoptosis [42]. We have observed lymphocytolysis in the spleen of cynomolgus macaques infected with *F. tularensis*. Diffuse and strong TUNEL staining was observed in areas of necrosis and non-specific (background) caspase-3 immunostaining within this area, which is consistent with the staining artifact. It appears that necrosis may play a stronger role in terminally *F. tularensis* is infected NHPs compared to *B. anthracis* NHPs, where histological evidence of apoptosis is very strong. Therefore, future studies should further define the mechanism of apoptosis in these animal models.

Discussions

Federally prioritized bio threat agents represent a major degree of variety in their biology and pathological process, presenting distinctive challenges to the scientific community planning to develop effective medicine. Understanding the variations within the pathological process between these agents is very important, however the proof that cell death is a vital unhealthful event shared amongst these pathogens provides a singular chance to develop a broad-spectrum therapeutic. Whereas the severity and pathway usually varies for the various pathogens, a vast loss of lymphocytes and different cells through cell death causes a high-degree of immune impairment. The conclusion is that lymphocytolysis could be a vital contributor to the pathological process of those pathogens, any drug that would forestall cell death of lymphocytes would possible ameliorate the malady course of those severe infections by providing the crucial immune cell populations necessary to traumatize infected target cells. Overcoming this immune impairment could considerably decrease mortality and morbidity when infection with one in all these pathogens. Experimental inhibition of cell death has centered on either modification of the signal process system to necrobiosis pathways or on inhibition of proteolytic enzyme activity to dam their execution. Murine sepsis models have been used in proof-of-concept studies with anti-apoptotic interventions that have been shown to improve survival [3]. This provides avenues for further research with anti-apoptotic therapies to potentially treat severe infections. However, the potential limitations of anti-apoptotic therapy should be taken into consideration given what is known regarding the pathogenesis of the particular disease [3].

References

1. Humlova Z, Vokurka M, Esteban M, Melkova Z (2002) Vaccinia virus induces apoptosis of infected macrophages. J Gen Virol 83: 2821-2832.
2. Franco C, Sell TK (2011) Federal agency biodefense funding, FY2011-FY2012. Biosecur Bioterror 9: 117-137.
3. Parrino J, Hotchkiss RS, Bray M (2007) Prevention of immune cell apoptosis as potential therapeutic strategy for severe infections. Emerg Infect Dis 13: 191-198.
4. Chapman JL, Nichols DK, Martinez MJ, Raymond JW (2010) Animal models of orthopoxvirus infection. Vet Pathol 47: 852-870.
5. Wasilenko ST, Banadyga L, Bond D, Barry M (2005) The vaccinia virus F1L protein interacts with the proapoptotic protein Bak and inhibits Bak activation. J Virol 79: 14031-14043.
6. Sanchez A, Geisbert, T, Feldmann H (2007) Filoviridae: Marburg and Ebola viruses. In: Fields Virology, Knipe DM, Howley PM(Ed.), 5thedn, Williams and Wilkins, Philadelphia, Lippincott.1409-1448.
7. Jahrling PB, Hensley LE, Martinez MJ, Leduc JW, Rubins KH, et al. (2004) Exploring the potential of variola virus infection of cynomolgus macaques as a model for human smallpox. ProcNatlAcadSci101: 15196-15200.
8. Warren TK, Warfield KL, Wells J, Enterlein S, Smith M, et al. (2010) Antiviral activity of a small-molecule inhibitor of filovirus infection. Antimicrob Agents Chemother 54: 2152- 2159.
9. Bray M, Davis K, Geisbert T, Schmaljohn C, Huggins J (1999) A mouse model for evaluation of prophylaxis and therapy of Ebola hemorrhagic fever. J Infect Dis 179: S248- 258.
10. Bradfute SB, Braun DR, Shamblin JD, Geisbert JB, Paragas J, et al. (2007) Lymphocyte death in a mouse model of Ebola virus infection. J Infect Dis 196: S296-304.
11. Gibb TR, Bray M, Geisbert TW, Steele KE, Kell WM, et al. (2001) Pathogenesis

of experimental Ebola Zaire virus infection in BALB/c mice. J Comp Pathol 125: 233-242.

12. Geisbert TW, Hensley LE, Gibb TR, Steele KE, Jaax NK, et al. (2000) Apoptosis induced in vitro and in vivo during infection by Ebola and Marburg viruses. Lab Invest 80: 171-186.
13. Geisbert TW, Hensley LE, Larsen T, Young HA, Reed DS, et al. (2003) Pathogenesis of Ebola hemorrhagic fever in cynomolgus macaques: evidence that dendritic cells are early and sustained targets of infection. Am J Pathol 163: 2347-2370.
14. Baize S, Leroy EM, Georges-Courbot MC, Capron M, Lansoud-Soukate J, et al. (1999) Defective humoral responses and extensive intravascular apoptosis are associated with fatal outcome in Ebola virus-infected patients. Nat Med 5: 423-426.
15. Olejnik J, Ryabchikova E, Corley RB, Muhlberger E (2011) Intracellular events and cell fate in Filovirus infection. Viruses 3: 1501-1531.
16. Reed DS, Hensley LE, Geisbert JB, Jahrling PB, Geisbert TW (2004) Depletion of peripheral blood T lymphocytes and NK cells during the course of Ebola hemorrhagic Fever in cynomolgus macaques. Viral Immunol 17: 390-400.
17. Sanchez A, Lukwiya M, Bausch D, Mahanty S, Sanchez AJ, et al. (2004) Analysis of human peripheral blood samples from fatal and nonfatal cases of Ebola (Sudan) hemorrhagic fever: cellular responses, virus load, and nitric oxide levels. J Virol 78: 10370-10377.
18. Pozner RG, Collado S, de Giusti CJ, Ure AE, Biedma ME, et al. (2008) Astrocyte response to Junin virus infection. NeurosciLett 445: 31-35.
19. McCormick JB, King IJ, Webb PA, Johnson KM, O'Sullivan R, et al. (1987) A case-control study of the clinical diagnosis and course of Lassa fever. J Infect Dis 155: 445-455.
20. Cashman KA, Smith MA, Twenhafel NA, Larson RA, Jones KF, et al. (2011) Evaluation of Lassa antiviral compound ST-193 in a guinea pig model. Antiviral Res 90: 70-79.
21. Gravell M, London WT, Leon ME, Palmer AE, Hamilton RS (1986) Differences among isolates of simian hemorrhagic fever (SHF) virus. ProcSocExpBiol Med 181: 112-119.
22. Xiao SY, Zhang H, Yang Y, Tesh RB (2001) Pirital virus (Arenaviridae) infection in the syrian golden hamster, *Mesocricetusauratus*: a new animal model for arenaviral hemorrhagic fever. Am J Trop Med Hyg 64: 111-118.
23. Rodas JD, Cairo C, Djavani M, Zapata JC, Ruckwardt T, et al. (2009) Circulating natural killer and gamma delta T cells decrease soon after infection of rhesus macaques with lymphocytic choriomeningitis virus. MemInstOswaldo Cruz 104: 583-591.
24. Carrion R, Jr., Brasky K, Mansfield K, Johnson C, Gonzales M, et al. (2007) Lassa virus infection in experimentally infected marmosets: liver pathology and immunophenotypic alterations in target tissues. J Virol 81: 6482-6490.
25. Walker DH, McCormick JB, Johnson KM, Webb PA, Komba-Kono G, et al. (1982) Pathologic and virologic study of fatal Lassa fever in man. Am J Pathol 107: 349-356.
26. Cote CK, Chabot DJ, Scorpio A, Blank TE, Day WA, et al. (2006) *Bacillus anthracis*: agent of bioterror and disease. In: Anderson B, Friedman H, Bendinelli M, editors. Microorganisms and Bioterroris. New York: Springer. pp. 83-111.
27. Twenhafel NA (2010) Pathology of inhalational anthrax animal models. Vet Pathol 47: 819- 830.
28. Bush LM, Perez MT (2011) The anthrax attacks 10 years later. Ann Intern Med 156: 41-44.
29. Young JA, Collier RJ (2007) Anthrax toxin: receptor binding, internalization, pore formation, and translocation. Annu Rev Biochem 76: 243-265.
30. Park JM, Greten FR, Li ZW, Ka 370 rin M (2002) Macrophage apoptosis by anthrax lethal factor through p38 MAP kinase inhibition. Science 297: 2048-2051.
31. Agrawal A, Pulendran B (2004) Anthrax lethal toxin: a weapon of multisystem destruction. Cell Mol Life Sci 61: 2859-2865.
32. Banks DJ, Barnajian M, Maldonado-Arocho FJ, Sanchez AM, Bradley KA (2005) Anthrax toxin receptor 2 mediates *Bacillus anthracis* killing of macrophages following spore challenge. Cell Microbiol 7: 1173-1185.
33. Cote CK, DiMezzo TL, Banks DJ, France B, Bradley KA, et al. (2008) Early interactions between fully virulent *Bacillus anthracis* and macrophages that influence the balance between spore clearance and development of a lethal infection. Microbes Infect 10: 613- 380 619.
34. Inglesby TV, Dennis DT, Henderson DA, Bartlett JG, Ascher MS, et al. (2000) Plague as a biological weapon: medical and public health management. Working Group on Civilian Biodefense. Jama 283: 2281-2290.
35. Banks DJ, Ward SC, Bradley KA (2006) New insights into the functions of anthrax toxin. Expert Rev Mol Med 8: 1-18.
36. Pechous RD, McCarthy TR, Zahrt TC (2009) Working toward the future: insights into *Francisella tularensis*pathogenesis and vaccine development. MicrobiolMolBiol Rev 73: 684-711.
37. Henry T, Brotcke A, Weiss DS, Thompson LJ, Monack DM (2007) Type I interferon signaling is required for activation of 390 the inflammasome during *Francisella* infection. J Exp Med 204: 987-994.
38. Weiss DS, Henry T, Monack DM (2007) *Francisella tularensis*: activation of the inflammasome. Ann N Y AcadSci 1105: 219-237.
39. Wickstrum JR, Bokhari SM, Fischer JL, Pinson DM, Yeh HW, et al. (2009) *Francisella tularensis*induces extensive caspase-3 activation and apoptotic cell death in the tissues ofinfected mice. Infect Immun 77: 4827-4836.
40. Lai XH, Golovliov I, Sjostedt A (2001) *Francisella tularensis* induces cytopathogenicity and apoptosis in murine macrophages via a mechanism that requires intracellular bacterial multiplication. Infect Immun 69: 4691-4694.
41. Lai XH, Sjostedt A (2003) Delineation of the molecular mechanisms of *Francisella tularensis*-induced apoptosis in murine macrophages. Infect Immun 71: 4642-4646.
42. Santic M, Pavokovic G, Jones S, Asare R, Kwaik YA (2010) Regulation of apoptosis and anti-apoptosis signalling by *Francisella tularensis*. Microbes Infect 12: 126-134.