Role of proapoptotic BAX in propagation of Chlamydia muridarum (the mouse pneumonitis strain of Chlamydia trachomatis) and the host inflammatory response

Jean-Luc Perfettini  
*Université Paris*

David M. Ojcius  
*Université Paris, dojcius@pacific.edu*

Charles W. Andrews Jr.  
*Sacred Heart Medical Center*

Stanley J. Korsmeyer  
*Université Paris*

Roger G. Rank  
*University of Arkansas for Medical Sciences*

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Authors
Jean-Luc Perfettini, David M. Ojcius, Charles W. Andrews Jr., Stanley J. Korsmeyer, Roger G. Rank, and Toni Darville

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Role of Proapoptotic BAX in Propagation of Chlamydia muridarum (the Mouse Pneumonitis Strain of Chlamydia trachomatis) and the Host Inflammatory Response*

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Jean-Luc Perfettini§, David M. Ojcius§§, Charles W. Andrews, Jr.**, Stanley J. Korsmeyer‡‡, Roger G. Rank§§, and Toni Darville§§§

From the §Université Paris 7, Institut Pasteur, Unité de Biologie Moléculaire du Gene, INSERM U277, Paris, France, **Sacred Heart Medical Center, Department of Laboratory Medicine, Spokane, Washington 99220, ‡‡Howard Hughes Medical Institute, Departments of Pathology and Medicine, Harvard Medical School, Dana-Farber Cancer Institute, Boston, Massachusetts 02115, and the §§Department of Microbiology and Immunology, University of Arkansas for Medical Sciences, Little Rock, Arkansas 72205

The BCL-2 family member BAX plays a critical role in regulating apoptosis. Surprisingly, bax-deficient mice display limited phenotypic abnormalities. Here we investigate the effect of BAX on infection by the sexually transmitted pathogen, Chlamydia muridarum (the mouse pneumonitis strain of Chlamydia trachomatis). Bax−/− cells are relatively resistant to Chlamydia-induced apoptosis, and fewer bacteria are recovered after two infection cycles from Bax−/− cells than from wild-type cells. These results suggest that BAX-dependent apoptosis may be used to initiate a new round of infection, most likely by releasing Chlamydia-containing apoptotic bodies from infected cells that could be internalized by neighboring uninfected cells. Nonetheless, infected Bax−/− cells die through necrosis, which is normally associated with inflammation, more often than infected wild-type cells. This study was confirmed in mice infected intravaginally with C. muridarum; since the infection disappears more quickly from Bax−/− mice than from wild-type mice, secretion of proinflammatory cytokines is increased in Bax−/− mice, and large granulomas are present in the genital tract of Bax−/− mice. Taken together, these data suggest that chlamydial-induced apoptosis via BAX contributes to bacterial propagation and decreases inflammation. Bax deficiency results in lower infection and an increased inflammatory cytokine response associated with more severe pathology.

Chlamydia species provoke serious infections of humans and animals worldwide, despite extensive work to better characterize the biology of the infection and develop effective vaccines (1–3). It is estimated that over 600 million persons are infected with Chlamydia trachomatis, whose strains include the most common sexually transmitted bacterial pathogen (4) as well as causative agents of conjunctivitis and trachoma. There are an estimated 4 million new cases annually of genital C. trachomatis infections of the male and female within the United States (5). In women, the most common consequence of chlamydial genital infection is salpingitis, which can lead to tubal obstruction and infertility (2).

An important element in the design of a vaccine for the prevention or control of chlamydial infections is a complete understanding of the immune response to infection. Little is known about the pathogenesis of human chlamydial infections, and most of our knowledge of acute infection has been obtained from animal models such as the mouse model with Chlamydia muridarum (the mouse pneumonitis (MoPn) strain of C. trachomatis) (6, 7) and the guinea pig model with the Chlamydia psittaci guinea pig inclusion conjunctivitis strain (8). In controlled studies in guinea pigs and mice (9–11), bacteria are initially detected in the cervical epithelium, but the pathology ascends in most animals to the endometrium and the oviducts within 7–9 days after intravaginal inoculation. Most of the damage due to Chlamydia is not due to the infection itself but to the inflammation and fibrosis that follow the infection (2).

Polymorphonuclear leukocytes are typically observed in the cervix as early as 2 days after infection, and acute inflammation in the uterine horns and oviducts follows within 5–7 days (2). A number of inflammatory mediators are present during infection, including interleukin-1 (IL-1) and tumor necrosis factor (TNF-α), which have been detected in the Fallopian tubes from humans infected with C. trachomatis (12) and in secretions from Chlamydia-infected mice and guinea pigs (13–15). TNF-α and other inflammatory cytokines may aid in eradicating Chlamydia infection but also may promote long term tissue damage (14).

Contrasting with the epidemiological and pathological diversity of Chlamydia infections is the relative uniformity of the chlamydial infectious process. All Chlamydia sp. are thought to enter into, survive, and multiply within mucosal epithelial cells by conserved mechanisms involving a unique obligate intracellular developmental cycle, consisting of two phases (16). The extracellular form of Chlamydia, the elementary body (EB), is infectious and is thought to be metabolically inert. The EB are internalized into host epithelial cells into small vacuoles resembling endosomes, most of which avoid fusion with host cell

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¶ These two authors share senior authorship.
To whom correspondence should be addressed: Institut Jacques Monod, Universite Paris 7, 2 place Jussieu, Tour 43, 75251 Paris cedex 05, France. Fax: 33-1-44278265; E-mail: ojcius@noos.fr.

1 The abbreviations used are: MoPn, C. trachomatis mouse pneumonitis strain; EB, elementary body; IL, interleukin; TNF, tumor necrosis factor; PS, phosphatidylserine; PI, propidium iodide; PMN, polymorphonuclear neutrophils; IFN, interferon.

9496 This paper is available on line at http://www.jbc.org
lysomes. The EB differentiate within the entry vacuole into metabolically active reticulate bodies, which are presumably noninfectious (17). The reticulate bodies proliferate within the same membrane-bound vacuole and, after several divisions, differentiate back into EB. After 2–3 days, the EB are released from the infected cell through unknown mechanisms and begin a new cycle of infection (16, 17).

This biphasic developmental cycle allows for multiple sites of communication between the chlamydial pathogen and the host cell, many of which probably play a significant role in the pathogen-host cell relationship and thus strongly impact the outcome of the infection. An example of such a communication are the chlamydial signals that block and then later induce apoptosis of the host cell. Like mycobacteria, Crypto- sporidium parvum, and the herpes virus (18–21), Chlamydia strains protect infected cells during early stages of the infection against apoptosis due to external stimuli (22–25) and induce apoptosis of the host cell during later stages of the infection cycle (26–29). The resistance to cell death may account for the observation that Fas- and perforin-dependent killer lymphocytes are not able to clear the infection in mice (30). Conversely, we had proposed that apoptosis due to the infection may be used by the chlamydiae to exit from infected cells and propagate within the host (29).

In mammalian cells, many of the morphological and biochemical features of apoptosis are due to activation of caspases, which can be initiated through engagement of cell surface receptors such as Fas (31) or following release from mitochondria of cytochrome c, which associates with the apoptosis regulator Apaf-1 and thereby activates caspase-9, which in turn associates with Bid and Bid' murine embryonic fibroblasts were described (37). All other cells and materials were described (28, 48).

Analysis of Cell Death—Murine embryonic fibroblasts were infected at a multiplicity of infection of 0.5. Cell death was measured by cytotoxicity assay using a neutral red dye that is taken up by cells and stain viable cells red and nonviable cells blue. The neutral red dye was removed by washing with PBS buffer. Cells were fixed with methanol, stained with crystal violet, and quantified with an optical microscope. The experiment was repeated on three separate occasions.

Animal Infections—Female Bax+/+ and Bax−/− mice on a C57BL/6 background (Jackson Laboratories, Bar Harbor, MA) were infected intravaginally with 10^6 inclusion-forming units of C. muridarum. The course of infection was monitored by periodic cervico-vaginal swabbing of individual animals (50). Chlamydiae were isolated from swabs in tissue culture according to standard methods, and inclusions were visualized and enumerated by immunofluorescence (51). Results are expressed as mean and S.E. of inclusion-forming units per ml. Experiments were repeated once, and there were five animals per experimental group. Groups of mice were sacrificed at 7 and 24 days after primary infection or followed through day 70 and administered a challenge infection or followed through day 70 and administered a challenge infection with 10^6 inclusion-forming units of MoPn on day 90, 7 days post-depo-provera treatment. Histopathology and cytokine secretion measurements were performed as described (50). Staining of cell surface antigens and qualitative evaluation of cell populations were performed as described by Morrison and Morrison (52). Vaginal secretions were assayed individually for cytokine or chemokine activity by enzyme-linked immunosorbent assay using commercial kits (R&D Systems, Minneapolis, MN). Antibody responses were measured in sera from mice and assayed by enzyme-linked immunosorbent assay as described (14). All mice were given food ad libitum and maintained in environmentally controlled rooms with a 12/12-h light/dark cycle. All animal studies were approved by the University of Arkansas Medical Sciences Institutional Animal Care and Use Committee.

RESULTS

Effect of BAX on Host Cell Death in Vitro—We have previously shown that BAX is activated in cells infected with Chlamydia (28). The effect of BAX activation on Chlamydia-
Effect of BAX Deficiency on Chlamydia Infection

Effect of BAX Deficiency on Chlamydia Infection—In order to distinguish between the possibility that apoptosis may be used by the bacteria to escape from the infected host cell, rather than by the host cell to eliminate bacteria, Bax−/− and Bax+/− cells were infected for 3 days, and the bacteria were harvested from supernatant and infected cells. The recovered bacteria were then used to reinfect wild-type cells, and the efficiency of infection was evaluated by immunofluorescence. A larger number of infectious chlamydiae were recovered from the Bax+/+ than the Bax−/− cells (Fig. 1C), suggesting that the bacteria may use apoptosis to exit from cells at the end of the first infection cycle before beginning a new round of infection. To rule out the possibility that Bax deficiency may be inhibiting growth of intracellular chlamydiae, the number of infectious vacuoles was also measured after a 24-h infection, before any apoptosis is observed; the infection at 24 h was the same in either Bax+/+ or Bax−/− cells (not shown). Since fibroblasts and epithelial cells express a PS receptor (56) that could be used to phagocytose Chlamydia-containing apoptotic bodies, these results suggest that Chlamydia may use apoptosis to release infectious bacteria from infected host cells in order to initiate a new infection cycle.

Effect of BAX on Bacterial Propagation during Genital Tract Infection—To confirm whether apoptosis has an effect on the yield of infectious bacteria in vivo, the infection was repeated with Bax+/+ and Bax−/− mice. The mouse model of Ch. muridarum infection of the female genital tract mimics human infection (2, 9, 10) and is a useful model for Chlamydia infection and adaptive immunity to infection. Bax-deficient mice are also convenient for studies on Chlamydia infection, since the mice are healthy, the levels of the antiapoptotic molecules BCL2 and BCL-Xl are unaffected, and the distribution of different lymphocyte populations (CD4+CD8−, CD4+CD8+, CD4−, and CD8−) are unaltered, compared with Bax+/+ mice (57). The infection was less efficient and disappeared more quickly in the Bax−/− mice than in control Bax+/+ mice (Fig. 2), consistent with a role for BAX-dependent apoptosis in the propagation of chlamydiae in vivo.

Effect of BAX on Cytokine Secretion during Genital Tract Infection—Prior studies in our laboratory have shown that murine chlamydial genital tract infection induces strong production of the proinflammatory cytokine, TNF-α, and of the murine CXC chemokine, macrophage inflammatory protein 2 (14, 50). These responses routinely peak during the first week of infection and decline toward base line during the second week. Enzyme-linked immunosorbent assay measurement of cytokines in genital tract secretions revealed similar kinetics in the Bax+/+ and Bax−/− mice in this study (Fig. 3). However, the proinflammatory mediators were significantly increased during the first week of infection in the Bax−/− mice compared with the Bax+/+ mice. Further, we detected extremely high levels of IFN-γ, a protein with marked antichlamydial effects, in the Bax−/− mice compared with Bax+/+ mice during the first

 induced apoptosis was therefore determined by infecting normal (Bax+/+) and Bax-deficient cells. The infection led to a high level of apoptosis in Bax+/+ cells, which was observed after 1 day of infection (Fig. 1A). At the same multiplicity of infection, the Bax deficiency resulted in a nearly 2-fold inhibition of apoptosis during infection (Fig. 1A), suggesting that this pathway of apoptosis requires, at least partially, BAX activation.

Engagement of surface death receptors such as Fas or TNFR1 results in cleavage of the BCL-2 family member BID, which triggers the oligomerization of proapoptotic family members BAK and BAX, leading to cell death (47). To determine whether BID cleavage may be required for BAX activation in infected cells, Bax+/+ and Bax−/− cells were infected with Ch. muridarum for 2 days, and apoptosis was measured. No difference was observed in sensitivity to apoptosis of wild-type and Bax-deficient cells (Fig. 1A), suggesting that BAX activation is initiated within the interior of the infected cell.

Cells that are prevented from dying through apoptosis still manage to die, but they often succumb later, dying through necrosis (53–55). To determine quantitatively whether any infected cells may be necrotic, cells were infected for 2 days, and necrosis was measured by double-labeling the cells with PI and annexin V, which binds to phosphatidylserine (PS) that becomes exposed on the surface of dying cells. Cells labeled only with annexin V are considered to be apoptotic, whereas cells labeled only with PI, which have thus lost their plasma membrane integrity, are necrotic; cells labeled with both PI and annexin V are either necrotic or late apoptotic (48). Evaluation by cytofluorimetry showed that the Bax+/+ cells were dying through necrosis more often than Bax−/− cells after a 2-day infection. Whereas 30% of the cells were apoptotic and 10% were necrotic in the Bax+/+ population, 7% were apoptotic and 34% were necrotic in the Bax−/− population (Fig. 1B).

Fig. 1. Effect of BAX on apoptosis and bacterial production in vitro. A, apoptosis of wild-type, Bax−/−, and Bid−/− cells. Cells were infected with Chlamydia muridarum for 2 days, and apoptosis of PI-labeled detergent-permeabilized cells was measured by cytofluorimetry (see "Experimental Procedures"). Black bar, spontaneous apoptosis of uninfected cells; white bar, apoptosis of infected cells. B, necrosis of infected cells. Bax+/+ and Bax−/− cells were infected for 48 h. Necrosis and apoptosis were quantified by double-labeling unpermeabilized cells incubated with PI and annexin V (see "Experimental Procedures"). The numbers in each quadrant refer to the percentage of cells in each quadrant. C, chlamydial production after at least two infection cycles. Subconfluent Bax−/− and Bax+/+ cells were infected at a multiplicity of infection of 0.1, and a 10-fold excess of uninfected Bax−/− cells was added after 24 h of infection. After an additional 2 days of infection, the yield of chlamydiae from adherent cells and cells in suspension was measured by titrating on uninfected HeLa cells (see "Experimental Procedures"). IFU, inclusion-forming units.

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week of infection (Fig. 3). The detection of higher levels of inflammatory mediators in the Bax−/− mice compared with the Bax+/+ mice is made more significant by the fact that the infection was much less efficient in the Bax−/− mice. These data are consistent with increased cell death by necrosis during chlamydial infection in the absence of BAX.

**Pathology Associated with Bax Deficiency of Infected Mice**—Histopathological and immunohistochemical examination of genital tract tissues from mice sacrificed on day 7 of primary infection revealed that the early inflammatory response was of similar quality and quantity in Bax+/+ and Bax−/− mice. Moderate to severe inflammation was detected in the endocervix and uterine horns with a predominance of polymorphonuclear neutrophils (PMNs) but high numbers of lymphocytes also being seen. By immunohistochemical staining, the median inflammatory score for PMNs was 4 for Bax−/− and 3 for Bax+/+ on day 7 (p = 0.375), and for lymphocytes it was 2.0 for Bax−/− and for Bax+/+ (p = 0.5) (analysis of variance on ranks). Most of the lymphocytes were CD4+ in both groups, with comparatively low numbers of CD8+ cells being found (median score for CD4+ T cells = 2.0 for both groups on day 7; CD8+ T cells = 1). Mild to moderate inflammation was detected in the oviducts in both Bax+/+ and Bax−/− mice, again with a predominance of PMNs being found. Tissues from mice sacrificed on day 24, at a time when infection had mostly resolved, revealed equal numbers of acute (PMNs) and chronic inflammatory cells (lymphocytes) in both Bax−/− and Bax+/+ mice. However, in 4 of 5 Bax−/− mice, large granulomatous nodules with marked central necrosis were found scattered throughout 9 of 10 uterine horns (Fig. 4). These nodules were seen in only 1 of 10 horns from Bax+/+ mice; p = 0.001, Fisher exact test). Thus, although infection is less efficient in Bax−/− mice, it results in greater release of inflammatory mediators and increased chronic tissue pathology.

**Acquired Immunity in Infected Wild-type and Bax-deficient Mice**—The acquired immune response, as determined by antibody titers in serum and by resistance to reinfection, was similar in Bax−/− and Bax+/+ mice. Both groups demonstrated high titers of IgG2a and low titers of IgG1 (Fig. 5), demonstrating that a Th1 response was stimulated in both cases. Both Bax+/+ and Bax−/− were also completely resistant to reinfection when challenged 70 days after primary vaginal inoculation (not shown). Thus, despite the increased release of inflammatory mediators and enhanced pathology after primary infection in Bax−/− mice, the absence of Bax did not affect the quality or magnitude of the acquired immune response.

**Fig. 2.** Chlamydial infection is decreased in Bax−/− mice. A, intensity and duration of primary lower genital tract infection. Female Bax+/+ (open circles) and Bax−/− (closed circles) mice were infected with C. muridarum, and the course of infection was monitored by cervico-vaginal swabbing, p < 0.001 by two-way analysis of variance for Bax+/+ versus Bax−/−. B, elimination of chlamydiae from wild-type and Bax−/− mice. Results are expressed as the percentage of animals positive for infection over time. Bax−/− mice (closed circles) resolved the infection more rapidly than Bax+/+ mice (open circles) with all of the Bax−/− mice being negative for infection by day 16. In contrast, 4 of 10 Bax+/+ mice were still positive for infection on day 20. IFU, inclusion-forming units.

**Fig. 3.** Secretion of inflammatory proteins is increased in Bax−/− mice. TNF-α (A) macrophage-inflammatory protein 2 (MIP-2) (B), and IFN-γ (C) levels were significantly increased in the Bax−/− (closed circles) mice compared with Bax+/+ (open circles) during the first week of infection. Genital tract secretions were eluted from vaginal sponges collected from individual animals before and after infection. Results are expressed as mean and S.E. of cytokine measurements from five animals.
yield of chlamydiae after two infection cycles decreases in Bax-deficient cells compared with wild-type cells. BAX could therefore contribute to exit of chlamydiae from infected cells before initiation of a new infection cycle. The fact that C. muridarum infection of the genital tract disappears more rapidly in Bax−/− mice than in Bax+/+ mice also reinforces the interpretation that BAX-dependent apoptosis could facilitate chlamydial propagation. Finally, Bid−/− cells are as sensitive to Chlamydia-induced apoptosis as Bax−/− cells. Ligation of the Fas or TNFR1 death receptors on the cell surface leads to cleavage of BID, which activates BAX (47). The lack of involvement of BID during Chlamydia infection suggests that BAX activation is initiated within the host cell. Activation could be related to infection-related metabolic stress (68), or it could be triggered by signals released from the chlamydial vacuole via type 3 secretion mechanisms (59–61). Activation of BAX is clearly advantageous for Chlamydia, and it is tempting to speculate that other intracellular microbes may use BAX-mediated apoptosis to enhance their propagation. These results thus reveal a novel function for a host cell proapoptotic protein, which until now has been known to promote apoptosis through induction of mitochondrial dysfunction and whose singular deficiency in mice results in only minor changes to the immune system (57).

Apoptotic cells and apoptotic bodies released from dying cells in vivo are cleared by professional scavengers such as macrophages, which express surface receptors that recognize apoptotic bodies and cells (62). Thus, PS exposed on the surface of dying cells interacts with PS receptors on human or murine macrophages, leading to phagocytosis of the corpses. However, the PS receptor is also expressed on the surface of fibroblasts and epithelial cell lines, including HeLa (derived from a carcinoma of the cervix) (56), and ubiquitously expressed molecules such as lectins or integrins could also participate in internalization of apoptotic bodies (63). Since an antibody against the PS receptor can block phagocytosis of apoptotic cells by fibroblasts and mammary epithelial cells (56), we propose that the PS receptor and/or similar receptors may be used to internalize Chlamydia-containing apoptotic cells and bodies by neighboring epithelial cells in the genital tract, thus beginning a new round of infection.

Despite the faster clearance of bacteria in Bax−/− mice, the secretion of inflammatory cytokines was higher in Bax−/− than in wild-type mice. The secretion of TNF-α, IFN-γ, and the murine equivalent of IL-8, macrophage inflammatory protein 2, have been previously reported during C. muridarum infection, but until now the extent of their secretion has always correlated with the intensity of infection (8, 13, 64). Whereas several interpretations of these data could be envisioned, we propose that apoptosis of infected cells in Bax−/− mice is postponed, causing the cells to die of necrosis more often than in Bax+/+ mice. This explanation is consistent with the observation that more necrotic cells are observed when Bax-deficient cells are infected in vitro than when wild-type cells are infected. Phagocytosis of apoptotic cells by macrophages leads to secretion of inflammatory cytokines such as IL-10 and transforming growth factor-β, but necrotic cells stimulate secretion of proinflammatory cytokines, including TNF-α, IL-1β, and IL-8 (65–67). Although these possibilities are not mutually exclusive, the resulting increase in IFN-γ observed in Bax−/− mice may also contribute to their faster resolution of infection. IFN-γ is a known inducer of aberrant forms of Chlamydia in vitro; the cytokine adversely affects normal growth and division of reticulate bodies and interrupts their redifferentiation into infectious EB (68). IFN-γ induction of aberrant, noninfectious forms of Chlamydia may thus contribute to reduced infection in the Bax−/− mice.

Most of the pathological damage observed during Chlamydia...
infection is thought to be due to the inflammatory response rather than to the microorganism itself (2, 8). The higher incidence of granulomatous nodules in the Bax–/– mice reinforces the notion that secretion of inflammatory cytokines by infected epithelial cells and neighboring macrophages may be responsible for the chronic tissue damage associated with Chlamydia infection. Although the hallmark of both ocular (trachoma) and urogenital chlamydial infections is the development of lymphoid follicles (69–72), granulomas have occasionally been reported in human (73), non-human primate (74, murine (75), and veterinary (76). Loss of function mutations in Bax have been reported in humans and may be associated with increased incidence and progression of cancer (77–80). Our data suggest that mutations in Bax might lead to an increase in the severity of chlamydial genital tract disease. This is the first report of the effect of Bax mutation in a infectious disease model.

Disordered cell death has been previously shown to have an impact on the immune system and human disease. Thus, reduced cell death and defective clearance of apoptotic material lead to uncontrolled immune responses, and macrophages secrete proinflammatory mediators following ingestion of cells undergoing secondary necrosis but not after ingestion of intact apoptotic cells (62, 81, 82). We find that defects within the core apoptotic program also lead to immunopathology. Whereas these diseases may share the common feature that more cells undergo necrosis when apoptosis is blocked, it is also conceivable that their pathogenesis may be multifactorial. However, they all demonstrate clearly that blocking the signaling pathways associated with apoptosis has consequences for antigens and infectious agents that are normally packaged into apoptotic bodies, with striking effects on host pathology.

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