Recruitment of BAD by the Chlamydia trachomatis vacuole correlates with host-cell survival.

Abstract:
Chlamydiae replicate intracellularly in a vacuole called an inclusion. Chlamydial-infected host cells are protected from mitochondrion-dependent apoptosis, partly due to degradation of BH3-only proteins. The host-cell adapter protein 14-3-3beta can interact with host-cell apoptotic signaling pathways in a phosphorylation-dependent manner. In Chlamydia trachomatis-infected cells, 14-3-3beta co-localizes to the inclusion via direct interaction with a C. trachomatis-encoded inclusion membrane protein. We therefore explored the possibility that the phosphatidylinositol-3 kinase (PI3K) pathway may contribute to resistance of infected cells to apoptosis. We found that inhibition of PI3K renders C. trachomatis-infected cells sensitive to staurosporine-induced apoptosis, which is accompanied by mitochondrial cytochrome c release. 14-3-3beta does not associate with the Chlamydia pneumoniae inclusion, and inhibition of PI3K does not affect protection against apoptosis of C. pneumoniae-infected cells. In C. trachomatis-infected cells, the PI3K pathway activates AKT/protein kinase B, which leads to maintenance of the pro-apoptotic protein BAD in a phosphorylated state. Phosphorylated BAD is sequestered via 14-3-3beta to the inclusion, but it is released when PI3K is inhibited. Depletion of AKT through short-interfering RNA reverses the resistance to apoptosis of C. trachomatis-infected cells. BAD
phosphorylation is not maintained and it is not recruited to the inclusion of Chlamydia muridarum, which protects poorly against apoptosis. Thus, sequestration of BAD away from mitochondria provides C. trachomatis with a mechanism to protect the host cell from apoptosis via the interaction of a C. trachomatis-encoded inclusion protein with a host-cell phosphoserine-binding protein.