The induction of apoptosis resistance as an important immune escape mechanism allowing Chlamydia to replicate inside the host cell

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Host cells infected with pathogenic *Chlamydia* are protected against many different apoptotic stimuli. The induction of apoptosis resistance is believed to be an important immune escape mechanism allowing *Chlamydia* to replicate inside the host cell. Apoptosis is primarily induced by two major pathways namely the 'extrinsic' or the death receptor-mediated or by the 'intrinsic' or the mitochondria-mediated pathways. Activation of the intrinsic pathway requires the permeabilization of the mitochondrial outer membrane (MOM) and the release of pro-apoptotic factors into the host cells cytosol. Cells infected with *Chlamydia* resist MOM permeabilization to several apoptotic stimuli [1–3]. Degradation of apoptosis regulators [4–6], their recruitment to the chlamydial inclusion [7] and the stabilization of inhibitor of apoptosis proteins complexes [8] have been suggested as mechanisms underlying apoptosis resistance in infected cells. We performed an RNA interference screen to identify host cell factors involved in the *C. trachomatis*-mediated inhibition of TNF-induced apoptosis. Apoptosis was determined by automated microscopy during the screen and by different biochemical and immunological analysis for detailed analysis. Primary hits were validated using chemical inhibitors. Of the 32 factors whose ablation sensitized infected cells to apoptosis, at least 6 targets affected the Ras/MAPK pathway and one of the prominent targets was the anti-apoptotic Bcl-2 family member Mcl-1. Infection with *C. trachomatis* activates the Raf/MEK/ERK pathway and the PI3K/AKT pathway and the inhibition of these two pathways by chemical inhibitors sensitized *C. trachomatis* infected cells to TNF- and also to granzyme B-mediated cell death. Infection leads to the Raf/MEK/ERK-mediated up-regulation and PI3K-dependent stabilization of Mcl-1. Consistently, interfering with Mcl-1 up-regulation sensitized infected cells for apoptosis induced via the TNF receptor, granzyme B, and other stress inducers. Our data suggest that Mcl-1 up-regulation is primarily required to maintain apoptosis resistance in *C. trachomatis* infected cells.

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