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Commentary

Chlamydia Anti-apoptosis – A By-product of Metabolic Reprogramming?

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The obligate intracellular pathogen *Chlamydia trachomatis* is the most frequent bacterial agent of sexually transmitted disease worldwide. Recent estimates of the World Health Organization suggested >100 million annual cases of *C. trachomatis* infections (Newman et al., 2015). While acute infections are asymptomatic in 50–70% of all cases, repeated and recurrent infections occur, increasing the risk for complications, such as pelvic inflammatory disease, ectopic pregnancy, and infertility (Schuchardt and Rupp, 2016).

Less well understood is whether *C. trachomatis* infection also represents a risk factor for the development of cervical cancer, because studies that explored this association reported contradictory findings (Zhu et al., 2016). Potential indirect pro-carcinogenic effects by *C. trachomatis* include its ability to promote the acquisition and persistence of human papilloma virus, the principal etiological agent in cervical cancer, and the establishment of a pro-inflammatory environment, which favors cellular damage and transformation (Zhu et al., 2016). In addition, *Chlamydia*-mediated reprogramming of infected cells, which includes modulation of cell signaling, metabolism, DNA integrity, genome stability, proliferation and survival, may directly sensitize cells to cellular transformation, while at the same time protecting them from death (Gagnaire et al., 2017). In this issue of *EBioMedicine*, Al-Zeer et al. describe a new mechanism by which *C. trachomatis* couples metabolic reprogramming of host cells via stabilization of the Myc oncogene and induction of hexokinase II (HK-II) expression with enhanced production of infectious *Chlamydia* particles and protection from apoptosis via mitochondrial effects of HK-II (Al-Zeer et al., 2017).

The fact that cells infected with *C. trachomatis* are protected from apoptosis has been known for decades (Fan et al., 1998). The apoptotic machinery in infected cells is blocked upstream of mitochondrial outer membrane permeabilization (Fan et al., 1998), preserving a major energy-generating system of the host cell. While the initial idea that this effect is mediated by degradation of pro-apoptotic BH3-only proteins was later disproved, other anti-apoptotic activities were described, including for instance the activation of pro-survival signaling pathways (Raf/MEK/ERK and PI3K/AKT) that mediate upregulation and stabilization of the anti-apoptotic protein Mcl-1 and degradation of p53 (Gonzalez et al., 2014; Rajalingam et al., 2008; Siegl et al., 2014). Down-regulation of p53 was also shown to protect mitochondrial architecture (Chowdhury et al., 2017) and to shift host cell metabolism towards aerobic glycolysis and the pentose phosphate pathway, which may benefit *Chlamydia* replication by providing anabolic substrates (Siegl et al., 2014). This suggests that apoptosis suppression by *Chlamydia* may constitute a by-product of the metabolic reprogramming of the host cell.

The current study by Al-Zeer et al. provides further evidence in favor of this idea (Al-Zeer et al., 2017). The authors first demonstrate that infection with *C. trachomatis* induces a major surge in Myc protein levels, presumably via Myc protein stabilization mediated by its PDPK1-PLK1-dependent phosphorylation. Moreover, in infected cells HK-II protein expression was upregulated in a Myc-dependent manner, and HK-II specifically enriched in mitochondrial fractions. Inspired by former reports that HK-II can inhibit apoptosis by binding to the outer surface of mitochondria through an interaction with the voltage-dependent anion channel (VDAC), the authors disrupted the hexokinase-mitochondria association and observed a strong resensitization of *Chlamydia*-infected cells to TNF-α induced apoptosis. Indeed, the level of resensitization appeared to be much higher than that observed in previous studies in which other branches of *Chlamydia* anti-apoptosis were disrupted. However, a direct comparison of the relative importance of different anti-apoptotic strategies during the course of the infection cycle still needs to be carried out.

The authors' observation that interference with hexokinase-mitochondria association disrupted the production of infectious bacterial progeny without inducing spontaneous apoptosis in *Chlamydia*-infected cells (Al-Zeer et al., 2017), is in line with the idea that the bacteria foremost depend on the metabolic, not the anti-

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apoptotic, effects of Myc signaling. In this context, it is noteworthy that, while inhibition of apoptosis can be primarily considered to be beneficial for the bacteria when viewed from the perspective of individual infected cells, the overall role of *Chlamydia*-mediated suppression of host cell death in pathogenesis is much less well understood and requires further investigation. The precise modality by which infected cells die in vivo (e.g. apoptosis vs. necrosis) could have substantial influence on bacterial spread, inflammatory and immune responses, and tissue damage. Studies on the significance of the anti-apoptotic trait could be facilitated by the recent introduction of techniques for genetic manipulation of *C. trachomatis*, which should enable the identification and genetic disruption of *Chlamydia* anti-apoptotic factors. However, it may be challenging, if not impossible, to identify death-suppressive molecules encoded by the *Chlamydia* genome that are not also involved in metabolic reprogramming of the host cell as well.

Whether the *Chlamydia*-mediated upregulation of the Myc oncogene or the inhibition of apoptosis can contribute to the establishment or longevity of infection-induced potentially pro-oncogenic cellular alterations, requires further investigation. Despite apoptosis inhibition, *Chlamydia*-infected cells are eventually lysed to release bacterial progeny. This naturally limits the pro-carcinogenic outcome of infection. However, in the complex setting of an in vivo infection some infected cells may survive, since antibiotics, immune responses, and unfavorable growth conditions can promote *Chlamydia* persistence, characterized by long-term but nonproductive intracellular survival, or clearance. Uninfected cells also potentially arise from infected cells during mitosis. In this context, it is noteworthy that upregulation of the Myc oncogene was not restricted to the infected cells contained in the infected cell population (Al-Zeer et al., 2017). It remains to be clarified whether this can be explained by paracrine effects, as suggested by the authors, or whether these cells had previously encountered intracellular *Chlamydia*. Future studies on the nature and longevity of cellular abnormalities in surviving and bystander cells could significantly enhance our understanding of the mechanisms by which *C. trachomatis* may contribute to carcinogenesis.

Taken together, the study by Al-Zeer et al. highlights the PDPK1-Myc signaling pathway and the metabolic reprogramming of host cells in general as potential targets for the development of new anti-chlamydial drugs. As already pointed out by the authors, the observation that cellular alterations in *Chlamydia*-infected cells resemble in some aspects those induced in cancer cells, suggests that certain drugs currently in use for anti-cancer therapy may be effective against *Chlamydia* as well.

Conflicts of Interest

The authors declare no conflicts of interest.

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