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 its ability to promote the acquisition and persistence of human fertility (Schuchardt and Rupp, 2016).

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 PDK1-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 C. trachomatis-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 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-
of C. trachomatis indicated by the recent introduction of techniques for genetic manipulation.

Aging is often refers to the signification of the anti-apoptotic trait could be facilitated by the recent introduction of techniques for genetic manipulation. However, it is noteworthy that, 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. 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 bystander cells may 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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