Trojan Horses: Microbes Subvert Mitochondria to Evade the Immune System

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ABSTRACT
Mitochondria are sentinels of the innate immune system, with critical roles in sensing and responding to pathogens. Yet, they are evolved from microbes and retain some features that may make them susceptible to microbial influence. A number of instances have shown that microbes can bypass these sentinels through toxins that alter mitochondrial function, creating a permissive environment. Such subversion of the host cell function, by recruitment of its microbe-like organelles, is likely to be a frequently seen motif amongst the many Trojan horse strategies used by intracellular pathogens infecting immune cells. Here we discuss the recent discovery, that Legionella pneumophila creates a permissive niche in human macrophages, by hijacking mitochondria, and rewiring the cellular metabolism. This is placed in context of the current understanding of this evolving area.

KEYWORDS: Mitochondria, Microbes, Immunity, Trojan horse, Legionella pneumophila

Recently, it has been shown that intracellular pathogens, such as the bacteria *Legionella pneumophila* (*L. pneumophila*), create a permissive niche in human macrophages by rewiring the cellular metabolism (Escoll et al., 2017). This is achieved by a bacterially encoded secretion system that injects mitochondria-interacting effector proteins, causing mitochondrial fragmentation and a shift from mitochondrial oxidative phosphorylation (OxPhos) to a state of aerobic glycolysis. This is similar to other examples, where pathogen encoded proteins target mitochondria to inhibit the host inflammatory responses (Jain et al., 2011; Stavru et al., 2011; Suzuki et al., 2014). It seems likely that this is an effective co-evolutionary strategy, by which microbes influence their distant relatives, the mitochondria, to gain advantage over host cells, for their survival.

Mitochondria are sentinels of the innate immune system, responding to metabolic as well as pattern recognition cues, such as electron steal or RIG-1 like receptors (RLR) signalling by viruses, respectively (Cloonan and Choi, 2013). Mitochondria are also, in turn, constantly monitored by cellular surveillance pathways that link mitochondrial signals to a conserved set of responses that constitute the evolutionarily conserved cell danger response (CDR) system (Cloonan and Choi, 2013). An evolutionary similarity with microbes, leading to cross-talk, and a central position in cellular metabolism, positions mitochondria as ideal sensors and effectors in the CDR system (Bajpai et al., 2017; Lartigue and Faustin, 2013). Mitochondrial proteins interact with a variety of pathogen associated molecular pattern (PAMP) effectors, thereby regulating the immune cascade (Cloonan and Choi, 2013). Mitochondrial health, characterized by elongated functional mitochondrial network and intact polarization, is essential for effective anti-viral response through the mitochondrial anti-viral signaling protein (MAVS) (Koshiba et al., 2011). Altered mitochondrial dynamics with mitochondrial fragmentation and inability to form peri-nuclear clusters has been shown to inhibit host inflammatory responses to diverse pathogens (Suzuki et al., 2014) (Jain et al., 2011). In extreme cases, as seen with *H. pylori*, bacterial toxins can hijack mitochondria to trigger host cell death (Jain et al., 2011). This can also be through subtle changes to mitochondrial dynamics, as seen in *Vibrio cholerae*, where the bacterial protein VopE interferes with the function of mitochondrial Rho GTPases Miro1 and Miro2 (Suzuki et al., 2014). This impairs mitochondrial motility and prevents stress associated reorganization of the mitochondrial network, ultimately inhibiting MAVS-mediated NF-κB signaling. Thus mitochondrial loss, depolarization or disruption of the mitochondrial network leads to a permissive environment for pathogens.

In this context, Escoll et al investigated how *L. pneumophila*, a Gram-negative intracellular bacterium that causes Legionnaires’ disease, infects and subverts alveolar macrophages, breaching a critical line of defense and causing serious pulmonary infection. *L. pneumophila* is a highly evolved intracellular pathogen that ensures its replication by injecting more than 300 bacterial proteins into the host cell, via a type IV secretion system (T4SS) (Isberg et al., 2009). A variety of effects, by which the host systems were subverted, had been reported including reports that the *Legionella*-containing vacuole (LCV) associates with mitochondria. The current work explored in detail, the LCV-mitochondria association and its relevance to pathogenicity. The key findings were that, the mitochondria cluster around LCV, independent of the T4SS or the strain, forming transient dynamic contacts. Translocation of T4SS system effectors, principally MitF, leads to mitochondrial...
fragmentation. While bacterially encoded toxins leading to mitochondrial fragmentation have been previously described for *H. pylori* and *L. monocytogenes*, as mentioned above, this is the first example of a bacterial protein being translocated to mitochondria and inducing fragmentation. The precise mechanism of mitochondrial fragmentation after MitF translocation remains to be deciphered, but altered cytoskeletal dynamics through a Ran-RanBP2-WASP/Arp2/3-DNM1L functional axis seems plausible. Notably, this is a well-known host protein pathway starting with a GTPase that is probably hijacked by MitF, and terminating in a mitochondrial fission factor that has dual roles in fission and apoptosis. The net effect is a drop in OxPhos and shift to aerobic glycolysis, as seen in cancer cells (Warburg effect), possibly protecting against apoptosis. Loss of OxPhos seems to be less important for bacterial replication than increase in glycolysis (Ogawa et al., 1994). A possible twist to this tale may lie in whether these metabolic shifts also lead to class switching of macrophages from an oxidative M2 type to an M1 glycolytic type (Gaber et al., 2017). M1 activated macrophages are typically considered to be more microbicidal than M2, with the switch to glycolytic metabolism being part of a strong inflammatory response (Kelly and O'Neill, 2015) While metabolic shifts are only one aspect of the immune phenotype, this seems to be an area that merits deeper exploration.

To end, we speculate that there has been a probable co-evolution of microbes and eukaryotic cells, whereby bacterially encoded proteins can translocate to and hijack mitochondrial functions, bypassing critical aspects of innate immunity. Mitochondria work for ‘us’, most of the time, but can be subverted by microbes to work for ‘them’. This dichotomy merits greater attention while devising new therapeutics.

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**Conflict of interest statement**
The author has declared that no competing or conflict of interests exist.

**Authors’ contributions**
VJ and AA contributed to the writing of manuscript.

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