underscore the importance of identifying genetic polymorphisms that impact autophagy, as these could influence the response to PZA/INH and the overall clinical outcome. This report also highlights the need for rapid and precise resistance genotyping of Mtb isolates in the field. While it is not clear if each antibiotic can boost autophagy responses, it would be ideal to utilize the most bactericidal combination to engage the autophagy pathway, as bacteriostatic agents were not found to boost autophagy in similar assays.

Infection with Mtb is well known to elicit a potent inflammatory cytokine response that is largely responsible for the disease pathology. Evidence from several groups has identified that cytokine production can in part be regulated by autophagy. In the current study, treatment of Mtb-infected cells with INH reduced the production of inflammatory cytokines TNF-α, IL-6, and IL-1β. Furthermore, blocking autophagy induction in Mtb-infected cells treated with INH resulted in enhanced inflammatory cytokine production. From these data, one can speculate that bacterial killing by autophagy and inflammatory cytokine production are tightly coupled such that as bacteria are destroyed, the need for inflammatory cytokines is reduced. Since inflammatory cytokines are themselves autophagy inducers, the data presented by Kim et al. (2012) persuasively suggest how autophagic killing and cytokine production could regulate each other to achieve a balance that bolsters host defense and limits cytokine-induced pathology. It is also interesting to consider that exuberant cytokine production during Mtb treatment may itself be diagnostic of a weak autophagy response and poor long-term prognosis. Additional studies will be necessary to examine this correlation as the potential to be a valuable clinical tool.

As we can continue to mine for new antibiotics that can treat Mtb infection, we should keep in mind that medicines that are decades old have been exploiting a newly appreciated cellular defense mechanism. Clearly, an ideal antibiotic would target a bacterial Achilles' heel but also enhance the activity of endogenous cellular defenses such as autophagy. It may also be possible to combine antibiotics with agents that act specifically on the host autophagy pathway to produce combination therapies. Large-scale chemical screens have begun to identify mammalian target of rapamycin (mTOR)-independent agents that may serve this purpose and avoid the immunosuppressive effects of rapamycin or similar agents. The current work demonstrates that focusing therapy on both the host and the pathogen would be an ideal combination to strive for in the future.

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Viral Infection Brings Mitochondrial Traffic to a Standstill

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Mitochondria are dynamic organelles with many functions. In this issue of *Cell Host & Microbe*, Kramer and Enquist (2012) show that mitochondrial motility and morphology are disrupted during alphaherpesvirus infection, which aids viral replication and transport in neurons.

Mitochondria have many functions in infected and noninfected cells, including energy generation, calcium homeostasis, innate immune signaling, and apoptosis. Disruption of mitochondrial function may help also drive neurodegeneration and contribute to Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS) (Detmer and Chan, 2007). Mitochondria are dynamic organelles, and their movement is mediated by microtubules and dynein/kinesin motor systems. Alphaherpesviruses encode proteins that alter mitochondrial localization and function, primarily to reduce apoptosis (Pomeranz et al., 2005). However, the mechanisms underlying virus-mediated alteration of mitochondrial dynamics are unclear, particularly in neurons.

Neurons are unique cells due to their electrical activity and length, which requires long-distance transport of cargoes including organelles and viruses.

Neurotropic viruses including herpesviruses, rabies virus, and poliovirus use the cellular transport machinery to move long distances in neurons. However, the effect of virus infection on transport of neural cargoes, including mitochondria, is unknown.

In this issue of *Cell Host & Microbe*, Kramer and Enquist report the first study of mitochondrial dynamics in alphaherpesvirus-infected neurons (Kramer and Enquist, 2012). They found that pseudorabies virus (PRV) or herpes simplex virus 1 infection of primary rodent neurons reduced mitochondrial motility and altered mitochondrial morphology, without major damage to the organelles. Importantly, disruption of mitochondrial transport was required for efficient PRV replication and transport in neurons.

The mechanism underlying reduced mitochondrial motility in infected neurons involves a unique feature of PRV infection: the generation of pores that electrically couple neurons independent of synaptic transmission (McCarthy et al., 2009). The viral envelope protein gB creates fusion pores that link the membranes of previously independent neurons, increasing spontaneous electrical activity. In effect, the pores create neural ''syncytia,'' and the resulting enhancement in action potential firing increases cytoplasmic calcium concentrations. The level of intracellular calcium is one of the factors known to regulate mitochondrial motion (Macaskill et al., 2009; Saotome et al., 2008; Wang and Schwarz, 2009). The mitochondrial outer membrane protein Miro senses high calcium through its ''hand'' domains (Fransson et al., 2003). This releases the Miro-mediated tether between mitochondria and kinesin, thus reducing microtubule-mediated mitochondrial movement. Kramer and Enquist found that PRV infection decreased levels of kinesin-1 heavy chain associated with mitochondria without detectable changes to levels of the microtubule motor protein dynein. The authors unveiled the mechanism of PRV-mediated mitochondrial transport defect with an elegant combination of experiments using mutant viruses lacking gB, a drug that enhances mitochondrial motility, a calcium chelator, a calcium channel blocker, and viruses expressing a version of Miro that is unable to sense calcium (Kramer and Enquist, 2012). Overall, this study may provide an explanation for part of the neural damage observed to be associated with alphaherpesvirus infections.

This work raises several interesting and important questions worthy of future investigation. First, while the calcium-dependent Miro-based mechanism of reduced mitochondrial transport is likely specific for mitochondrial movement, is transport of other organelles altered during alphaherpesvirus infection? One can imagine that increased cytoplasmic calcium induced by PRV infection has broad consequences for many organelles. Second, are additional viral and/or cellular factors involved in limiting mitochondrial transport? The authors point out that reduced mitochondrial transport occurs before the virus-induced action potential firing and enhanced calcium begin. Therefore, other viral and/or cellular factors may contribute to limited mitochondrial movement, particularly early in infection. Third, do similar alterations in mitochondrial motility and morphology occur in vivo, and what are the long-term consequences in animals? This study demonstrates that PRV infection reduces mitochondrial motility for a relatively long time period (72 hr) in primary neurons. How would this process affect animals during infection? Does it contribute to neurodegeneration later in life? Fourth, do viruses in other families impact mitochondrial dynamics in neurons or other cell types? Several viral families contain members that are neurotropic. Are the effects on mitochondrial dynamics specific to alphaherpesviruses?

Finally, the virus-mediated reduction in mitochondrial motility promotes PRV replication and transport, but is this effect direct or indirect? Is mitochondrial motility directly targeted by PRV, or is it a side effect of increased calcium concentrations? How does reduced mitochondrial motility benefit alphaherpesviruses? Since alphaherpesviruses rely on kinesin for transport, it is possible that they benefit from the increased pool of available kinesin generated by mitochondrial release. Another possibility is that viruses benefit from mitochondria trapped in certain cellular locations, for location-specific energy production or sequestration of apoptotic machinery. Examining the specificity of mitochondrial effects with other viral systems may help answer these questions.

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