HHS Public Access

Author manuscript

Cell Host Microbe. Author manuscript; available in PMC 2015 March 24.

Published in final edited form as:

Cell Host Microbe. 2012 May 17; 11(5): 420–421. doi:10.1016/j.chom.2012.05.001.

Viral infection brings mitochondrial traffic to a standstill

Lauren N. Luethy[1] and **Julie K. Pfeiffer**[1,*]

[1]Department of Microbiology University of Texas Southwestern Medical Center 5323 Harry Hines Blvd. Dallas, TX 75219 USA

Abstract

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

*corresponding author Julie.Pfeiffer@UTSouthwestern.edu.

level of intracellular calcium is one of the factors known to regulate mitochondrial motion (Macaskill et al., 2009, Saotome et al., 2008 and 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.

Acknowledgments

J.K.P. is funded by National Institutes of Health grant AI74668, American Cancer Society Research Scholar grant RSG-11-059-01-MPC, and a World Health Organization Global Poliovirus Eradication Initiative grant.

References

Detmer SA, Chan Nat DC. Rev. Mol. Cell Biol. 2007; 8:870–879.

Fransson A, Ruusala A, Aspenstrom P. J. Biol. Chem. 2003; 278:6495–6502. [PubMed: 12482879]

Kramer T, Enquist LW. Cell Host Microbe. 2012; 11:504–514. this issue. [PubMed: 22607803]

Macaskill AF, Rinholm JE, Twelvetrees AE, Arancibia-Carcamo IL, Muir J, Fransson A, Aspenstrom P, Attwell D, Kittler JT. Neuron. 2009; 61:541–555. [PubMed: 19249275]

McCarthy KM, Tank DW, Enquist LW. PLoS Pathog. 2009; 5:e1000640. [PubMed: 19876391]

Pomeranz LE, Reynolds AE, Hengartner CJ. Microbiol. Mol. Biol. Rev. 2005; 69:462–500. [PubMed: 16148307]

Saotome M, Safiulina D, Szabadkai G, Das S, Fransson A, Aspenstrom P, Rizzuto R, Hajnoczky Proc G. Natl. Acad. Sci. USA. 2008; 105:20728–20733.

Wang X, Schwarz Cell TL. 2009; 136:163–174.