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ESPS Peer-review Report
Name of Journal: World Journal of Clinical Infectious Diseases
ESPS Manuscript NO: 12262
Title: SUBVERSION OF CELLULAR STRESS RESPONSES BY POXVIRUSES
Reviewer code: 02521807
Science editor: Fang-Fang Ji
Date sent for review: 2014-07-01 10:27
Date reviewed: 2014-07-03 04:51

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[ ] Grade B (Very good)	[Y] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[Y] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	[ ]Rejection
[ ] Grade D (Fair)	[ ] Grade D: rejected	BPG Search:	[ ] Minor revision
[ ] Grade E (Poor)		[ ] Existed	[Y] Major revision
		[ ] No records	

COMMENTS TO AUTHORS

This is an interesting review. They describe diverse strategies that poxviruses use to subvert host cell stress responses. The manuscript needs a thorough re-editing job so that scientists both in and outside the immediate filed can better follow it. In this sense, they should offer a brief introduction of the cellular stress responses and their several cascades of events. The authors only represent in a Figure those events ascribed to unfolded protein response. It is a useful tool to follow the description on text. They should incorporate additional figures –besides Figure 1- representing other events (such as heat shock response; host translational shutoff; hypoxic response; oxidative stress response; DNA damage response) related with poxviruses immune escape. By this strategy, some descriptions could be shortened thus appearing more clear. Most of the mechanisms described are related to "poxviruses". It should be specified whether are related to vaccinia (most of the references are related with), or another well-defined poxvirus. Minor comments Golgi is a last name, so it must be written with Upper case.

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ESPS Peer-review Report
Name of Journal: World Journal of Clinical Infectious Diseases
ESPS Manuscript NO: 12262
Title: SUBVERSION OF CELLULAR STRESS RESPONSES BY POXVIRUSES
Reviewer code: 00503124
Science editor: Fang-Fang Ji
Date sent for review: 2014-07-01 10:27
Date reviewed: 2014-07-06 05:03

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[Y] Grade B (Very good)	[Y] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[ ] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	[ ]Rejection
[ ] Grade D (Fair)	[ ] Grade D: rejected	BPG Search:	[ ] Minor revision
[ ] Grade E (Poor)		[ ] Existed	[Y] Major revision
		[ ] No records	

COMMENTS TO AUTHORS

This seems to be an important review of poxvirus interactions with and effects on cell stress. However some issues need to be addressed: 1. The authors state, The inhibition of HSP90 function by novobiocin during infection impairs intermediate and late viral gene expression and, therefore, reduces viral DNA replication[115; 116' This is a confusing statement because intermediate and late viral gene expression occur after DNA replication, not before DNA replication. In addition, what the authors state here is completely contradicted by the abstract from the article they reference: Novobiocin inhibits vaccinia virus replication by blocking virus assembly. Novobiocin inhibits the replication of vaccinia virus in cultured BSC40 cells. All classes of viral proteins were synthesized during synchronous infection in the presence of drug. The onset of DNA replication was delayed slightly, yet the extent of DNA replication in the presence of novobiocin was comparable to that of a control infection. A delay in the temporal transition to late viral protein synthesis was in keeping with the effects on DNA replication. Although the precursor forms of the major viral structural proteins were synthesized normally at late times, the proteolytic processing of these polypeptides was inhibited, which suggested an impediment to virus assembly. Electron microscopy revealed that novobiocin blocked virus morphogenesis at an early stage. Conversion of the concatemeric DNA replication intermediates into hairpin telomeres occurred in the presence of novobiocin, confirming that telomere resolution was not coupled to virus assembly. Novobiocin is the latest addition to a class of antipoxviral agents, which includes rifampin and IMCBH, that arrest morphogenesis. 2. How does the author know that C16 orthologs are non essential for virus replication? Have any been tested? Or is the author just assuming this? Authors should be careful in generalizing too

much about poxviruses. 3. On XBP1, authors could mention TLR regulation of XBP1 activation. (Martinon, Nat. Imm. 2010). Vaccinia has a number of proteins that interfere with TLR signal transduction. 4. On the discussion of CHOP, GADD34, ATF3[55, authors could include that E3L knockout significantly increases ATF3 expression. (Ludwig, JVI 2005) 5. On IRE1/ATF6 dependent stress pathways, TRAF 2 is a binding partner for IRE1, and vaccinia interferes with TRAF2 (Ember, JGV 2011; Haga, JVI 2014) 6. There are several problems with references. Authors should go through the entire list to check for accuracy. Authors state that C16 play an important role in cell biochemistry, but the reference does not support this statement. There are no data on cellular biochemistry in that manuscript. Reference 40 that is supposed to be on ROS accumulation is on urbanization of house finches with no data on ROS. Reference 23 does not appear to be related to the sentence on "poxviruses that … encode their own redox machinery in order to mediate disulfide bond formation in newly made viral proteins." Ref 139, is this correct on IRE dependent stress pathways? 7. Authors state "Poxviruses increase intracellular ROS accumulation[40] to promote growth of infected cells and immune evasion." Do the authors mean all poxviruses do this? Or only myxoma virus? Teoh ML, Turner PV, Evans DH. JV 2005. 8. Language: Under HOST TRANSLATIONAL SHUTOFF, it should say Most Viruses, as obligate intracellular parasites,… Under Oxidative stress, I do not know what "Poxviruses explore…" means In the miscellaneous cell signaling section, the meaning of this sentence is unclear, "promoting Akt phosphorylation and downstream events leading to the suppression of apoptosis and cell growth, survival, and proliferation[146; 129]. Is promoting AKT phosphorylation leading to the suppression of apoptosis, cell growth, survival and proliferation, or is it leading to the suppression of apoptosis and cell growth and