

	Título de la Publicación	Nombre de la Revista / Libro	Vínculo o DOI	Indexador	Autoría
2018	Identification of Poxvirus Genome Uncoating and DNA Replication Factors with Mutually Redundant Roles	JVI	https://doi.org/10.1128/JVI.02152-17	SCOPUS	CO
<p>Importancia: Una larga búsqueda de proteínas involucradas en la replicación fue culminada con este artículo, reportándose varias proteínas involucradas en la replicación del Poxvirus. Ese conocimiento tiene importancia en el campo de las vacunas.</p>					



GENOME REPLICATION AND REGULATION
OF VIRAL GENE EXPRESSION



Identification of Poxvirus Genome Uncoating and DNA Replication Factors with Mutually Redundant Roles

Baoming Liu,^a Debasish Panda,^a Jorge D. Mendez-Rios,^{a*} Sundar Ganesan,^b Linda S. Wyatt,^a Bernard Moss^a

^aLaboratory of Viral Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA

^bBiological Imaging Section, Research Technologies Branch, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA

ABSTRACT Genome uncoating is essential for replication of most viruses. For poxviruses, the process is divided into two stages: removal of the envelope, allowing early gene expression, and breaching of the core wall, allowing DNA release, replication, and late gene expression. Subsequent studies showed that the host proteasome and the viral D5 protein, which has an essential role in DNA replication, are required for vaccinia virus (VACV) genome uncoating. In a search for additional VACV uncoating proteins, we noted a report that described a defect in DNA replication and late expression when the gene encoding a 68-kDa ankyrin repeat/F-box protein (68k-ank), associated with the cellular SCF (Skp1, cullin1, F-box-containing complex) ubiquitin ligase complex, was deleted from the attenuated modified vaccinia virus Ankara (MVA). Here we showed that the 68k-ank deletion mutant exhibited diminished genome uncoating, formation of DNA prereplication sites, and degradation of viral cores as well as an additional, independent defect in DNA synthesis. Deletion of the 68k-ank homolog of VACV strain WR, however, was without effect, suggesting the existence of compensating genes. By inserting VACV genes into an MVA 68k-ank deletion mutant, we discovered that M2, a member of the poxvirus immune evasion (PIE) domain superfamily and a regulator of NF- κ B, and C5, a member of the BTB/Kelch superfamily associated with cullin-3-based ligase complexes, independently rescued the 68k-ank deletion phenotype. Thus, poxvirus uncoating and DNA replication are intertwined processes involving at least three viral proteins with mutually redundant functions in addition to D5.

IMPORTANCE Poxviruses comprise a family of large DNA viruses that infect vertebrates and invertebrates and cause diseases of medical and zoological importance. Poxviruses, unlike most other DNA viruses, replicate in the cytoplasm, and their large genomes usually encode 200 or more proteins with diverse functions. About 90 genes may be essential for chordopoxvirus replication based either on their conservation or individual gene deletion studies. However, this number may underestimate the true number of essential functions because of redundancy. Here we show that any one of three seemingly unrelated and individually nonessential proteins is required for the incompletely understood processes of genome uncoating and DNA replication, an example of synthetic lethality. Thus, poxviruses appear to have a complex genetic interaction network that has not been fully appreciated and which will require multifactor deletion screens to assess.

KEYWORDS gene redundancy, genome replication, genome uncoating, poxvirus replication, recombinant DNA technology, synthetic lethality, vaccinia virus

Received 8 December 2017 Accepted 2 January 2018

Accepted manuscript posted online 17 January 2018

Citation Liu B, Panda D, Mendez-Rios JD, Ganesan S, Wyatt LS, Moss B. 2018. Identification of poxvirus genome uncoating and DNA replication factors with mutually redundant roles. *J Virol* 92:e02152-17. <https://doi.org/10.1128/JVI.02152-17>.

Editor Rozanne M. Sandri-Goldin, University of California, Irvine

Copyright © 2018 American Society for Microbiology. All Rights Reserved.

Address correspondence to Bernard Moss, bmoss@nih.gov.

* Present address: Jorge D. Mendez-Rios, Informedic International, Panama City, Republic of Panama.

Downloaded from <http://jvi.asm.org/> on August 26, 2020 by guest