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2019	SPI-1 is a missing host-range factor required for replication of the attenuated modified vaccinia Ankara (MVA) vaccine vector in human cells	PLoS Pathog	https://dx.doi.org/10.1371/journal.ppat.1007710	SCOPUS	CO
Importancia: Después de varias décadas de investigación sin frutos, se logró encontrar un gen, SPI-1 que explica la atenuación del virus MVA, lo permite entender mejor la seguridad necesaria en vacunas con virus atenuado. Citas:4					

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RESEARCH ARTICLE

SPI-1 is a missing host-range factor required for replication of the attenuated modified vaccinia Ankara (MVA) vaccine vector in human cells

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Data Availability Statement: All sequence files have been deposited in GenBank. Accession numbers are provided in manuscript. Genome sequences of rMVA 44.1, 44/47.1, 47.1 and 51.2 were deposited as GenBank Accession Numbers MK314710, MK314711, MK314712 and MK314713.

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Abstract

Modified vaccinia virus Ankara (MVA) is the leading poxvirus vector for development of vaccines against diverse infectious diseases. This distinction is based on high expression of proteins and good immunogenicity despite an inability to assemble infectious progeny in human cells, which together promote efficacy and safety. Nevertheless, the basis for the host-range restriction is unknown despite past systematic attempts to identify the relevant missing viral gene(s). The search for host-range factors is exacerbated by the large number of deletions, truncations and mutations that occurred during the long passage history of MVA in chicken embryo fibroblasts. By whole genome sequencing of a panel of recombinant host-range extended (HRE) MVAs generated by marker rescue with 40 kbp segments of vaccinia virus DNA, we identified serine protease inhibitor 1 (SPI-1) as one of several candidate host-range factors present in those viruses that gained the ability to replicate in human cells. Electron microscopy revealed that the interruption of morphogenesis in human cells infected with MVA occurred at a similar stage as that of a vaccinia virus strain WR SPI-1 deletion mutant. Moreover, the introduction of the SPI-1 gene into the MVA genome led to more than a 2-log enhancement of virus spread in human diploid MRC-5 cells, whereas deletion of the gene diminished the spread of HRE viruses by similar extents. Furthermore, MRC-5 cells stably expressing SPI-1 also enhanced replication of MVA. A role for additional host range genes was suggested by the restoration of MVA replication to a lower level relative to HRE viruses, particularly in other human cell lines. Although multiple sequence alignments revealed genetic changes in addition to SPI-1 common to the HRE MVAs, no evidence for their host-range function was found by analysis thus far. Our finding that SPI-1 is host range factor for MVA should simplify use of high throughput RNAi or CRISPR/Cas single gene methods to identify additional viral and human restriction elements.