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VIRAL PATHOGENESIS

Bovine factors aid foot and mouth

Foot and mouth is one of the most infectious diseases of cloven-hoofed livestock and places a heavy economic burden on afflicted areas. It is caused by a picornavirus, foot-and-mouth disease virus (FMDV), that uses host cell proteins to enter the host cell, replicate and form infectious progeny. However, knowledge about the specific proteins that affect replication and propagation is limited. In a study published in the *Journal of Virology*, Piccone and colleagues describe a systematic antisense RNA-based approach to screen for host factors subverted by FMDV.

A lentivirus-based library that contains approximately 40,000 human expressed sequence tags (ESTs) was used to generate antisense RNAs to randomly inactivate chromosomal gene expression in a bovine kidney cell line (LF-BK) infected with FMDV. The authors chose to carry out the screen in LF-BK cells owing to their high susceptibility to FMDV infection. Following four rounds of infection, no wild-type LF-BK cells had survived; however, following infection of cells containing the EST library, 180 FMDV-resistant surviving clones were isolated. Several of the ESTs corresponded to host genes that have been implicated in other viral infections, such as interferon regulatory factor 7 and signal peptide peptidase.

One clone that showed prominent resistance to FMDV production contained the EST insert of the gene encoding ectonucleoside triphosphate diphohydrolase 6 (NTPDase 6), which belongs to a family of enzymes that modulate nucleoside concentrations. Downregulation of NTPDase 6 decreased viral production by more than 90%. However, immunofluorescence studies using monoclonal antibodies raised against viral structural proteins showed that although total cellular levels of virus decreased, the percentage of cells containing viral proteins was similar in NTPDase 6 knockdown clones and wild-type cells. This suggests that NTPDase 6 plays a part in FMDV replication rather than cell entry. When the authors generated 30 additional clones that express antisense RNA to knock down NTPDase 6 levels, they found some variation in the ability of the antisense RNA to limit FMDV production, perhaps owing to differences in expression of the antisense RNA. Importantly, none of the clones showed a change in susceptibility to infection by other picornaviruses, such as porcine enterovirus, indicating that NTPDase 6 has a specific role during FMDV infection.

FMDV vaccines are available. However, the virus is antigenically variable and there is no cross-protection among the different FMDV serotypes. Targeting host factors such as NTPDase 6 could provide a useful method of circumventing the inherent antigenic variation of the virus and provide a strategy for broad antiviral intervention.

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> “Downregulation of NTPDase 6 decreased viral production by more than 90%.”

ORIGINAL RESEARCH PAPER Piccone, M. E. *et al.* Identification of cellular genes affecting the infectivity of foot and mouth disease virus. *J. Virol.* 15 Apr 2009 (doi:10.1128/JVI.01729-08)