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## Relationship between within-Host Fitness and Virulence in the Vesicular Stomatitis Virus: Correlation with Partial Decoupling.

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### Abstract

Given the parasitic nature of viruses, it is sometimes assumed that rates of viral replication and dissemination within hosts (**within-host fitness**) correlate with **virulence**. However, there is currently little empirical evidence supporting this principle. To test this, we quantified the **fitness** and **virulence** of 21 single- or double-nucleotide mutants of the **vesicular stomatitis virus** in baby hamster kidney cells (BHK-21). We found that, overall, these two traits correlated positively, but significant outliers were identified. Particularly, a single mutation in the conserved C terminus of the N nucleocapsid (U1323A) had a strongly deleterious **fitness** effect but did not alter or even slightly increased **virulence**. We also found a double mutant of the M matrix protein and G glycoprotein (U2617G/A3802G mutant) with high **fitness** yet low **virulence**. We further characterized these mutants in primary cultures from mouse brain cells and in vivo and found that their relative **fitness** values were similar to those observed in BHK-21 cells. The mutations had weak effects on the **virus**-induced death rate of total brain cells, although they specifically reduced neuron death rates. Furthermore, increased apoptosis levels were detected in neurons infected with the U2617G/A3802G mutant, consistent with its known inability to block interferon secretion. In vivo, this mutant had reduced **virulence** and, despite its low brain titer, it retained a relatively high **fitness** value owing to its ability to suppress competitor viruses. Overall, our results are in broad agreement with the notion that viral **fitness** and **virulence** should be positively correlated but show that certain mutations can break this association and that the **fitness-virulence relationship** can depend on complex **virus**-host and **virus-virus** interactions.

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