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The cytoplasmic tail of the rabies virus G protein is an essential domain controlling death/survival in human neuronal cells

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The balance between death/survival issues of infected cells is an important factor of viral pathogenicity, which can be controlled by one protein and sometimes by a few mutations only.

Indeed, infected human neurons can undergo death or survival depending of the Rabies virus (RABV) strains. This is the case for two laboratory strains, one promoting neuronal death and the other one driving neuronal survival.

We, and others, have shown that RABV G protein is a key determinant for this phenotype. The two glycoproteins G-death and G-survival are different by only six amino acids, 2 of which being located in the cytoplasmic tail. To investigate the domains involved in the control of death/survival balance, we isolated by reverse genetic a series of G-mutants in the SN0 strain of RABV. All recombinant viruses were viable. Growth kinetics, transcription/replication as well as G protein expression were monitored in human neuroblastoma cells. Analysis of apoptosis (Hoescht 33342 and Annexin V) or survival (phosphorylation of AKT) of human neuroblastoma cells mapped the cytoplasmic tail as a critical protein domain for these phenotypes.

Interestingly one of the two mutations in the C-domain corresponds to a binding site (BS) for PDZ domain. The use of endswap RABV mutants showed the critical involvement of the BS-PDZ in this control. High scale two-hybrids experiments were undertaken with a human brain bank and cellular interactors were identified. These proteins harbour PDZ domains. Therefore it strongly supports our hypothesis that the balance between death and survival might be determined by these specific protein-protein interactions.

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