Dominance of the Rabies Virus G Protein Carrying a Non-Pathogenic Determinant over the G Protein Carrying a Pathogenic Determinant

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RV G protein is not only the major RV antigen responsible for induction of protective immunity but also the major contributor to RV pathogenesis. Several rabies virus (RV) vaccine strains containing aspartic acid (Asp) or glutamic acid (Glu) instead of arginine (Arg) at position 333 of the RV glycoprotein (GAN) are apathogenic in immunocompetent mice. This makes these variants suitable as live-attenuated vaccines. A recombinant RV carrying two identical Arg333→Glu333 G genes (SPBNGAN-GAN) over-expressed the RV G and conferred protective immunity in a variety of animals, superior to that of a RV variant carrying only a single GAN protein (SPBNGAN).

A major problem with the use of live attenuated RV vaccines is reversion to the pathogenic phenotype. It has been shown that a Asn194→ Lys194 mutation in G (GAK) was solely responsible for the emergence of the pathogenic phenotype. To investigate whether the presence of two G genes can actually increase the possibility for reversion to pathogenicity, we constructed RVs that contain both the GAN and GAK gene (SPBNGAN-GAK or SPBNGAK-GAN). Additionally, we constructed a RV containing two GAK genes (SPBNGAK-GAK). While SPBNGAK-GAK was pathogenic, both SPBNGAN-GAK and SPBNGAK-GAN were non-pathogenic after i.c. infection of adult mice. This indicates that the non-pathogenic phenotype determined by GAN is dominant over the pathogenic phenotype associated with GAK. Most interestingly, virus growth and RV RNA transcription/replication rates were significantly higher in SPBNGAN- as compared to SPBNGAK-infected neuroblastoma cells. In cells infected with SPBNGAN-GAK or SPBNGAK-GAN, virus growth kinetics and RV RNA transcription rates were similar to those seen SPBNGAN-infected cells, indicating that the pathogenicity of RV correlates inversely with its transcription/replication rate. From these data we conclude that an rRV carrying two identical attenuated G genes is not only more immunogenic but also exhibits a lower risk for reversion to the pathogenic phenotype.

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