IDENTIFICATION OF GENETIC DETERMINANTS OF JUNIN VIRUS ATTENUATION

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The New World arenavirus Junin (JUNV) is the causative agent of Argentine hemorrhagic fever (AHF) that is associated with high morbidity and significant mortality. Several pathogenic strains of JUNV have been documented, and a highly attenuated vaccine strain (Candid #1) was generated and used to vaccinate human population at risk. The identification and functional characterization of viral genetic determinants associated with AHF and Candid #1 attenuation would contribute to the elucidation of the mechanisms by which JUNV causes AHF and development of better vaccines and therapeutics. To this end we used reverse genetics to rescue from cloned cDNAs the pathogenic Romero (rRomero) and the attenuated Candid #1 (rCandid #1) strains of JUNV. Both rRomero and rCandid #1 had the same growth properties and phenotypic features in cultured cells and in vivo as their corresponding parental viruses. Infection with rRomero caused 100% mortality in guinea pigs whereas rCandid #1 infection was asymptomatic and provided protection against a lethal challenge with Romero. Recombinant intersegment chimeric JUNV containing one genomic RNA segment originated from Romero and the other from Candid #1 strain of JUNV were rescued using our cDNA-based reverse genetics system. To examine the contribution of the viral genes encoded by the genomic RNA segments S and L to JUNV pathogenesis, we generated rRomero viruses rRom/CanGPC, rRom/CanNP, rRom/CanZ, and rRom/CanLP, where ORF for either GPC, NP, Z, or LP gene, respectively, was substituted with ORF for the corresponding gene of Candid #1 origin. In vitro characteristics of the chimeric recombinant viruses including growth properties, size and morphological appearance of plaques were determined in Vero and A549 cells. Pathogenicity of the generated recombinant viruses was evaluated in a guinea pigs model of lethal infection that closely resembles human disease.