ABSTRACT

Potent Neutralization of Rift Valley Fever Virus By Human Monoclonal Antibodies Through Fusion Inhibition

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Rift Valley fever virus (RVFV), an emerging arboviral and zoonotic bunyavirus, causes severe disease in livestock and humans. Here, we report the isolation of a panel of monoclonal antibodies (mAbs) from the B cells of immune individuals following natural infection in Kenya or immunization with MP-12 vaccine. The B cell responses of individuals who were vaccinated or naturally infected recognized similar epitopes on both Gc and Gn proteins. The Gn-specific mAbs and two mAbs that do not recognize either monomeric Gc or Gn alone but recognized the hetero-oligomer glycoprotein complex (Gc+Gn) when Gc and Gn were coexpressed exhibited potent neutralizing activities in vitro, while Gc-specific mAbs exhibited relatively lower neutralizing capacity. The two Gc+Gn–specific mAbs and the Gn domain A-specific mAbs inhibited RVFV fusion to cells, suggesting that mAbs can inhibit the exposure of the fusion loop in Gc, a class II fusion protein, and thus prevent fusion by an indirect mechanism without direct fusion loop contact. Competition-binding analysis with coexpressed Gc/Gn and mutagenesis library screening indicated that these mAbs recognize four major antigenic sites, with two sites of vulnerability for neutralization on Gn. In experimental models of infection in mice, representative mAbs recognizing three of the antigenic sites reduced morbidity and mortality when used at a low dose in both prophylactic and therapeutic settings. This study identifies multiple candidate mAbs that may be suitable for use in humans against RVFV infection and highlights fusion inhibition against bunyaviruses as a potential contributor to potent antibodymediated neutralization.

Keywords: Potent neutralization, Rift Valley fever virus, Human monoclonal antibodies, Fusion inhibition