MS110.O05

Complex structure of MERS-CoV spike glycoprotein with human receptor DPP4

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Recently identified the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) causes severe and fatal acute respiratory illness in human. No prophylactic and therapeutic agents specifically against MERS-CoV are currently available. Entry of MERS-CoV into the target cells depends on binding of receptor-binding domain (RBD) on viral envelope spike glycoprotein to the cellular receptor dipeptidyl peptidase 4 (DPP4). We report the 3.0 angstrom-resolution crystal structure of MERS-CoV RBD bound to the extracellular domain of DPP4. The structure shows that MERS-CoV RBD consists of a core and a receptor binding subdomain. MERS-CoV RBD and related SARS-CoV RBD share a high degree of structural similarity in their core subdomains, but are notably divergent in the receptor binding subdomain. Structural and mutagenesis analyses identified several key residues in the receptor binding subdomain of RBD that are critical for viral binding to DPP4 and entry into the target cell. Two RBD-specific potent human neutralizing monoclonal antibodies were derived from single-chain variable region fragments (scFvs) of nonimmune human antibody library. They inhibited infection of both pseudotyped and live MERS-CoV with IC50 at nanomolar concentration. Biochemical analysis indicated that these two antibodies blocked RBD interaction with DPP4 on the cell surface.

Keywords: coronavirus, viral entry, neutralizing antibody