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The spike receptor binding motif G496S substitution determines the replication fitness of SARS-CoV-2 Omicron sublineage

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The replication and pathogenicity of SARS-CoV-2 Omicron BA.2 are comparable to that of BA.1 in experimental animal models. However, BA.2 has rapidly emerged to overtake BA.1 to become the predominant circulating SARS-CoV-2 variant worldwide. Here, we compared the replication fitness of BA.1 and BA.2 in cell culture and in the Syrian hamster model of COVID-19. Using a reverse genetics approach, we found that the BA.1-specific spike mutation G496S compromises its replication fitness, which may contribute to BA.1 being outcompeted by BA.2 in the real world. Additionally, the BA.1-unique G496S substitution confers differentiated sensitivity to therapeutic monoclonal antibodies, which partially recapitulates the immunoevasive phenotype of BA.1 and BA.2. In summary, our study identified G496S as an important determinant during the evolutionary trajectory of SARS-CoV-2.