Somatic hypermutation increases antibody binding and enhances coverage of emerging SARS-CoV-2 variants

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Introduction: After SARS-CoV-2 infection, virus neutralizing antibody responses and memory B cells expressing hypermutated antibodies are induced. We hypothesized that hypermutated antibodies exhibit enhanced binding and neutralizing capacity of the infecting virus. Hence, we investigated the potency and coverage of hypermutated antibodies to emerging SARS-CoV-2 variants of concern (VOCs).

Methods: SARS-CoV-2 spike-specific B cells were isolated from individuals who recovered from wild type virus infection before and after vaccination. V(D)J sequences of their antibodies were deciphered and expressed as monoclonal antibodies (mAb). To determine the neutralizing potency and breath of the expressed hypermutated mAbs against VOCs, the neutralization activity of six mAb were compared with their germline versions. Forty mAbs forming a cluster of related clones with different levels of hypermutation were also investigated for their neutralizing activity. Neutralization assays were performed using VSV-SARS-CoV-2 pseudo particles encoding for the spike protein of six different VOCs.

Results: It was observed that some hypermutated mAbs showed significantly enhanced virus binding ability and neutralization while others showed similar binding and neutralization ability when compared with their germline counterparts. Notably, some hypermutated mAbs showed enhanced breadth in neutralization of VOCs. In one cluster of related mAbs, diverse hypermutations had different impacts on the neutralizing capacity and breath of the VOCs. This suggests that even though the overall mAb scaffold was identical, different hypermutations determined how the mAbs bind the spike of SARS-CoV-2.

Conclusion: After SARS-CoV-2 exposure, memory B cells undergo diversification by hypermutation leading to an increased antibody neutralizing potential of VOCs. Different hypermutations diversify antibodies in a manner that they neutralize virus variants that might emerge in the future. Thus, our results not only show that hypermutations can massively enhance the neutralization potential of single antibodies, but that infection and/or vaccination can also result in the generation of diversified antibody repertoire that is primed to neutralize newly emerging virus variants.