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## Affinity-independent memory B cell origin of the early antibody-secreting cell response in naive individuals upon SARS-CoV-2 vaccination

Memory B cells (MBCs) formed over the individual's lifetime in response to antigenic challenge constitute nearly half of the adult peripheral blood B cell repertoire in humans. It is well known that these MBCs mediate fast humoral responses of great magnitude and affinity upon exposure to the same antigens. However, little is known about their differentiation trajectories in response to antigens for which they show low levels of cross-reactivity that they have not encountered previously. To assess their response to novel antigens, we tracked the origin and followed the differentiation paths of MBCs in the early anti-S response to mRNA vaccination in SARS-CoV-2-naive individuals on single-cell and monoclonal antibody level. Newly generated and pre-existing MBCs differed in their differentiation paths despite similar levels of SARS-CoV-2 S-reactivity. Pre-existing highly mutated MBCs showed no signs of germinal center re-entry and rapidly developed into mature antibody secreting cells (ASCs). In contrast, newly generated MBCs derived from naive precursors showed strong signs of antibody affinity maturation before differentiating into ASCs. Thus, although pre-existing human MBCs have an intrinsic propensity to differentiate into ASCs, the quality of the anti-S antibody and MBC response improved through the clonal selection and affinity maturation of naive precursors. Our findings provide new insights in the association between antigen-binding and cell differentiation paths in human naive and memory B cells beyond the concept of original antigenic sin (OAS).

**Keywords**
SARS-CoV-2, mRNA vaccination, affinity maturation, pre-existing memory B cells, germinal center, somatic hypermutation

**Biography**
My name is Zhe Li. In March 2025, I established my independent research group and currently serve as an Assistant Professor at ShanghaiTech University. I obtained my Ph.D. from Heidelberg University under the supervision of Prof. Henri-Jacques Delecluse, where my research focused on virology, particularly the pathogenesis of Epstein-Barr virus (EBV)-associated cancers. My representative work, published as first author in Nature Microbiology (2019) and PNAS (2021). During my second postdoctoral fellowship, I worked with Prof. Hedda Wardemann, shifting my focus to B cell immunology. Using SARS-CoV-2 as a model, we studied the immune response of memory B cells after infection in humans at the single-cell level. My selected work, published as first author in Immunity (2024).



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