Interplay between Extra-Germinal Center expansion of memory B cells and affinity maturation during the humoral recall response

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According to the WHO, vaccines have saved more lives than any other medical intervention in history. Current estimates suggest vaccines save millions of lives annually. The importance of vaccines was recently highlighted by effective vaccines that curtailed the SARS-CoV-2 pandemic. Vaccines prime the immune system to mount tailored responses against antigens, like pathogen-derived proteins. However, some viruses can evolve to evade these immune responses. Targeting the regions of viral proteins that are conserved during such evolution is a goal of rational vaccine design. Achieving this goal requires a better understanding of how immune memory is generated and recalled.

Upon vaccination or infection, B cells and the antibodies they secrete, undergo a Darwinian evolutionary process in the Germinal Center (GC) to generate tailored memory and antibodies. Memory B cells generated in the GC can be recalled in extra-germinal center processes (EGC) to create a large, rapid antibody response. During the recall response, new GCs also form. In this thesis, I explore the EGC's role in the recall response, and the interplay between GC and EGC processes. The mechanistic understanding that has emerged is pertinent to effectively targeting conserved epitopes, amplifying antibody responses, and providing broad protection against mutable variant pathogens. This thesis uses a variety of computational models describing the GC and EGC processes, aiming to enhance our understanding of the generation of immune memory and its subsequent recall to create antibodies.

The first study that is reported sheds light on why coupled EGC and GC processes may have evolved. During the primary immune response, GCs produce memory B cells with a high affinity for the infecting pathogen or vaccine antigen, but they also generate many low affinity memory B cells. During the recall response, the EGC plays a crucial role by selecting and expanding the best pre-existing memory B cells to the infecting pathogen or booster antigen. Upon infection with a variant, the memory B cells expanded are the low affinity B cells produced in the primary GC. Over much longer times secondary GCs generate tailored high affinity B cells to variant antigens. These results suggest that the GC and EGC evolved to protect us against families of variant pathogens.

This thesis also provides a mechanistic explanation for the surprising observation of increased antibody breadth after a third homologous SARS-CoV-2 vaccine. After the second vaccine dose, effective antigen presentation and epitope masking enables B cells with lower germline affinities to enter the secondary GC. These subdominant B cells target different epitopes than the immunodominant response generated after the first shot. As a result, the second dose generates a broad memory pool that is expanded in the EGC after the third vaccine dose to create a broad antibody response capable of binding to variants like Omicron.

Finally, we build on the studies above to investigate the phenomenon known as Original Antigenic Sin, where a heterologous boost with a related variant antigen can generate an immune response worse than a prime with the variant.