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B-cell diversity in immune system's germinal centers may be key to broad-spectrum vaccines

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When it comes to selecting for B cells that produce antibodies to hostile viruses and bacteria, the immune system hedges its bets. Within the germinal centers that form in the body's lymph nodes during an immune response are B cells that produce antibodies with a range of affinities to an invading pathogen. Darwinian-like cycles of mutation and selection of the fittest lead to an increase in the average affinity across the B cell population.

This new finding from Whitehead Institute scientists overturns a previously held notion that only a handful of B cells producing the highest affinity antibodies are allowed to survive in the germinal center. Instead, less strict competition allows multiple B cell lineages to evolve simultaneously, whereas winner-take-all events are relatively rare. This revised understanding may aid development of effective vaccines against HIV, influenza, and other viruses that mutate rapidly.

"Our research suggests that we may have a window to rescue B cells that produce antibodies protecting against a family of viruses instead of against one strain," says Whitehead Fellow Gabriel Victora. "These antibodies may initially have lower affinity, so the B cells that produce them need to be preserved before they are outcompeted."

Within the lymph nodes' germinal centers, B cells are presented with antigens—pieces of an invading virus or cell. In response, the B cells

produce antibodies that attach firmly to these antigens. Invaders tagged with antibodies are identified as foreign and destroyed by phagocytes or neutralized by other aspects of the immune system. The higher the antibodies' affinity for an interloper's antigens, the more likely the immune system will be able to defeat the infection.

To produce these high-quality antibodies, B cells undergo a selection process in the germinal centers. B cells mutate their antibody genes randomly, yielding a population of descendants with a range of different affinities. Those producing less effective antibodies are edged out by B cells whose antibodies "stick" better to the invader. Researchers had thought that this evolution in miniature would likely continue until only the few B cells creating the fittest antibodies survive.

But a team led by Victora lab scientists Jeroen Tas and Luka Mesin saw something different. After they used fluorescent proteins to permanently tag individual B cells and their progeny, they watched as the B cells underwent selection. While the predicted jackpot events were indeed observed in some germinal centers, most germinal centers contained a variety of B cells, so that, in the same response, germinal centers spanned the full spectrum of heterogeneity, from those with complete domination by the progeny of one B cell, to some with a moderate variety of B cells, to others with a wide array of B cells. The team's work is described this week online in the journal *Science*.

"There is a benefit to preserving diversity," says Mesin, a postdoctoral researcher. "It makes sense that, while the cells that are the 'best' for the ongoing response are selected, also those with the potential to be the 'best' for future responses to related pathogens are maintained. This is the essence of evolution, and it's happening every day in our bodies."

For scientists working to improve vaccines for HIV or to create vaccines with broad protection for numerous strains of influenza, the insight into

germinal center B cell diversity could be immensely helpful.

"These viruses mutate frequently, yet certain conserved regions of them are difficult to change," says Tas, who is a former graduate student in the Victora lab and currently at Harvard Medical School. "If those parts do change, often the viruses are unable to function. However, many antibodies targeting these stable regions appear to start out with lower affinity, and are thought to be mostly lost due to competition. By increasing our understanding of how germinal centers function we might be able to encourage the immune system to actively mutate these antibodies, eventually generating broadly neutralizing antibodies for these viruses."

More information: Visualizing Antibody Affinity Maturation in Germinal Centers, DOI: 10.1126/science.aad3439

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