Imaging studies reveal how high-affinity antibodies are selectively generated by immunization

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Circulating antibodies play a crucial role in host defense against microbial infections, and antibody-based vaccines remain the best hope for preventing infections by deadly viruses such as HIV and Ebola. To combat viruses, antibodies need not only to recognize specific features of the microbe, or so-called antigen, but also to bind to the antigen tightly enough, a condition called having a high affinity. High-affinity antibodies typically form after intimate collaborations between T and B lymphocytes, two types of white blood cells, in a specialized lymphoid tissue domain called germinal center. As reported recently in *Nature*, by imaging the germinal center in living animals, researchers have now discovered a new feed-forward mechanism that controls how T and B cells interact in the germinal center and drives high-affinity antibody formation.

B cells are responsible for producing antibodies, while T cells provide accessory signals that can help them to do so. One B cell can only produce one antibody that specifically recognizes one antigen, whereas a particular antigen can be recognized by thousands of B cells with differing affinities, as a result of either inborn characteristics or a somatic mutation-based diversification process that takes place in the germinal center. It is known T cells are a critical limiting factor that determines which of the competing antigen-binding B cells would win and become dominant in antibody-producing plasma cell populations. However, it was not clear how T cells select for those "winning" B cells

and, given the presumably random and free-for-all competition that underlies the selection, whether we can somehow manipulate the outcome of such affinity-based selection processes in order to develop better vaccines.

Taking advantage of 2-photon microscopy that reveals how immune cells dynamically behave during immune responses, a group of researchers led by Dr. Hai Qi from Tsinghua University in Beijing, China, has carefully analyzed T-B cell interactions in the germinal center. They found that unlike what was previously observed in other tissue sites, T-B contacts lasted for a much shorter duration but involved extensive areas of contact between the two types of cells. Through such contact surface, T cells can rapidly deliver pre-formed help signals to B cells. They term these brief but extensive membrane contacts "entanglement".

ICOSL, a surface molecule expressed by B cells and implicated in inflammatory diseases and immuno-deficiencies, can bind to its receptor ICOS on the T cells. ICOS stimulation leads to better calcium responses that drive more extensive membrane contact and more efficient externalization and delivery of help signals from the T cells to the B cells. Interestingly, B cells that acquire more T cell help would increase ICOSL levels, leading to better entanglement with T cells and more efficient acquisition of help. This positive feedback loop between T and B cells gives rise to the "Matthew Effect" of the germinal center: High-affinity B cells can naturally acquire more antigen, better entangle with T cells and receive more help, and consequently express more ICOSL and more efficiently acquire help.

When the researchers selectively deleted ICOSL from germinal center B cells, the cell-cell competition and the antibody-diversifying process all remained the same, whereas the selection of high-affinity variants was stalled, severely impairing the dominance by high-affinity plasma cells that normally ensues in an immune response. "After all, germinal center

competition is not simply random," says Dr. Hai Qi. "ICOSL sort of marks the chosen cells and, through the feed-forward mechanism, ensures they can be selected out in the rather chaotic germinal center competition process." This research team thinks ICOSL and related pathways could, in the future, be manipulated to design vaccines with desired affinity features.

More information: Dan Liu, Heping Xu, Changming Shih, ZurongWan, Xiaopeng Ma, Weiwei Ma, Dan Luo &Hai Qi. "T–B-cell entanglements and ICOSL-driven feed-forward regulation of germinal centre reaction." *Nature*, 2014 Oct. 15, on line. DOI: 10.1038/nature13803

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