Immunology

Naive and memory B cells respond to flu vaccine

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Influenza vaccination induces a protective memory immune response. The finding that human naive and memory B cells enter vaccine-induced germinal-centre structures suggests that both cell types aid this memory response. **See p.127**

Between yearly vaccinations and seasonal infections, people repeatedly mount an immune response against the influenza virus. A flu vaccination is recommended each year to aid the body's ability to fight the latest flu strain in circulation. To improve the effectiveness of vaccination, researchers need to understand how this immunological history affects the immune memory induced by each subsequent flu vaccination. On page 127, Turner *et al.*[1] investigate the human immune response to seasonal-flu vaccination, and report direct data on which of the various types of an immune cell called a B cell participates in events in highly organized structures called germinal centres. These events are crucial for the process by which immune cells join and diversify the pool of cells that form what is termed the immune-memory compartment.

Protective immunity to the flu virus is driven mainly by antibodies (Fig. 1) made by B cells[2]. Each B cell expresses a B-cell receptor (BCR) that recognizes a particular ligand, called an antigen, such as part of a protein from the surface of a virus. The antibodies made by a particular B cell have the same antigen specificity as the cell's BCR. The immense diversity of BCRs in the population of B cells enables the body to recognize a wide variety of disease-causing agents (pathogens). The first time that a BCR binds to an antigen, the B cell, termed a naive B cell, that has this BCR undergoes rapid proliferation, differentiation and migration. This cell might then enter a germinal centre, located in lymphatic organs such as lymph nodes.

In a germinal centre, a B cell repeatedly proliferates and also mutates the BCR-encoding gene. This process, called somatic hypermutation, generates a lineage of related cells with different abilities to bind to the antigen that the BCR recognizes. These cells compete to bind to that antigen, and the winners survive; this completes one round of a process termed affinity maturation. The survivors can be selected to keep maturing or to leave the germinal centre. Those that leave become either long-lived plasma cells that reside in the bone marrow and constantly release antigen-specific antibodies into the blood, or long-lived memory B cells that persist in the blood and tissues and that, on detecting the antigen again, rapidly give rise to antibody-secreting cells called plasmablasts[3]. To be effective, flu vaccines must induce B cells to participate in germinal centres to generate these long-lived memory B cells, but this crucial intermediate step has not been analysed previously in humans.

Although the flu virus mutates rapidly each year, strains from different years can still share many antigens. Extensive research indicates that flu-specific memory B cells generated by a previous flu exposure dominate the rapid plasmablast response to vaccination, but that work did not determine whether these memory B cells also dominated the germinal-centre response[2,4].

Mouse studies tracked the fate of memory B cells after repeat immunization with the same antigen. This revealed that memory B cells that had previously undergone affinity maturation in germinal centres predominantly formed plasmablasts on repeat exposure to the antigen, whereas naive or memory B cells that had not previously been through a germinal centre drove the formation of new germinal centres on vaccination[5–8]. However, those studies did not investigate the outcome if the second immunization involved a variant of the original antigen, which is more similar to the situation that arises with annual flu vaccination. Investigating this is technically challenging because it is more difficult to

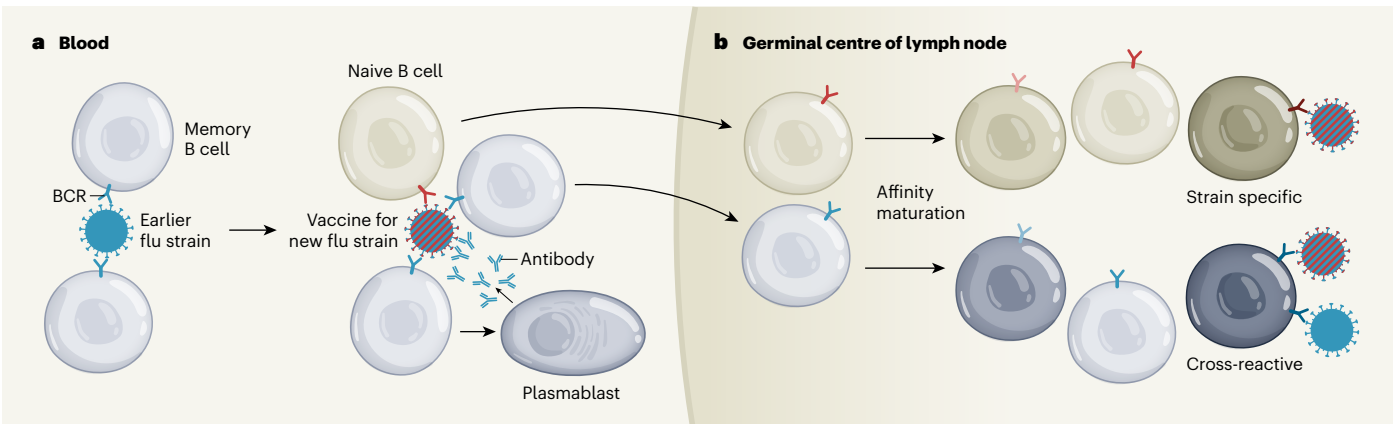

Figure 1 | The response to influenza vaccination. Turner *et al.*[1] analysed immune cells from people who had received an annual flu vaccine. **a**, By means of their B-cell receptor (BCR), immune cells called memory B cells can recognize a part — called an antigen — of a viral protein on the surface of an earlier flu strain. The vaccine given was a disabled version of the flu virus, corresponding to the new strain expected to circulate. The memory cells recognized an antigen in the vaccine shared with the earlier flu strain and gave rise to a type of cell called a plasmablast that secretes antibodies that recognize this antigen and bind to the virus to prevent infection. Another type of B cell called a naive B cell, which has a BCR that hasn't previously recognized an antigen, also bound to the virus, recognizing an antigen found only in this new flu strain. **b**, Both types of B cell entered a structure called a germinal centre in an organ termed a lymph node; the cells divided and the gene encoding the BCR was mutated (different colours denote different BCR versions). Only the cells most effective at binding to viral antigens ultimately survived this process, termed affinity maturation. The naive-cell-derived B cells of the germinal centre bound specifically to the new strain, whereas the memory-cell-derived cells were cross-reactive and could bind to both old and new flu strains.

obtain samples of immune cells from germinal centres in lymph nodes than it is to obtain immune cells from the blood. Such an investigation in humans is necessary because the varied history of flu exposure in individuals might influence the results, and this is not easily reproduced in animal models.

Turner *et al.* studied this elusive process by sampling B cells over time from the blood and lymph nodes of eight people who were immunized with the 2018–19 flu vaccine. The authors sampled the lymph node that the vaccination site drained into, using fine-needle aspiration — a routine clinical technique used previously to study germinal-centre responses in monkeys[9–11]. Turner and colleagues found that all individuals mounted a rapid plasmablast response to the vaccine, and germinal-centre B cells were detected in the samples from each person.

In five individuals, the percentage of B cells in the germinal centre in lymph-node samples increased after vaccination, suggesting the formation of a vaccine-induced germinal centre. The best evidence for this was the detection of flu-specific germinal-centre B cells in three of these five people. This indicates that the technique can track human germinal-centre B-cell responses to vaccination. However, more individuals should be studied to determine whether the observed variability in the detection of flu-specific B cells in the germinal centre arose because of sampling inconsistency or individual variability in the generation of such cells.

The authors investigated which types of flu-specific B cell were induced by the vaccine to form a germinal centre and thus potentially become long-lived memory cells. There is enough BCR variation between different naive B cells for BCRs to serve as 'barcodes' to track a cell's progeny as they proliferate and mutate in the germinal centre. For the three individuals who had flu-specific B cells, Turner and colleagues found that many of the BCRs on germinal-centre B cells were shared with those of plasmablasts derived from rapidly responding memory B cells. This suggests that those memory B cells — formed in response to a different, earlier, flu strain — proliferated in response to recognition of vaccine antigen, and that some progeny cells became plasmablasts, whereas others entered germinal centres.

The authors also found germinal-centre B cells that did not share BCRs with plasmablasts in the three individuals. To determine whether these B cells were derived from naive B cells or from memory B cells that had previously been through a germinal centre but which produced plasmablasts that were not isolated during sampling, the authors measured BCR mutations. Such mutations are uncommon in naive-cell populations because they have not undergone somatic hypermutation in a germinal centre. The authors found that the germinal-centre B cells that did not share BCRs with the plasmablasts were likely to have been derived from naive cells because the cells had fewer mutations than did the germinal-centre B cells probably derived from memory B cells. However, the germinal-centre B cells that did not share BCRs with plasmablasts might also be derived from memory B cells that had not previously been through a germinal centre, because such cells also have low numbers of BCR mutations and do not rapidly form plasmablasts on antigen detection. Distinguishing between these possibilities will require experiments in animal models.

Although the data presented by Turner and colleagues come from just a few people, the result suggests that both naive and memory B cells contributed to germinal centres in response to flu vaccination. Studies of more individuals will be needed to confirm this finding, and such work could go even further to assess how a particular vaccine and its similarity to historical and current flu strains affects the relative immune contribution of naive and memory B cells.

The ultimate goal of flu vaccination is to generate antibodies that can recognize a wide spectrum of flu strains. Such antibodies might be derived from flu-specific memory B cells that re-enter germinal centres for further selection, through affinity maturation, to generate cells that can make antibodies capable of cross-strain reactivity[12]. A naive B cell that responds to flu vaccination will probably recognize only the vaccine strain, because this cell has not previously responded to other flu strains.

"Such investigations might also be relevant for a SARS-CoV-2 vaccine."

To determine whether the vaccine had induced cross-reactive and strain-specific B cells, the authors assessed the ability of antibodies made by the flu-specific germinal-centre B cells to recognize a wide variety of flu strains. Satisfyingly, the probable naive-derived B cells made strain-specific antibodies, whereas the probable memory-derived B cells made cross-reactive antibodies. In the future, it will be crucial to determine whether naive-derived, memory-derived, or both types of germinal-centre B cells exit the germinal centre and become long-lived memory B cells.

The authors' investigation sets out a blueprint for the studies needed to unravel the complexity in the immune response that this work suggests. The study is of particular relevance to candidate 'universal' flu vaccines (those that aim to provide protection from multiple flu strains) and malaria vaccines, because these use repeat immunization to drive the generation of protective antibodies and the vaccines must work in people who have been previously exposed to the pathogen[13,14]. Such investigations might also be relevant for a SARS-CoV-2 vaccine if, like flu, the virus that causes COVID-19 establishes seasonal infections. Understanding how to direct experienced or naive B cells into the long-lived repertoire of memory immune cells will be crucial for developing these vaccines.

Turner and colleagues' experimental approach could also be used to study how manipulating other immune-system components, such as memory B cells that are resident in lymph nodes, or immune cells called CD4 T cells[15], could influence which B cells contribute to germinal centres and become long-lived memory cells. Performing these studies on human lymph nodes will be challenging. Thus, continued innovation in tracking immune responses in blood will allow even more researchers to investigate these crucial issues.

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