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IMMUNOLOGY

Nervous crosstalk to make antibodies

Immune cells called T cells help immune-system B cells mature to produce antibodies. This entails signalling between cells using the molecule dopamine — a surprising immunological role for this neurotransmitter.

HAI QI

The production of antibodies by the B cells of the immune system is essential for an animal's defence against infection. The process involves close communication and collaboration between B cells and immune cells called T cells. In a paper online in *Nature*, Papa *et al.*[1] present a study investigating this step, and report that a molecule better known for its function in nerve-cell signalling also has a role in the interactions between immune cells that underlie antibody generation.

For the immune system to efficiently fight infection, B cells must mature into antibody-producing cells known as plasma cells. To do this, B cells need help from a type of T cell that expresses the protein CD4 and is known as a follicular helper T cell (T_{FH} cell)[2,3]. When a B cell and a T_{FH} cell recognize a pathogen, they become activated, proliferate and migrate to structures called germinal centres, which are mainly found in lymph nodes and in the spleen[4].

In germinal centres, highly mobile T cells and B cells specific for the same pathogen can directly interact with each other through the formation of dynamic specialized surface structures called T–B immunological synapses[5]. Through these structures, T_{FH} cells deliver signals to promote B-cell maturation, while also receiving signals from B cells to maintain their own functional state. How these immunological synapses facilitate the exchange of signals between the two cells and ensure that this interaction efficiently generates antibody-producing cells was not known.

Papa and colleagues tested samples of human tonsils, and found that T_{FH} cells strongly express molecules, including the protein chromogranin B, that have roles in the synapses that form connections between neurons in the nervous system. Chromogranin B is a component of a type of intracellular vesicle at neuronal synapses known as a large dense-core vesicle, which concentrates and transports the neurotransmitter dopamine and related neurotransmitters[6]. Using a sensitive and direct mass-spectrometry method to detect dopamine, the authors found that human T_{FH} cells contained abundant dopamine. However, this was not found in other cells tested, including mouse T_{FH} cells and different types of human T cell. They also observed that human T_{FH} cells released dopamine on stimulation by germinal-centre B cells. Moreover, dopamine augmented the level of *in vitro* maturation of germinal-centre B cells into plasma cells that is induced by the T_{FH}-cell proteins CD40 ligand (CD40L) and interleukin-21.

In further investigation of dopamine-mediated effects, Papa *et al.* found that, among many molecules important for germinal-centre functions, the human protein ICOSL was specifically and rapidly upregulated on the cell surface of germinal-centre B cells after dopamine stimulation. ICOSL is the ligand for the ICOS receptor protein present on the surface of T_{FH} cells.

In mouse germinal centres[7,8], ICOSL promotes T_{FH}–B-cell entanglement, a transient immune-synaptic contact between two mobile cells, and the strength of this interaction is reflected mainly in the size of the engaged cell surface rather than in the duration of contact. Mouse ICOSL interacting with ICOS on the surface of T_{FH} cells promotes the release of stored CD40L to the T_{FH} cell surface[7]. CD40L interacting with CD40 in turn stimulates upregulation of ICOSL expression in mouse germinal-centre B cells, thereby creating a positive-feedback loop between T_{FH} and B cells that facilitates a process known as affinity-based selection[7]. This is the process whereby B cells with the potential to produce antibodies that bind most strongly to their targets are selected for[4].

In contrast to the functioning of mouse ICOSL, Papa and colleagues found that, in human germinal-centre B cells, a substantial fraction of ICOSL was already present and stored intracellularly (Fig. 1). Human ICOSL was not upregulated by CD40L stimulation, but instead, the stored protein was rapidly released in response to dopamine. With a similar effect to that of mouse ICOSL, human ICOSL also increased the area of contact between T_{FH} and B cells, and promoted the release of CD40L onto the T_{FH}-cell surface. Interestingly, human ICOSL was found to promote the transport of chromogranin B vesicles in T_{FH} cells towards the immunological synapse, and to promote dopamine release from T_{FH} cells. This means that there is also a positive-feedback loop between human T_{FH}

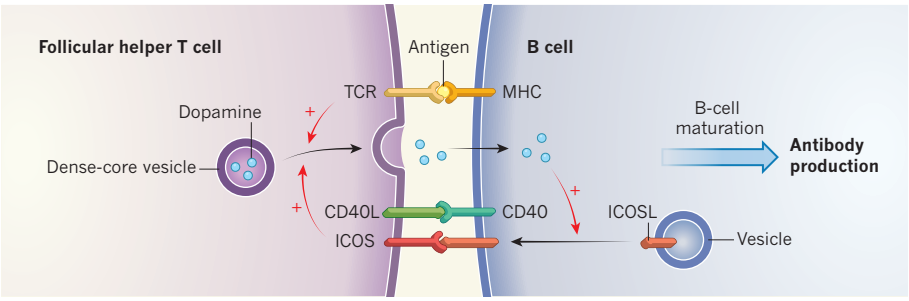

Figure 1 | Dopamine aids maturation of antibody-producing immune cells. Papa *et al.*[1] investigated the interaction between two types of human immune-system cell, known as B cells and follicular helper T cells, that leads to the formation of antibody-producing plasma cells. When a T-cell receptor (TCR) recognizes a peptide fragment, called an antigen, that is bound by proteins encoded by the major histocompatibility complex (MHC), this results in signalling interactions between B cells and T cells. The authors unexpectedly found that some of these signalling interactions are driven by the neurotransmitter molecule dopamine, which is present in T cells in a type of vesicle known as a dense-core vesicle. Dopamine released by a T cell is taken up by an interacting B cell, which leads to vesicle-mediated transport of the protein ICOSL to the B-cell surface. The ligand ICOSL then binds to the ICOS receptor protein on T cells. This ligand–receptor interaction leads to an increase in signalling between another receptor protein (CD40) and ligand molecule (CD40L) that is important for B-cell maturation. These examples (red arrows) of signalling crosstalk (dopamine driving the upregulation of ICOSL on the cell surface, and ICOS and TCR signalling promoting dopamine release) are proposed to promote B-cell maturation into an antibody-producing cell.

and B cells through the immunological synapse, similar in principle to that in mice, but distinct in molecular detail.

Although dopamine has long been implicated in the regulation of immune responses[9,10], Papa *et al*. now establish that it has a role in signal transmission across human immunological synapses. Dopamine has a half-life of 1 to 2 minutes in the bloodstream[11], and probably a similarly short extracellular half-life in germinal-centre tissues. These features might be desirable for ensuring that signals are transmitted between mobile T_{FH} cells and B cells, both efficiently and with a high degree of specificity[3]. Out of all the subclasses of CD4-expressing T cells, T_{FH} cells probably have the most stringent requirement for efficiency and specificity at the immunological synapse to enable their proper functioning. Consistent with this idea, Papa and colleagues found that dopamine is used by human T_{FH} cells, but not by human T cells of other subclasses.

A surprising finding made by the authors is that mouse T_{FH} cells do not seem to use dopamine to communicate with B cells, even though other immune signalling molecules such as CD40L can be released and removed from T cells with fast kinetics in mice. It will be interesting to discover how human T_{FH} cells develop to acquire the machinery for dopamine synthesis and storage, and at what stage and how mouse T_{FH} cells develop differently from their human counterparts. How B cells trigger dopamine release from T_{FH} cells is another interesting question that is prompted, and only partially resolved, by Papa and colleagues' work.

The existence in both the human and mouse systems of an intercellular positive-feedback loop highlights the importance of this aspect of the system for productive germinal centres[3]. Previous evidence from mouse experiments[7] suggests that a feedback loop promotes the antibody affinity-selection process in B cells. On the basis of computer modelling, Papa *et al*. speculate that the fast dopamine–ICOSL feedback kinetics in the human system accelerates the formation of plasma cells, but does not affect the affinity-selection process. This prediction could be tested in future experiments.

Human B cells express many types of G-protein-coupled dopamine receptor, and it is not always straightforward to pinpoint their specific roles using chemical inhibitors, activators or blockers. Papa and colleagues' study provides an impetus to use genetic approaches to systematically investigate the relationship between dopamine-receptor function and the regulation of B-cell biology. Closer attention should also be paid to whether any mutations in dopamine-related pathways cause immune-system defects. Moreover, when disease characteristics or treatment options are associated with changes in dopamine, the possible involvement of, and implications for, antibody-mediated immunity should be considered. ■

Hai Qi *is at the Institute for Immunology, Department of Basic Medical Sciences, School of Medicine, Tsinghua University, Beijing 100084, China, and the Tsinghua-Peking Center for Life Sciences.*
e-mail: qihai@tsinghua.edu.cn

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