demonstrated its viability in space, this simple and efficient system could be a game-changer for systems using small satellites[3]. The number of small satellites launched into space increased steadily from 39 in 2011 to 389 in 2019, before jumping to 1,202 in 2020 (see go.nature.com/3ggb3yc). There is therefore much research going on globally into the development of similar engines. Busek, a spacecraft-propulsion company in Natick, Massachusetts, has a line of thrusters with powers ranging from 100 W to 20 kW. All of these engines are capable of operating using xenon or iodine, depending on the requirements of the mission.

The drive to reduce the cost and increase the lifetime of space assets is now stronger than ever — a push designed to capitalize on the lower costs associated with reusable rockets that can launch multiple satellites simultaneously. For large satellite constellations, such as the 42,000-satellite Starlink system planned by aerospace-manufacturer SpaceX in Hawthorne, California, changing the propellant from xenon or krypton to iodine would lead to multi-million-dollar savings. Further savings could come from simplifying the propellant's storage and supply technology, which would also save money by decreasing the mass of the thruster.

Satellite constellations are not the only type of space mission that could benefit from this technology. For example, the research company Varda Space Industries in Torrance, California, is building the world's first commercial zero-gravity industrial park in space. The facility will manufacture products that are difficult to build on the surface of Earth owing to the effects of gravity, such as 3D-printed arteries and hearts, and certain pharmacological drugs. The feasibility of 3D printing tissue constructs in space was demonstrated in 2018 by the Moscow-based biotechnology company 3D Bioprinting Solutions, working at the International Space Station[4]. Cheap iodine-based thrusters might reduce the cost of in-orbit manufacturing and help the factory to manoeuvre the product out of orbit and back to Earth.

However, the use of iodine thrusters is not without its challenges. Iodine is highly corrosive, presenting a potential danger to electronics and other satellite subsystems — Rafalskyi and co-workers had to use ceramics and polymers to protect the metal components of their system. They also needed to strengthen the solid iodine by embedding the crystals in a porous aluminium oxide matrix, which added to the weight and volume of the system. Finally, solid iodine requires a relatively long time (around 10 minutes) to be heated to sublimation temperature, which might not make the thruster responsive enough to avoid collisions while in orbit. These challenges need to be addressed before this technology can be incorporated safely into working satellites. Nevertheless, now that it has been validated in space, the system developed by Rafalskyi and colleagues is an impressive contribution to the rapidly changing landscape of electric propulsion technologies.

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**The authors declare no competing interests.**

Immunology

# A neurotransmitter limits antitumour responses

**Daniel L. Kaufman**

Analysis of immune cells shows that, unexpectedly, B cells secrete GABA, a molecule best known as a neurotransmitter. B-cell-derived GABA can modulate immune responses against tumours, raising the prospect of new therapies. **See p.471**

Efforts to better understand how immune cells function hold the promise of providing information that might lead to improved clinical treatments. On page 471, Zhang *et al.*[1] present results that point the way to the development of new approaches to enhance anticancer therapies.

The authors investigated changes in metabolite molecules that occurred in mouse lymph nodes — a tissue rich in immune cells — after the animals had been exposed to a foreign protein through immunization. Using state-of-the-art technologies, Zhang and colleagues compared the metabolites in lymph nodes near the immunization site with those in lymph nodes on the opposite side of the animal's body. They found that levels of around 200 metabolites were significantly different in lymph nodes near the immunization site, particularly metabolites associated with activation of a system called the glutamate pathway.

Zhang and colleagues repeated this experiment using mice deficient in immune cells called B cells and T cells, and, by comparing these animals with those not lacking immune cells, found that the predominant metabolic changes after immunization occurred in B cells (which are antibody-producing cells). Surprisingly, the major metabolite upregulated in response to immunization was γ-aminobutyric acid (GABA), which was not previously known to be made by B cells. GABA acts as a neurotransmitter in the brain, with key roles in neurodevelopment. It is linked to certain neurological disorders[2], and is produced through the glutamate pathway.

To explore GABA synthesis in immune cells, the authors investigated B cells and T cells from mice and humans. They activated the cells *in vitro* using antibodies that bound to a key defence receptor on the cells. They then exposed the cells to a pulse of an amino acid called glutamine that was labelled with an isotope, and traced its metabolism. As expected, the glutamine was converted into glutamate, a molecule that was then made into GABA by the enzyme glutamic acid decarboxylase (two versions of this enzyme are dubbed GAD65 and GAD67). Levels of labelled GABA in B cells, but not in T cells, increased following activation of the cell, and B cells secreted labelled GABA. The authors report that T cells do not express GAD65 or GAD67, whereas B cells express GAD67. Together, these results demonstrate that immune stimulation induces mouse and human B cells to synthesize and secrete GABA (Fig. 1).

Previous studies investigating autoimmunity found that T cells express type A GABA ($GABA_A$) receptors. Activation of these receptors through GABA binding opens a chloride channel in the receptor. This opening leads to the inhibition of inflammatory types of T cell called helper CD4 T cells and killer CD8 T cells[3–6], and both T-cell types are key contributors to tissue damage in autoimmune disease. Activation of $GABA_A$ receptors also boosts the numbers of a type of T cell called a regulatory T cell, which dampens

inflammation[5,7]. Other cells of the immune system, called antigen-presenting cells, also have $GABA_A$ receptors. They include macrophages, dendritic cells and NK cells, which aid defence by presenting fragments of foreign proteins called antigens to T cells. The activation of $GABA_A$ receptors on these antigen-presenting cells reduces their pro-inflammatory properties[4,8,9]. Several laboratories have harnessed the anti-inflammatory actions of molecules that activate $GABA_A$ receptors to inhibit autoimmunity in mouse models of diseases such as type 1 diabetes, multiple sclerosis and rheumatoid arthritis, as well as to tackle severe disease caused by a coronavirus that infects mice[4–7,9].

GABA inhibits neurotransmission by preventing the neuronal depolarization process that is needed for signal transmission by neurons. By contrast, the activation of T-cell $GABA_A$ receptors leads to depolarization, which limits calcium entry into the cell and reduces cellular replication and inflammatory activities[10]. Extending those previous studies, Zhang and colleagues report evidence from *in vitro* experiments that a drug called muscimol that specifically activates $GABA_A$ receptors limits the activation and proliferation of CD8 T cells, whereas a $GABA_A$-receptor inhibitor called picrotoxin boosts calcium levels in mouse and human CD8 T cells.

The authors investigated whether GABA secreted by B cells affected antitumour responses *in vivo*. They focused on a type of cancer called colon carcinoma, and studied a mouse model of this tumour in which cancer growth is reduced in animals deficient in B cells, a finding that suggests that B-cell-derived factors limit antitumour responses in this model[11,12]. The authors report that tumours in B-cell-deficient mice had more tumour-infiltrating CD8 T cells than did tumours in control animals (tumour-bearing wild-type mice that had B cells). Moreover, the CD8 T cells in the B-cell-deficient mice had higher levels of molecules associated with cell-killing capacity (cytotoxic molecules) and with inflammation than did such T cells in the control mice.

GABA administration had no effect on tumour growth in wild-type mice, whereas in B-cell-deficient mice it increased the tumour to a size closer to that of tumours found in the wild-type mice. This GABA treatment lowered the number of tumour-infiltrating CD8 T cells and reduced the production of cytotoxic and inflammatory molecules in B-cell-deficient mice. Moreover, in control animals given a $GABA_A$-receptor-specific inhibitor, tumour size was reduced and the cytotoxicity of tumour-infiltrating CD8 T cells increased. These findings indicate that B-cell-secreted GABA dampens the response of tumour-cell-killing CD8 T cells *in vivo*.

Immune responses to tumours can sometimes fail to curb cancer growth because the inflammatory anticancer immune response in the tumour is dampened. Tumour-associated macrophages often have a role in this suppression. Continuing to work with the colon cancer mouse model, the authors observed that tumour-associated macrophages in B-cell-deficient mice showed enhanced expression of pro-inflammatory pathways compared with such macrophages in control mice. These pathways were reduced if the B-cell-deficient mice received GABA. Furthermore, tumour-associated macrophages isolated from wild-type mice that had received a $GABA_A$-receptor inhibitor showed increased expression of genes related to calcium signalling and inflammatory cytokines. GABA also enhanced the differentiation and numbers of macrophages that had anti-inflammatory characteristics. Hence, B-cell-secreted GABA can shift the antitumour responses of both tumour-associated macrophages and CD8 T cells towards less inflammatory activity.

Finally, the authors generated mice whose B cells did not express GAD67 and that were therefore GABA-deficient. Crucially, tumour cells implanted into these mice showed reduced growth, and the animals' tumour-infiltrating CD8 T cells had greater cytotoxicity and stronger pro-inflammatory properties than did tumour cells in control animals whose B cells expressed GAD67.

Together, Zhang and colleagues' evidence convincingly demonstrates the surprising finding that B cells secrete GABA, which can promote anti-inflammatory macrophages and inhibit the antitumour responses of CD8 T cells through their $GABA_A$ receptors. The results should stimulate further preclinical (animal) and clinical studies.

One question to be considered is whether GABA, which is widely consumed in various health supplements, could have adverse effects in humans. The authors found that GABA administration increased tumour size in B-cell-deficient mice to be more like that in wild-type mice, but did not affect tumour size in the wild-type mice. Currently, there have not been associations reported between GABA consumption in supplements, or the use of drugs that specifically enhance $GABA_A$-receptor activity – such as alprazolam (Xanax), which is used to treat anxiety disorders – and changes in tumour mass. However, this possibility should be examined. It will be of interest to elucidate the types of tumour for which B-cell-secreted GABA modulates antitumour responses, and whether this modulation occurs in the bone marrow, lymph nodes and tumour microenvironment.

Another area for future study will be to investigate the effect of B-cell-secreted GABA on pro-inflammatory CD4 T cells, and whether the response of regulatory T cells is enhanced in tumours[11] and in tissues that have become inflamed through autoimmune disease. Moreover, it would be worth further investigating pharmacological inhibition of immune-cell $GABA_A$ receptors, or the use of $GABA_A$-receptor-deficient T cells or antigen-presenting cells that have been modified to boost their attack on tumour cells (in what are known as adoptive-cell anticancer treatments), for their potential

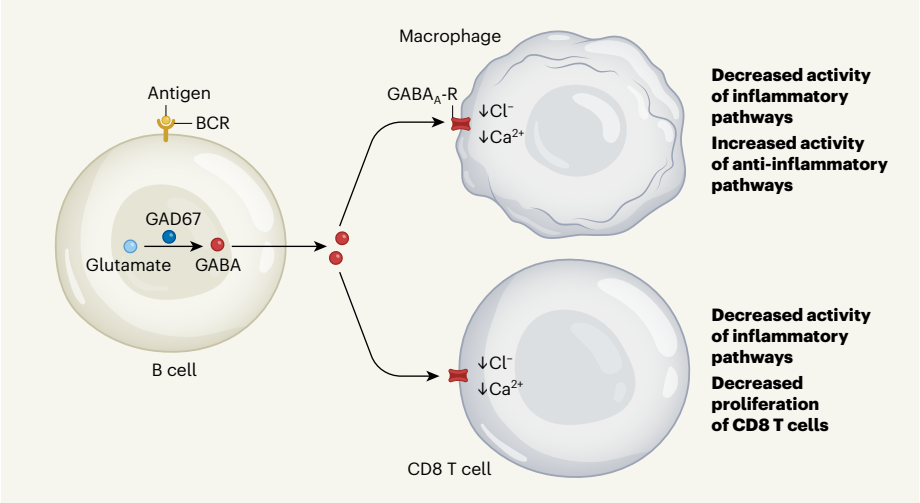


**Figure 1 | Release of GABA by B cells inhibits antitumour responses of immune cells.** Zhang *et al.*[1] report that mammalian immune cells called B cells secrete the molecule GABA, which is also a neurotransmitter in the brain. B cells synthesize GABA when they detect a protein fragment called an antigen (from a foreign protein, for example) through their B-cell receptor (BCR). These activated B cells use the enzyme GAD67 to convert the molecule glutamate into GABA, which is then secreted, presumably not within a vesicle, as occurs in neurons[13]. GABA can bind to and activate type A GABA receptors ($GABA_A$-Rs) on nearby immune cells, such as macrophages and CD8 T cells. This opens ion channels in the receptors, reducing the intracellular levels of calcium ($Ca^{2+}$) and chloride ($Cl^-$) ions. These changes dampen inflammatory pathways in, and the proliferation of, immune cells and boost anti-inflammatory pathways, thereby hindering antitumour immune responses.

as therapeutic approaches. If promising evidence emerges from preclinical studies, such investigations could set the stage for clinical trials.

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**The author declares competing interests. See go.nature.com/3bbtr19 for details.**
**This article was published online on 3 November 2021.**

In retrospect

# Fifty years of the brain's sense of space

**Isabel I. C. Low & Lisa M. Giocomo**

Neurons in a brain region called the hippocampus were found to be selectively active when rats are in a specific spatial location during natural navigation. The discovery launched research efforts into how the brain supports spatial memory.

Nearly all of our conscious experiences incorporate a sense of space: the restaurant where we ate, our route home, where we found our teacup, navigating to our favourite chair. This sense of space is how we know where we are, remember where we have been and plan where we want to go. But how the brain generates this sense and uses it for memory or navigation remained a mystery for many years. A landmark paper in 1971 by John O'Keefe and Jonathan Dostrovsky, published in *Brain Research*, offered the first glimpse into how neurons in the mammalian brain compute an animal's sense of space[1].

In their short communication, O'Keefe and Dostrovsky used microelectrodes that had been developed a few years previously to record the electrical signals, known as action potentials, from neurons in the brains of rats. Studying animals exploring a raised platform, the authors targeted the microelectrodes to a region nestled below the brain's surface called the hippocampus, because work in humans and rodents had demonstrated that damage to the hippocampus impaired memory and navigation[2,3]. There was no particular task at hand — the rats spontaneously ate, groomed, drank, slept and moved around naturally. Strikingly, the activity of some hippocampal neurons was tightly correlated with the animal's location in physical space. These neurons were silent as the rat moved through much of the environment but became active when the animal reached one small portion of the platform (Fig. 1). Because each neuron often fired action potentials while the animal was in just one position, O'Keefe and Dostrovsky called these neurons place cells and dubbed the location in the animal's environment where the neuron showed the most activity the neuron's place field.

Before O'Keefe and Dostrovsky's seminal study, researchers had proposed that animals, through exploration, could learn associations between environmental features (such as landmarks) and their own position to build an internal model — or 'cognitive map' — of the external world[4,5]. This cognitive map would allow animals to flexibly navigate their environment. It seemed possible that place cells might support such a cognitive map. If so, then, rather than these cells simply responding to a specific sensory cue (such as a visual feature visible only when in one portion of the environment), place-cell activity should represent a more abstract calculation of the animal's position. Further experiments supported this possibility, showing that some place cells remained active in the dark[6] and that place-cell activity was largely consistent, regardless of the direction in which the animal was heading[7].

The memory and navigation research field ignited, ultimately extending the role of place cells from signalling an animal's spatial position to functioning as a potential substrate for spatial memory. The electrode-recording approaches used by O'Keefe and Dostrovsky became the workhorse for studying the electrical signals of hippocampal neurons for decades, supporting stable and robust recordings of place-cell activity across a vast repertoire of environments and behavioural tasks. Using environments that differed in shape or landmark features, studies revealed that place cells 'learn' about and respond to changes to an environment[8,9]. For example, when rats explore a square box and then a circular arena,

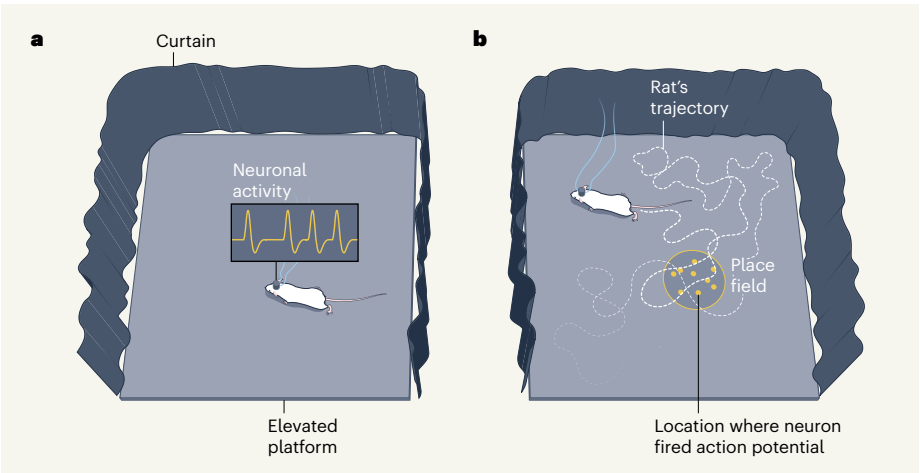


**Figure 1 | The discovery of place cells representing a rat's position in space. a**, In their 1971 paper, O'Keefe and Dostrovsky[1] recorded the electrical activity (including signals called action potentials) of neurons in a part of the brain called the hippocampus in rats exploring an elevated platform with a curtain around three sides. **b**, The authors found that some neurons showed activity only when the rat was in a particular region of the environment. The authors dubbed these neurons place cells and the region in which they became active, their place fields. A schematic illustration of an example place cell's place field, defined by the occurrence of action potentials when the animal was in that region, is shown here.