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Glutamate joins the ranks of immunomodulators

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Abstract

Elevated amounts of glutamate, which acts as a neurotransmitter but is also a neurotoxin, are a hallmark of the autoimmune neurological disease multiple sclerosis and may contribute to its pathology. The discovery that a receptor for glutamate can inhibit the development of autoimmunity and protect from neuroinflammation in a mouse model of multiple sclerosis suggests that glutamate may also have a protective role and that its receptor may represent a therapeutic target (pages 897–902).

Although we are inclined to view the nervous and immune systems of the body as separate entities, the reality is far more complex. At the molecular level, crosstalk between the nervous and immune systems has been well documented. Many molecules and mediators are common to both, and substances produced by the immune system act on the nervous system and vice versa. As an example, the cytokine interleukin-1 (IL-1), which is fundamental to the process of inflammation, was discovered largely because of its role in immunoreactive innervation of the hypothalamus to elicit fever¹. Conversely, the neurotransmitter nitric oxide is also produced by cells of the immune system and has a role in inflammation and immunomodulation^{2,3}.

In this issue of *Nature Medicine*, Fallarino *et al.*⁴ add the neurotransmitter glutamate to the list of substances that participate in crosstalk between the nervous and immune systems. High amounts of glutamate are found in the brain of individuals with multiple sclerosis, and whereas this is widely thought to contribute to neurotoxicity, the authors now present an alternative possibility—a role for glutamate in driving a regulatory T cell response that ameliorates neuroinflammation in a mouse model of this paralyzing disease. They show that this increase in regulatory T cells is mediated by the metabotropic glutamate receptor-4 (mGluR4) expressed on dendritic cells (DCs), a cell type crucial for supporting an immune response. Their data suggest that glutamate may have a protective role in inflammatory neurodegenerative diseases.

Glutamate is a highly abundant excitatory neurotransmitter and is essential for many aspects of normal brain function such as learning and memory⁵. Its actions are mediated by ionotropic (ion channel-forming) and by metabotropic (G protein-activating) glutamate receptors⁵. In excess, however, glutamate is harmful and causes neuronal death through a massive calcium influx via ionotropic glutamate receptor channels, with consequent damage to mitochondria and activation of proapoptotic genes. Glutamate toxicity occurs as part of the ischemic cascade associated with spinal cord injury, stroke, traumatic brain injury and in

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various diseases of the central nervous system, including Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease and multiple sclerosis⁵.

The adaptive immune response is orchestrated by antigen-specific T cells, which differentiate after activation into one of several functionally distinct T 'helper' lineages known as T_H1, T_H2 and T_H17 (ref. ⁶). Each produces a distinct assortment of cytokines and chemokines under control of their respective lineage-specific transcription factors T-bet, GATA3 and ROR- γ t. Whereas their role is to protect us from various types of pathogens, they can also be involved in tissue pathology⁶. For example, T_H2 cells are involved in allergy and asthma, and T_H1 cells, and even more so T_H17 cells, are involved in autoimmune diseases such as experimental autoimmune encephalomyelitis (EAE), a model of multiple sclerosis induced in mice by immunization with an antigenic peptide derived from brain myelin.

T cells respond to their antigen displayed on the surface of DCs, which also express co-stimulatory molecules and polarizing cytokines, and direct the responding T cells to adopt a particular lineage (Fig. 1). For example, IL-12 and IL-27 produced by DCs will specifically drive T-bet expression in the T cell, promoting a T_H1 response dominated by the cytokine interferon- γ . Alternatively, release of transforming growth factor- β ; (TGF- β), IL-1, IL-6 and IL-23 leads to ROR- γ t expression by the T cells and differentiation toward the T_H17 lineage. Expression of TGF- β in the absence of IL-6 also directs the induction of another T cell transcription factor known as FoxP3. FoxP3 can directly suppress expression of ROR- γ t and causes the T cells to adopt a regulatory phenotype, yielding T regulatory cells (T_{reg} cells) that inhibit inflammatory effector T cells.

Through the expression of these different cytokines, DCs act as master regulators of the immune response, controlling not only whether an inflammatory immune response will occur, but also its nature, depending on the T cell lineage that is induced⁶. What environmental cues control the function and decision making of these master regulators? Fallarino *et al.*⁴ show that one of these cues is glutamate, which acts through metabotropic glutamate receptors that are expressed by DCs.

Previous studies have examined the effect of various neurotransmitters on the immune response, but they preceded the identification of T_H17 cells as pathogenic effectors and largely ignored a role for DCs. Armed with the information now available regarding the T_H17 response, the authors used a combination of mice deficient in mGluR4 and specific allosteric compounds that enhance mGluR4 receptor signaling in wild-type mice to examine the role of this receptor in EAE⁴. They found that mice deficient in mGluR4 developed exacerbated disease with a higher mortality, whereas enhanced glutamate signaling through mGluR4 ameliorated disease and favored the induction of T_{reg} cells at the expense of T_H17 development⁴. Interestingly, although high receptor expression was found on T cells and on DCs, the protective effect of mGluR4 signaling was mediated entirely by DCs and occurred via mGluR4's inhibitory effect on intracellular activation of cAMP. Inhibition of cAMP activation prevents IL-6 and IL-23 production and skews the DC cytokine response to a profile favoring induction of T_{reg} cells, which turn out to be responsible for the resulting protection from EAE in mice—as shown by the ability of T cells obtained from mice protected by mGluR4 stimulation to transfer protection to untreated recipients, which was reversed by removal of T_{reg} cells.

Notably, human DCs also expressed mGluR4, and activation of this receptor with the same allosteric stimulator used in mice had comparable effects in human DCs. Currently approved therapies for autoimmune neurological diseases have variable efficacy, major side effects and can only slow, and not stop, the neurodegenerative process⁷. Although the data of

Fallarino *et al.*⁴ are promising, more studies are needed to clarify issues relevant to the clinical setting. Protection, for instance, does not seem to be maintained after treatment cessation, despite the development of T_{reg} cells—a disappointing result. Further treatment, however, is not required to maintain T_{reg} cell-mediated protection upon transfer of these cells to new recipients⁴. Whereas mGluR4 stimulation is effective in disease prevention, it is unclear whether it would be effective after the onset of clinical symptoms.

This study also raises questions relevant to an ongoing clinical trial for treatment of Parkinson's disease in which a mGluR4 enhancer is used to reduce glutamate release in the brain⁸. If this therapy proves effective, could hitherto unknown immunological effects be involved? Could suppression of T_H17 responses, important in antimicrobial defense, be an unwanted side effect of this treatment? Answers to these questions could have implications not only for treatment of conditions associated with glutamate toxicity, but also for a broad range of debilitating autoimmune disorders that have been linked to aberrant T_H17 responses, including rheumatoid arthritis, psoriasis, inflammatory bowel disease and uveitis^{9,10}.

The study by Fallarino *et al.*⁴, and others to come, will continue to blur the distinctions between the signals driving the nervous, immune and endocrine systems, revealing unknown therapeutic potential and also highlighting the consequences that perturbing one of them may have on the others.

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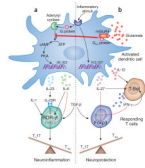


Figure 1.

Glutamate activation of mGluR4 signaling in dendritic cells prevents the production of IL-6 and IL-23, favoring the development of T_{reg} cells over T_{H17} cells in EAE. In the absence of mGluR4, DCs respond to an inflammatory signal such as LPS by upregulating both T_{H1} -specific (IL-12 and IL-27) and T_{H17} -specific (IL-6 and IL-23) cytokines through different pathways. Transcription of IL-6 and IL-23 is induced via the production of cAMP, which is catalyzed from ATP by the enzyme adenylyl cyclase, and, in turn, activates downstream mediators such as protein kinase A (PKA), which leads to gene expression. These cytokines, along with TGF- β and IL-1, induce the transcription factor ROR- γ t in the responding T cell, upregulating T_{H17} -specific cytokines and the IL-23 receptor, which is required later for maintenance of the T_{H17} phenotype. IL-6 directly suppresses Foxp3, leading to the promotion of T_{H17} at the expense of T_{reg} cells and the development of neuroinflammation. Fallarino *et al.*⁴ show that activation of mGluR4 by glutamate inhibits adenylyl cyclase and the production of cAMP, preventing expression of IL-6 and IL-23. In their absence, Foxp3 is upregulated by the activating T cell in the presence of TGF- β and blocks T_{H17} differentiation by direct inhibition of ROR- γ t, tipping the balance toward a neuroprotective response. The T_{H1} response is unaffected by this process, and IL-27 and interferon- γ (IFN- γ) also contribute to the promotion of T_{reg} cell differentiation through inhibition of ROR- γ t.