What are intracellular and extracellular antibodies and what do the differences mean for patients with autoimmune encephalitis?

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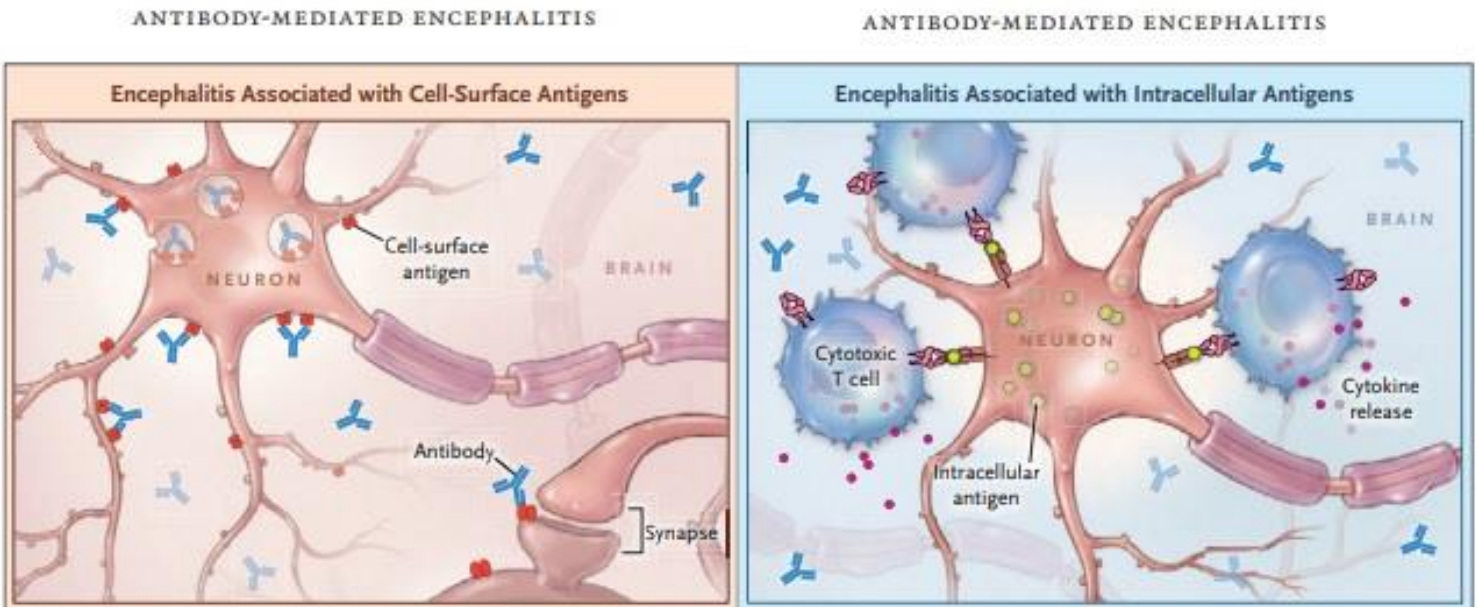
The staff at IAES is proud to present to all of you another wonderful article/blog from the amazing team at PennNeuroKnow. Since 2019 IAES has been extremely lucky to be in partnership with the PennNeuroKnow(PNK) team to help us all better understand complex medical issues related to AE and neurology in general. The talented PNK team continues to keep us up-to-date and help clarify the complexities we face each day along our AE journey, and we are eternally grateful! You can find out much more about this stellar group at: https://pennneuroknow.com/

There are many subtypes of autoimmune encephalitis (AE) that vary in their causes, the symptoms that patients experience, and what treatments are most effective. One of several factors that distinguish these different subtypes of AE is whether they involve intracellular or extracellular antibodies. In this post, we will explore exactly what these terms mean and how they contribute to the differences between types of AE.



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What are intracellular and extracellular antibodies?

When a virus or bacteria enters our body, our immune system mounts an attack to destroy the foreign invader and protect us from harm. If our immune system is like an

army ready for battle, then **antibodies** are like the scouts sent ahead of the battalion, patrolling for signs of a threat. Just like security personnel might scan ID badges to determine who is allowed in a building, each antibody is tasked with looking for a particular feature of something that the body has deemed harmful, called an **antigen**[1]. You might have heard antibodies discussed in reference to COVID-19, where infection with COVID-19 or vaccination can cause your body to produce antibodies that recognize features of the COVID-19 virus[2]. When antibodies are already present in the body, they can recognize the newly-arrived COVID-19 virus and mount an attack more quickly, helping to avoid a more serious infection.

This ability to quickly mount a defense against a threat before getting too sick is what makes antibodies an important part of our body's immune system army. However, antibodies are only helpful if they recognize and defend against foreign substances that are harmful. Unfortunately, this isn't the case in AE. Patients with AE have antibodies that bind to proteins found in their own cells, called **autoantibodies** (the prefix "auto" means self, so autoantibodies are antibodies that bind the body's own proteins)[3]. Autoantibodies trigger the body's immune system to attack itself, leading to the many symptoms of AE.

Each antibody can recognize only a small part of a whole cell, and there are many different parts of a cell that an antibody can recognize. What distinguishes extracellular from intracellular antibodies is whether their antigen (the ID badge they're looking for) is inside or outside of the cell[1,4]. **Extracellular antibodies** recognize antigens that are on the outer surface of the cell ("extra" meaning outside). Conversely, **intracellular antibodies** recognize antigens that are inside the cell ("intra" meaning inside). The intracellular antibodies inside the cell trigger a different set of immune reactions than the extracellular antibodies outside of the cell.

Which kinds of AE involve intracellular versus extracellular antibodies?
Subtypes of AE are distinguished by what kind of autoantibody a patient has[4], which is why they are typically named after the antigen that the autoantibody recognizes. For example, patients with anti-NMDAR AE have antibodies that recognize NMDA receptors. Types of AE associated with antigens outside the cell involve extracellular antibodies and types of AE associated with antigens inside the cell involve intracellular antibodies.

Many of the most common subtypes of AE involve extracellular antibodies[4,5]. Most are associated with antibodies that recognize a kind of protein that sits on the surface of the cell called a **receptor**. Receptors recognize and bind specific molecules and send signals that tell the cell how to respond. The receptors on neurons, a type of brain cell, are especially important because one neuron communicates with another by releasing molecules that can be recognized by the other neuron's receptors. When antibodies bind the receptors, they activate an immune response and disrupt the ability of those receptors to participate in neural signaling. This leads to the many neurological symptoms of AE. Subtypes with these kinds of antibodies include anti-NMDAR AE[6],

anti-AMPAR AE[7], anti-mGLUR5 antibody encephalitis[4,5], GlyR antibody encephalitis[4], anti-$GABA_a$ AE[8], and anti-$GABA_b$ AE[9]. Several other extracellular antibodies associated with AE have antigens that sit on the cell's surface and help with neuronal signaling but aren't receptors themselves. Subtypes of AE with these kinds of antibodies include LGI1-antibody encephalitis[10], CASPR2-antibody encephalitis[11], and DPPX-antibody encephalitis[4,5].

Subtypes of AE associated with intracellular antibodies are less common[4,5]. One example is GAD-antibody encephalitis[12]. Patients with this form of AE have antibodies that target Glutamic Acid Decarboxylase (GAD), a protein found inside the cell that is needed to synthesize GABA, a special type of molecule that is necessary for some kinds of neural signaling. Other subtypes of AE that target intracellular proteins are anti-Hu encephalitis[5], and Ma2-antibody encephalitis[13].

How are subtypes of AE associated with intracellular antibodies different from subtypes of AE associated with extracellular antibodies?

One big distinction is that most subtypes of AE associated with intracellular antibodies are also associated with tumors[4]. These subtypes of AE are called **paraneoplastic**. Paraneoplastic AE can occur when tumor cells express proteins on their surface that are normally expressed elsewhere. Sometimes this includes proteins that are normally found inside healthy neurons. To recognize and fight the tumor, the body's immune system creates antibodies that recognize these proteins. These antibodies don't distinguish the proteins found in the tumor cells from the healthy proteins found in neurons, so when they reach the brain, they also bind the naturally-occurring proteins in neurons and trigger the immune response responsible for the symptoms of AE[14].

Patients with subtypes of AE associated with intracellular antibodies also tend to have poorer outcomes and respond worse to immunotherapy than patients with subtypes associated with extracellular antibodies[4,15]. This is because many of the symptoms of AE associated with extracellular antibodies are thought to result from the antibodies disrupting the normal function of the cell-surface proteins that they target. Conversely, the presence of intracellular autoantibodies typically accompanies an immune response against neurons more broadly that results in neuronal death. This means that successful treatment can often reverse symptoms of AE resulting from extracellular antibodies, as limiting the action of the antibodies allows the neurons to function normally, whereas even after treatment, symptoms do not typically reverse in subtypes of AE associated with intracellular antibodies, as many neurons have already died. For patients with paraneoplastic AE, removing the tumor is also an important step toward relieving symptoms[15].

Despite general differences in outcomes for subtypes of AE associated with extracellular and intracellular antibodies, early detection and treatment are key to successful outcomes for all subtypes of AE[4]. Determining which type of AE a patient has can have an important impact on how doctors choose to treat and manage the disease. This distinction is also important for researchers developing new treatments

and possible cures, as approaches that might work for one type of AE may not work for others. Determining which patients will be most receptive to a particular new treatment leads to better outcomes for clinical trials, which means more treatment options for all patients.

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