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Review

Molecular and cellular mechanisms underlying anti-neuronal antibody mediated disorders of the central nervous system

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ABSTRACT

Over the last decade multiple autoantigens located on the plasma membrane of neurons have been identified. Neuronal surface antigens include molecules directly involved in neurotransmission and excitability. Binding of the antibody to the antigen may directly alter the target protein's function, resulting in neurological disorders. The often striking reversibility of symptoms following early aggressive immunotherapy supports a pathogenic role for autoantibodies to neuronal surface antigens. In order to better understand and treat these neurologic disorders it is important to gain insight in the underlying mechanisms of antibody pathogenicity. In this review we discuss the clinical, circumstantial, in vitro and in vivo evidence for neuronal surface antibody pathogenicity and the possible underlying cellular and molecular mechanisms. This review shows that antibodies to neuronal surface antigens are often directed at conformational epitopes located in the extracellular domain of the antigen. The conformation of the epitope can be affected by specific posttranslational modifications. This may explain the distinct clinical phenotypes that are seen in patients with antibodies to antigens that are expressed throughout the brain. Furthermore, it is likely that there is a heterogeneous antibody population, consisting of different IgG subtypes and directed at multiple epitopes located in an immunogenic region. Binding of these antibodies may result in different pathophysiological mechanisms occurring in the same patient, together contributing to the clinical syndrome. Unraveling the predominant mechanism in each distinct antigen could provide clues for therapeutic interventions.

Contents

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1. Introduction

Immune responses affecting neurons of the central or peripheral nervous system can result in a broad spectrum of neurological syndromes ranging from encephalomyelitis to peripheral neuropathies. Sometimes these immune responses are parainfectious (e.g. Guillain Barré syndrome) and the neurological symptoms result from molecular mimicry. In other patients the disorder is paraneoplastic (e.g. anti-Yo paraneoplastic cerebellar degeneration (PCD) in ovarian cancer) in which ectopic expression of neuronal antigens by cancer cells induces immune activation. However, in many patients with suspected immune-mediated neurological syndromes the trigger of the immune response remains to be identified. When the central nervous system (CNS) is involved, these syndromes are generally called autoimmune encephalitis. Patients predominantly present with limbic encephalitis (LE), but other syndromes, including cerebellar ataxia (CA) and stiff persons' syndrome (SPS), have also been reported.

Starting with HuD in 1991 [1], many paraneoplastic antigens were identified using cDNA expression libraries in *Escherichia coli*. Strikingly, all the antigens determined using this method are located intracellularly. Since 2000, autoantibodies against neuronal cell surface antigens have been identified in autoimmune encephalitis patients, with or without an underlying tumor. The first antigens (metabotropic glutamate receptor 1 (mGluR1) and N-methyl D-aspartate receptor (NMDAR) [2,3]) were identified by recognition of an antigen specific staining pattern in rat brain sections. Subsequently, antigens (e.g. α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), gamma-aminobutyric-acid-B receptor ($GABA_BR$) and delta/notch-like epidermal growth factor-related receptor (DNER) [4–6]) were found by immunoprecipitation of the antigen using the patients' serum followed by mass spectrometry analysis.

Autoantibodies against paraneoplastic intracellular antigens, such as HuD, are probably an epiphenomenon of a hypothesized T-cell mediated immune response. They do not appear to be directly pathogenic but can be very useful as a marker of disease. Because of cytotoxic neuronal damage, these patients often do not respond well to immunotherapy and their symptoms are mostly irreversible. Antibodies to neuronal cell surface molecules can be pathogenic by disrupting the function of the target protein. Often these are molecules involved in neurotransmission and binding of the antibodies directly leads to disrupted neuronal function. The neurological symptoms may be reversible and respond relatively well to immune suppressive therapy (for review see [7]).

Since 2007, the focus of autoimmune encephalitis research has mainly been on identification of new surface antigens and providing a description of the clinical features, diagnostic tests and therapeutic options in patients with antibodies to cell surface molecules (for review see [8]). However, it is important to strengthen the evidence for antibody pathogenicity and to deepen our understanding of the pathophysiological mechanisms involved in autoimmune encephalitis. Such improved understanding will not only provide cues for therapeutic interventions but can also teach us about the physiological function of the target proteins.

In this review we summarize the evidence for pathogenicity of antibodies directed against neuronal cell surface antigens in the CNS (for overview see Table 1). Witebsky et al. drew up criteria to provide direct proof of the pathogenicity of autoantibodies, modeled after Koch's postulates: 1) antibodies have to be present in body fluids or bound to the site of pathology; 2) the antigenic target of the autoantibody should be known; 3) direct injection of patients' IgGs or immunization with a known antigen should clinically and pathologically reproduce the disorder in experimental animals [9]. One extra criterion was added by Drachman et al. in 1990; a reduction in antibody titer should co-occur with an improvement in clinical symptoms [10]. We classify the evidence of autoantibody pathogenicity into three distinct groups: The first group comprises clinical and circumstantial evidence, including symptom similarity following genetic or pharmacological disruption of the antigen, and response to immunotherapy. The second group includes studies in which functional effects of the antibodies have been demonstrated in vitro; the third group contains studies showing similar effects in vivo (Table 2).

In addition, we address the possible cellular and molecular mechanisms by which antibody–antigen interaction could disrupt the function of the target protein. These mechanisms include agonistic or antagonistic effects on the receptor by binding of the antibody to the ligand binding site or allosteric binding site (Fig. 1A). An example is antagonistic autoantibodies acting on mGluR1 [2]. Furthermore, antibodies might block the pore of ion channels. Though this has not been shown for autoantibodies, antibodies experimentally generated against the extracellular domain of different types of voltage gated ion channels are able to block the pore and selectively reduce ion currents [11]. Furthermore, disruption of the interaction with neighboring molecules (auxiliary subunits, anchoring molecules, other receptors/cell surface proteins) could interfere with antigen localization as has been shown for the NMDAR and Ephrin-B2 receptor [12] (Fig. 1B). A different effect of