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Review

Autoimmune channelopathies in paraneoplastic neurological syndromes☆

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ABSTRACT

Paraneoplastic neurological syndromes and autoimmune encephalitides are immune neurological disorders occurring or not in association with a cancer. They are thought to be due to an autoimmune reaction against neuronal antigens ectopically expressed by the underlying tumour or by cross-reaction with an unknown infectious agent. In some instances, paraneoplastic neurological syndromes and autoimmune encephalitides are related to an antibody-induced dysfunction of ion channels, a situation that can be labelled as autoimmune channelopathies. Such functional alterations of ion channels are caused by the specific fixation of an autoantibody upon its target, implying that autoimmune channelopathies are usually highly responsive to immuno-modulatory treatments. Over the recent years, numerous autoantibodies corresponding to various neurological syndromes have been discovered and their mechanisms of action partially deciphered. Autoantibodies in neurological autoimmune channelopathies may target either directly ion channels or proteins associated to ion channels and induce channel dysfunction by various mechanisms generally leading to the reduction of synaptic expression of the considered channel. The discovery of those mechanisms of action has provided insights on the regulation of the synaptic expression of the altered channels as well as the putative roles of some of their functional subdomains. Interestingly, patients' autoantibodies themselves can be used as specific tools in order to study the functions of ion channels. This article is part of a Special Issue entitled: Membrane channels and transporters in cancers.

Contents

1. Introduction

Paraneoplastic neurological syndromes (PNS) are disorders of the nervous system occurring in association with a cancer that are not related to any metabolic, infectious, degenerative, metastatic or iatrogenic cause [1]. PNS are thought to be secondary to an autoimmune reaction

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against neuronal antigens ectopically expressed by the underlying tumour (Fig. 1) [2]. The discovery of autoantibodies targeting such antigens has greatly improved our knowledge of these syndromes as they proved to be useful diagnostic and prognostic tools. In particular, autoantibodies targeting neuron membrane proteins such as ion channels, but not intracellular antigens, were associated to better outcomes and can improve with immunotherapy [3]. The standardization of antigen characterization techniques such as immunoprecipitation coupled to mass spectrometry has allowed the identification of numerous specific antigens involved in antibody-mediated neurologic syndromes, including ion channels or proteins modulating the functions of ion channels [4–7]. Ion channels expressed at the cell membrane are distributed throughout the nervous system and play an essential role in its homeostasis by tuning the polarization of neural cells. Ions traffic through resting membrane channels keeps the basal polarization of neural cells steady while activation of voltage or ligand-gated ion channels regulate excitation and inhibition of neurons by inducing either a depolarized or a hyperpolarized state, respectively [8]. In several autoimmune neurological syndromes, including PNS, patients' autoantibodies targeting ion channels or their associated proteins were shown to alter *in vitro* and *in vivo* the function of their targets, leading to the concept of neurological autoimmune channelopathies (NACs), that is, a group of various autoimmune neurological diseases sharing antibody-mediated ion channel dysfunction as a common pathogenesis. In this chapter, we will systematically review the autoimmune neurological syndromes related to antibodies against neuronal ion channels (Table 1), with a particular focus on the molecular mechanisms of ion channels dysfunction and the immunological mechanisms of autoantibody generation.

2. Anti-NMDA receptor encephalitis

N-methyl-D-aspartate receptors (NMDAR) are major ionotropic glutamate receptors of the central nervous system (CNS). NMDAR are mainly post-synaptic, and when activated they mediate an input of calcium and sodium that generates excitatory post-synaptic currents [9]. NMDAR activation requires the binding of glutamate and a co-agonist, either D-serine or glycine, and prior depolarization of the post-synaptic neuron [10,11]. Due to those characteristics, NMDAR act as molecular coincidence detectors and are involved in two major mechanisms of synaptic plasticity: long-term potentiation (LTP) and depression (LTD), which consist in respectively long-lasting enhancement and reduction of the synaptic transmission between two neurons after repetitive stimulation [9]. Those properties underlie the involvement of NMDAR in physiological and pathological processes such as memory [12], executive functions [13], excitotoxicity [14] and psychiatric disorders including schizophrenia [15]. NMDAR forms a heterotetrameric cation channel composed of a mix of an obligatory subunit, GluN1, with a variable composition of auxiliary subunits, GluN2 (A-D) and/or GluN3 (A-B) [16].

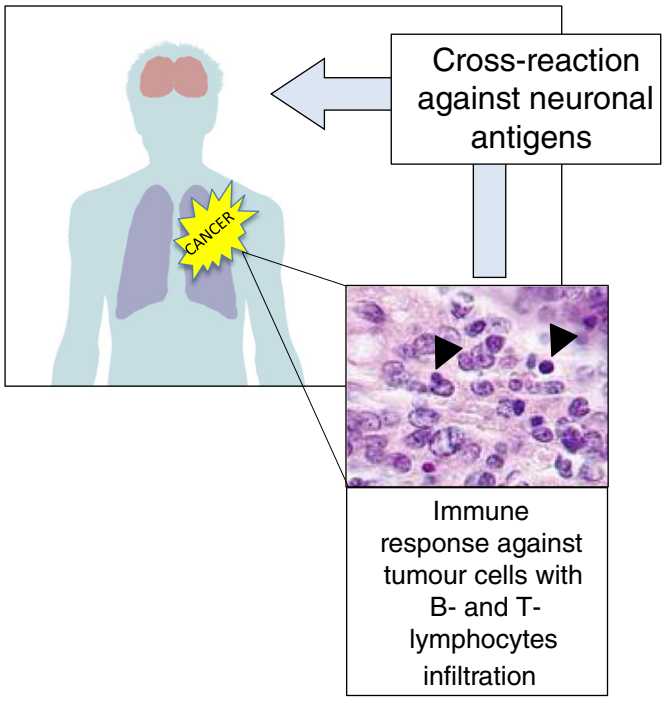

Fig. 1. Pathogenesis of the paraneoplastic neurological syndromes. Ectopic neuronal antigens expressed by some tumours are presented to the lymphocytes present within inflammatory infiltrates (arrowheads), leading to a cross-reaction against the same antigens normally expressed by neurons. As a result, an autoimmune reaction against the nervous system can develop and progress independently of the triggering cancer.

Autoimmune encephalitis with antibodies against the GluN1 subunit of NMDAR (NMDAR encephalitis) was described in 2007 and turned out to be one of the most frequent acute autoimmune encephalitis [7,17,18], even outnumbering infectious aetiologies in young patients [19]. NMDAR encephalitis mostly involves women less than 45 years [20]. A paraneoplastic origin is documented in 38-58% of the patients and involves an ovarian teratoma in 94% of the cases [17,20]. The disease follows a stereotyped course [17]. Seventy percent of patients experience prodromal symptoms such as fever, nausea, diarrhoea and upper respiratory tract disorders. The neurologic presentation usually begins with acute psychiatric symptoms and cognitive impairment, followed in days to weeks by a loss of consciousness alternating with periods of agitation and/or catatonia associated with oro-lingual and limbs dyskinesias. Dysautonomic symptoms and central hypoventilation are frequent and severe. During the comatose phase, dissociated responses to stimuli, similar to the effect of NMDAR antagonists such as ketamine, may be observed. Seizures can occur at any point of the disease course. Although the disease progression is approximately similar, initial presentation is slightly different in children who tend to experience more movement disorders and atypical neurological signs [20,21], and in men who are more subject to seizures [22]. More importantly, cancers are much less frequent in men and children [20,22], rending the diagnostic strategy less clear. Outcome is good in 81 % of the patients, but the recovering phase may last more than two years [20]. Relapses occur in 12-22% of the patients [20,23]. Prognosis seems to depend on the precocity of immunotherapy initiation, while immunotherapy after the first event is associated with a lower frequency of relapses [20,24]. Considering NMDAR encephalitis as a primarily antibody-mediated disease, the utility of B-cell depleting treatments, such as the monoclonal anti-CD20 antibody rituximab, has been emphasized [25,26].

Anti-NMDAR antibodies' epitope is thought to be located on a small region of the GluN1 amino-terminal domain (Fig. 2) and may depend on post-translational modifications, hence the peculiar pattern of patients' anti-NMDAR antibodies observed on rat brain immunohistochemistry [27,28]. The biological effects of anti-NMDAR antibodies have been extensively studied over the recent years (Fig. 3). Patients' antibodies applied on cultured hippocampal neurons alter NMDAR synaptic currents [29,30] while AMPAR currents are preserved [31]. NMDAR deregulation is likely not mediated by direct receptor inhibition [30] but rather by a decrease in surface receptor density [31]. Indeed, NMDAR capping by the autoantibodies results in receptor cross-linking [31] and disruption of its interaction with EphB2R [32]. As a consequence, the surface trafficking of the receptor is altered [32], leading to a time and dose dependant NMDAR internalization through recycling endosomes and lysosomes [27,30,31]. Intracerebro-ventricular infusion of mice with patients' CSF induce memory deficits and a depressive-like behaviour [33]. In rats infused with CSF from NMDAR-E patients, excessive extracellular glutamate concentrations are observed, likely due to an imbalance between NMDA and AMPA receptors [34]. Alternatively, down-regulation of pre-synaptic NMDAR on the GABAergic neurons may