Highlights

1. Autoantibodies to neuronal proteins are promising biomarkers of neurodegenerative diseases

2. Mounting data suggests dissociation of autoantibody profiles and neurodegeneration in CNS

3. Autoantibody profiles may be influenced by neurodegeneration beyond CNS

4. Constitutive turnover of enteric neurons provides a continuous supply of neuronal antigens

Perspective

Adult Neurogenesis in the Gut, Homeostatic Autoimmunity and Neurodegenerative Disease Biomarkers

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Conflict of interest: The author reports no potential conflict of interest

Abstract

Autoantibodies to neuronal antigens are viewed as potential biomarkers for neurodegenerative diseases. Increasing evidence, however, suggests a dissociation of the neurodegenerative process in the central nervous system and dynamics of neuronal proteins in peripheral circulation with prevalence of a wide variety of immunoglobulins reactive to neuronal antigens reported also in the blood of healthy subjects, including children. Recently discovered physiological turnover of neurons in enteric nervous system with release of neuronal proteins in circulation may account for this conundrum and provide a new perspective on molecular biomarkers of neurodegenerative diseases and immunotherapy.

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Keywords

Adult neurogenesis; enteric nervous system; autoimmunity; neurodegenerative disease; tau; biomarkers

Abbreviations

NDD – neurodegenerative diseases; CSF – cerebrospinal fluid; Ig – immunoglobulins; Aab – autoantibodies; BBB – blood-brain barrier; CNS – central nervous system; AD – Alzheimer's disease; NF – neurofilament; LB – Lewy bodies; PD – Parkinson's disease.

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Main

Early detection of neurodegenerative diseases (NDDs) and targeted intervention are considered essential for successful future therapies. Although the slow progression of neuronal degeneration offers ample window for therapeutic intervention, at present, there are no rigorous methods for detecting pathological changes during the initial stages of the disease. Major efforts are underway toward developing sensitive methods for identifying subtle damage to brain tissue, based on alterations in neuronal proteins in cerebrospinal fluid (CSF) and peripheral circulation (Obrocki, Khatun et al. 2020, Zetterberg and Blennow 2021). A range of immunoassays has been designed using traditional detection methods and fluorescence-based techniques (proximity ligation assays, PLA), yielding higher sensitivity and multiplexing capacities (Obrocki, Khatun et al. 2020).

With the expanding portfolio of neuron-specific immunoglobulins (Ig) in biofluids of patients, the stakes are high for specific biomarkers of neuronal degeneration. It is generally assumed that during neurodegeneration, antigens released by injured neurons pass across the disrupted blood-brain barrier (BBB), inducing an immune response with production of specific autoantibodies (Aab). The rising evidence from clinical studies, while generally supportive of this premise, has challenged the expected correlation of Aab changes with the degenerative process in the central nervous system (CNS). Indeed, increasing data from Alzheimer's disease (AD) patients show the dissociation of the dynamics of anti-Aβ Ig in peripheral circulation from amyloid pathology in the brain (Kocurova, Ricny et al. 2022). Most Aβ42 and Aβ40 Aab studies, for instance, showed a lower titer of Ig in sera of patients compared to healthy groups, despite the flaring amyloid pathology in the brain (Du, Dodel et al. 2001, Qu, Gong et al. 2014, Lang and Pruss 2017, Kocurova, Ricny et al. 2022). The dissociation of Aab profiles in the blood from the neurodegenerative process in the CNS has been also reported for other neuronal markers, including microtubule-associated protein tau, axonal neurofilaments (NF) and α-

synuclein (Zetterberg and Burnham 2019, Gordon 2020, Kocurova, Ricny et al. 2022). Notably, tau-reactive Aabs were found in immunoglobulin pools of large cohorts of healthy subjects, including children (Kuhn, Rogosch et al. 2018, Kocurova, Ricny et al. 2022). Moreover, some reports have shown a reduction of tau reactive Aabs in the serum of clinical AD patients, as compared to healthy controls, with Ig concentration declining further with the progression of the pathology (Bartos, Fialova et al. 2018, Kocurova, Ricny et al. 2022). Similar to Aβ and tau Aabs, NF-reactive immunoglobins were also reported in the plasma of healthy subjects (Kocurova, Ricny et al. 2022).

The abundance of immunoglobins reactive to neuronal antigens in healthy individuals of different age groups advocates their possible physiological role. Although the significance and mechanisms of the production of neuron-specific Aabs in healthy subjects remain to be elucidated, one explanation for the deviation of the primary pathology in CNS and changes in neuronal antigens in the periphery might be that the neurodegenerative process is not confined to the brain and spinal cord but extends over the peripheral nervous system, which may not strictly correlate with the pathology in the CNS. A detailed analysis of the distribution of Lewy Bodies (LB) in patients affected by Parkinson's disease (PD), Lewy body dementia (LBD) and AD, using phosphorylated α-synuclein assays have shown high densities proteinaceous deposits in paraspinal sympathetic ganglia, vagus nerve, enteric plexus of the intestinal tract as well as endocrine organs (Braak, de Vos et al. 2006, Beach, Adler et al. 2010, Natale, Pasquali et al. 2011). Inclusions of α-synuclein were also found in parasympathetic preganglionic projecting neurons of the dorsal motor nucleus of the vagus, sympathetic preganglionic neurons, and post-ganglionic neurons of celiac ganglion (Braak, de Vos et al. 2006). Research is currently underway elucidating the peripheral pathology with neuronal injury in NDDs, with prion-like transmission to the lower brain stem nuclei and further up to forebrain structures. While highly instructive for appreciation of the complexity of the pathobiology of NDDs, these

findings cannot explain the abundance of Aabs reactive to neuronal proteins in the peripheral circulation of healthy subjects.

Recent studies of the enteric nervous system, which comprises the largest collection of neurons outside of the CNS, have provided important clues that not only may explain the dissociation between dynamics of neuron-specific Aabs in the blood and primary neuropathology in the CNS but also can account for the presence of Aabs to neuronal injury proteins in the circulation of healthy subjects. Despite the long-established view of the absence of adult neurogenesis in the intestinal nervous system, the results of cytochemical and immunofluorescence analysis of the enteric nervous system suggest a continuous proliferation of neuronal progenitors with a supply of new neurons (Pham, Gershon et al. 1991, Laranjeira, Sandgren et al. 2011, Kulkarni, Micci et al. 2017). This steady stream of fresh neurons ensures the replacement of the rapidly degenerating old cells, keeping in check the neuronal population of the intestine (Kulkarni, Micci et al. 2017). It was reported that at any given time, over 10 % of myenteric neurons are positive for cleaved caspase 3, implying that they are on their way out. With over 30% of these cells perishing within a week or so, the intense neuronal disintegration in the intestinal wall mounts up to 4-5 % of neurons dying every day, releasing large quantities of antigens in the circulation for disposal by the immune system (Kulkarni, Micci et al. 2017). Given the critical role of the immune system in tissue homeostasis and regeneration, the constitutive apoptosis of enteric neurons and the constant production of endogenous antigens warrant a constant production and release of neuronal immunoglobins in the peripheral circulation.

In summary, circulating in the blood Aabs targeting neuronal proteins, thus, emerge as an important feature of homeostatic autoimmunity. With the onset of NDDs, it is conceivable that part of the neuronal Aab portfolio acquires a new functionality - neutralizing neuronal antigens released into circulation from the CNS. Although major gaps remain in understanding

the significance of homeostatic autoimmunity to neuronal proteins under physiological and disease conditions, the outlined here model provides clues explaining the prevalence of neuronal Aabs (and antigens) in healthy and NDDs subjects and offers a new conceptual framework for making testable predictions in future studies. Filling the knowledge gaps in the biology of neuronal autoimmunity should not only elucidate the highly complex and dynamic relationship between the neurodegenerative process in the CNS and immune response but also help to improve diagnostic assays and facilitate the development of effective immunotherapies.

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Figure 1

Schematic of the life journey of neurons in healthy ageing and neurodegenerative disease-affected CNS (A), and in healthy intestinal nervous system (B). (A) In the course of development, in CNS, neurons derived from neuronal progenitors mature (red arrows) and progress through healthy ageing (blue arrows) or undergo neurodegeneration (grey arrows), releasing neuronal antigens, i.e., β-amyloid, α-synuclein, MAP tau, NF etc., which leak in peripheral circulation through injured blood-brain barriers (BBB, grey broken line), to stimulate the production of natural autoantibodies (Aab). (B) In the intestinal nervous system, on the other hand, there is an extensive physiological turnover of neurons, with dying nerve cells constantly releasing antigens, i.e., β-amyloid, α-synuclein, MAP tau etc., into the blood stream (across endothelium), activating homeostatic autoimmune response, which plays a key role in integrity of intestinal functions.

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Figure