Zeitschrift: Bulletin der Schweizerischen Akademie der Medizinischen Wissenschaften = Bulletin de l'Académie suisse des sciences médicales = Bollettino dell' Accademia svizzera delle scienze mediche

Herausgeber: Schweizerische Akademie der Medizinischen Wissenschaften

Band: - (1981-1982)

Artikel: Immunological aspects of demyelination

Autor: Steck, Andreas J.

DOI: https://doi.org/10.5169/seals-308264

Bull. Schweiz. Akad. Med. Wiss., 109 - 112 (1982)

Service de Neurologie, Centre Hospitalier Universitaire Vaudois

IMMUNOLOGICAL ASPECTS OF DEMYELINATION

ANDREAS J. STECK

Abstract

Important progresses made recently have allowed the development of markers that can be used to characterize the myelin oligodendrocyte compartment. Application of these immunological methods to the investigation of a wide range of disorders of the nervous system has proved extremely valuable.

The author selects one example that concerns a group of demyelinating neuropathy associated with a monoclonal protein and presents evidence suggesting that one myelin constituent, a myelin associated glycoprotein, may induce autoimmunity in humans.

Oligodendroglial cells have the important role of producing the myelin sheath of axons in the central nervous system (CNS), while this function is taken by the Schwann cells in the peripheral nervous system (PNS). The formation of myelin results in changes that facilitate the conduction of the nerve impulse. The study of oligodendrocytes, Schwann cells and myelin is therefore of considerable importance and has relevance to several human diseases, particularly multiple sclerosis in the CNS and demyelinating neuropathy in the PNS. Important progresses made recently have allowed the development of markers that can be used to characterize the myelin oligodendrocyte compartment and to identify myelin constituents that are involved in autoimmunity in humans.

The immunochemical approach has made it possible to recognize the major cell types of the central nervous systems in a number of different species. Phosphorycholine binding myeloma proteins (1) and tetanus toxin (2) have a selective affinity to neurons. Glial fibrillary acidic protein is a specific intracellular marker for both protoplasmic and fibrons astrocyte (3). Oligodendrocytes share major antigenic determinants with the myelin membrane which is consistent with the fact that myelin represents an extension of the plasma membrane of the

oligodendrocytes. Galactocerebroside, a major glycolipid of white matter, has been recognised as a specific cell surface antigenic marker for oligodendrocytes (4). The mapping of cell surface antigens has demonstrated major differences in immunological properties between the mature oligodendrocytes and clonal lines of oligodendroglioma cells (5). It appears that differentiation implies not only the expression of galactocerebroside at the cell surface, but also the presence of additional surface markers that are absent on the neurotumor cell lines. More recently many of these observations on the immunological properties of isolated mature oligodendrocytes have been confirmed by studying oligodendroglia in mixed cell culture systems (6-7). In vitro preparations show the developmental increases of differentiated properties of oligodendrocytes, such as expression of galactocerebroside. Additional benefits should also be derived from recent improvements in the preparation of separate cultures of astroglia and oligodendroglia.

Application of these immunological methods to the investigation of a wide range of disorders of the nervous and muscular systems has proved extremely valuable. It is not possible in a brief space to do justice to the vast amount of information that has accrued in clinical neuroimmunology. I would like to select one example that concerns a group of demyelinating neuropathy associated with a monoclonal protein (8-9) and present evidence suggesting that one myelin constituent, a myelin associated glycoprotein (MAG), may induce autoimmunity in humans.

CNS and PNS myelin contains a variety of proteins, lipids and carbohydrates that may serve as immunogens in provoking immune responses (10). The two membranes have different polypeptides composition. Proteolipid protein and the 18 K dalton basic protein are the major proteins of CNS myelin, while the Po glycoprotein and the neuritogenic P2 protein are major proteins of PNS myelin. The MAG is an integral membrane glycoprotein of 110 K dalton which is quantitatively a minor component of purified CNS and PNS myelin.

Its presence in purified CNS myelin was first demonstrated by radioactive labelling with sugar precursors (11). Subfractionation experiments suggested that MAG was not present in compact CNS myelin but was concentrated in closely associated oligodendroglial membranes (12). In the PNS, immunocytochemical studies have shown that MAG is present in periaxonal membranes, Schmidt-Lantermann incisures and paranodal portions of PNS myelin sheaths (13). Integral membrane glycoproteins are believed to be involved in cell-cell recognition and in interactions between cell membranes (14).

Recent work has now demonstrated the presence of monoclonal antibodies against MAG in the serum of patients with a neuropathy associated with a gammopathy (15-16). These patients present a slowly progressive sensori-motor neuropathy. Peripheral nerve biopsy reveals changes

typical of demyelinating neuropathy. Onion bulb formation and splitting of the myelin lamellae at the intraperiod line has been observed in a typical patient (16). Serum IgM but not IgG from these patients recognise a myelin protein that is similar in size to the MAG (15). That this glycoprotein may be the specific antigen recognised by the patient's IgM is suggested by the following: a) comigration of the immunostain of PNS or CNS myelin with that of the purified MAG. b) binding to myelin was completely inhibited by absorption of the serum with purified MAG (16).

There has been increasing evidence to suggest the involvement of immunological mechanisms in neuropathy associated with abnormal serum immunoglobulins.

In some cases deposition of immunoglobulins in nerve has been shown by immunofluorescence (17-18). These findings taken together with the present evidence would suggest that MAG may be an antigen involved in autoimmune demyelinating disease of the PNS. Further studies of myelin constituents susceptible of inducing autoimmunity, particularly in humans, should provide new insight in the pathogenesis of demyelinating diseases of the central and peripheral nervous system.

1. Hooghe-Peters E.L., Fowlkes B.J., Hooghe R.J.: A new neuronal marker identified by phosphorylcholine-binding myeloma proteins. Nature 281, 376-378, 1979.
2. Dimpfel W., Huang R.T.C., Habermann E.: Gangliosides in nervous tissue cultures and binding of ^{125}I-labelled tetanus toxin, a neuronal marker. J.Neurochem. 29, 329-334, 1977.
3. Bignami A., Dahl D.: Astrocyte-specific protein and neuroglial differentiation. J.Comp. Neurol. 153, 27-37, 1974.
4. Raff M.C., Mirsky R., Fields K.L., Lisak R.P., Dorfman S.H., Silberberg D.H., Gregson N.A., Leibowitz S., Kennedy M.C.: Galactocerebroside is a specific cell surface antigenic marker for oligodendrocytes in culture. Nature 274, 813-816, 1978.
5. Steck A.J., Perruisseau G.: Characterization of membrane markers of isolated oligodendrocytes and clonal lines of the nervous systems. J.Neurol.Sci. 47, 135-144, 1980.
6. McCarthy K.D., de Vellis J.: Preparation of separate astroglial and oligodendroglial cell cultures from rat cerebral tissue. J.Cell.Biol. 85, 890-902, 1980.
7. Bologa-Sandru L., Siegrist H.P., Z'Graggen A., Hofman K., Wiesmann U., Dahl D. and Herschkowitz N.: Brain research 210, 217-229, 1981.
8. Latov N., Sherman W.H., Nemni R., Galassi G., Shyong J.S., Penn A.S., Chess L., Olarte M.R., Rowland L.P., Osserman E.F.: Plasma-cell dyscrasia and peripheral neuropathy with a monoclonal antibody to peripheral-nerve myelin. New Engl.J. of Med. 303, 618-621, 1980.
9. Dalakas M.C., Engel W.K.: Polyneuropathy with monoclonal gammopathy: studies of 11 patients. Annal.Neurol. 10, 45-52, 1981.
10. Whitaker J.N.: The Protein Antigens of peripheral nerve myelin. Ann.Neurol. 9 (suppl) 56-64, 1981.
11. Quarles R.H., Everly J.L., Brady R.O.: Evidence for the close association of a glycoprotein with myelin rat brain. J.Neurochem. 21, 1177-1191, 1973.

12. Quarles R.H.: Glycoproteins in myelin and myelin-related membranes. In: Complex Carbohydrates of the Nervous System. Margolis R.U., Margolis R.K. ed. Plenum Press, New York 1979, 209-233.
13. Trapp B.D., Quarles R.H.: Presence of the myelin-associated glycoprotein correlates with alterations in the periodicity of peripheral myelin. J.Cell.Biol. 92, 877-882, 1982.
14. Hughes R.C.: Membrane glycoprotein: a review of structure and function. Butterworth Publishers Inc., Woburn, Mass., 1976.
15. Latov N., Braun P.E., Gross R.B., Sherman W.H., Penn A.S., Chess L.: Plasma cell dyscrasia and peripheral neuropathy: Identification of the myelin antigens that react with human paraproteins. Proc.Natl.Acad.Sci. USA 78, 7139-7142, 1981.
16. Steck A.J., Murray N., Meier C., Page N., Perruisseau G.: Demyelination Neuropathy associated with a monoclonal IgM antibody to the major myelin associated glycoprotein. (submitted for publication)
17. Swash M., Perrin J., Schwartz M.S.: Significance of immunoglobulin deposition in peripheral nerve in neuropathies associated with paraproteinemia. J.Neurol.Neurosurg. and Psych. 41, 215-219, 1978.
18. Kahn S.N., Smith I.S., Eames R.A., Thomas P.K., Lacey B.W.: IgM paraproteinemia and autoimmune peripheral neuropathy. New Engl.J. of Med. 344, 1430-1431, 1981.

Address: Dr. Andreas Steck, P.D., Service de Neurologie, Centre Hospitalier Universitaire Vaudois, 1011 Lausanne (Suisse)