Report

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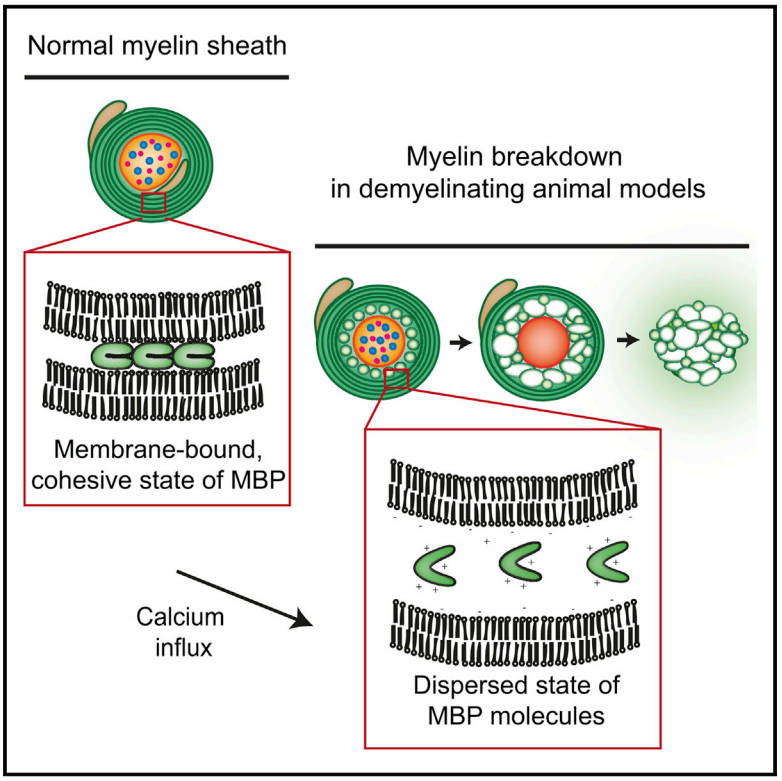
Loss of Myelin Basic Protein Function Triggers Myelin Breakdown in Models of Demyelinating Diseases

Graphical Abstract



Highlights

- Characterization of myelin sheath pathology close its native state
- Vesiculation of inner sheath layers is a common feature of myelin pathology
- Loss of MBP function triggers myelin vesiculation
- Elevation of intracellular Ca^{2+} triggers MBP phase transition

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In Brief

Using high-pressure freezing and electron microscopy, Weil et al. show that that the vesicular disruption of the myelin sheath is a common feature of myelin degeneration in demyelinating diseases. The authors suggest that the underlying mechanism is the aberrant transition of MBP molecules from their cohesive state to their non-adhesive state.

Weil et al., 2016, Cell Reports *16*, 314–322
July 12, 2016
http://dx.doi.org/10.1016/j.celrep.2016.06.008

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Loss of Myelin Basic Protein Function Triggers Myelin Breakdown in Models of Demyelinating Diseases

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http://dx.doi.org/10.1016/j.celrep.2016.06.008

SUMMARY

Breakdown of myelin sheaths is a pathological hallmark of several autoimmune diseases of the nervous system. We employed autoantibody-mediated animal models of demyelinating diseases, including a rat model of neuromyelitis optica (NMO), to target myelin and found that myelin lamellae are broken down into vesicular structures at the innermost region of the myelin sheath. We demonstrated that myelin basic proteins (MBP), which form a polymer in between the myelin membrane layers, are targeted in these models. Elevation of intracellular Ca^{2+} levels resulted in MBP network disassembly and myelin vesiculation. We propose that the aberrant phase transition of MBP molecules from their cohesive to soluble and non-adhesive state is a mechanism triggering myelin breakdown in NMO and possibly in other demyelinating diseases.

INTRODUCTION

Myelin is the target of several autoimmune diseases, among which multiple sclerosis (MS) is the most common (Popescu and Lucchinetti, 2012). The primary target of the autoimmune attack in MS is not known but thought to be localized on the surface of the myelin sheath, from where the damage may spread in a retrograde fashion to the oligodendrocyte cell body ("outside in"). In addition, "inside-out" models of myelin damage in MS have been suggested (Henderson et al., 2009; Traka et al., 2016).

In neuromyelitis optica (NMO), another demyelinating disease, humoral immune reaction against aquaporin-4 (AQP4) on astrocytic endfeet (Jarius et al., 2008; Lennon et al., 2005) induces secondary oligodendrocyte cell death followed by myelin loss (Wrzos et al., 2014). The damage in NMO is believed to spread from the cell body to the myelin sheath in an inside-out fashion. Although the primary autoimmune effectors are different, the final result is, in both cases, the rapid breakdown of myelin sheaths. The purpose of this study was twofold: to determine the patterns of myelin fragmentation in different models of myelin diseases, and to understand the molecular basis of myelin degeneration.

Since myelin basic protein (MBP) is the only structural myelin protein known to be absolutely required for generating compact myelin sheaths, we hypothesized that it is also the key to our understanding of myelin degeneration. One defining feature of MBP is its intrinsically disordered polypeptide chain with a strong basic character (Musse et al., 2008). When MBP binds to two opposing negatively charged cytoplasmic leaflets of the myelin membrane, the positive charge in MBP is neutralized, and self-assembly into a polymeric network is induced. This process resembles a phase transition as it converts the soluble and freely dispersed MBP molecules into a liquid-like condensed state, thereby bringing together the cytoplasmic surfaces of the myelin bilayer and generating the tightly compacted multilamellar membrane stacks (Aggarwal et al., 2013). Phase transitions of proteins into condensed liquid states are emerging as a universal process underlying cellular organization (Hyman et al., 2014; Weber and Brangwynne, 2012). A challenge confronting this field is to connect in vitro protein phase behavior with in vivo processes. Here, we use models of demyelinating diseases to target the myelin sheath directly or indirectly and combined morphological and molecular analyses to