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Review

Relationships between cobalamin, epidermal growth factor, and normal prions in the myelin maintenance of central nervous system

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ABSTRACT

Cobalamin (Cbl), epidermal growth factor (EGF), and prions (PrPs) are key molecules for myelin maintenance in the central and peripheral nervous systems. Cbl and EGF increase normal prion (PrP^C) synthesis and PrP^C levels in rat spinal cord (SC) and elsewhere. Cbl deficiency increases PrP^C levels in rat SC and cerebrospinal fluid (CSF), and decreases PrP^C-mRNA levels in rat SC. The administration of anti-octapeptide repeat PrP^C region antibodies (Abs) to Cbl-deficient (Cbl-D) rats prevents SC myelin lesions and a local increase in tumor necrosis factor (TNF)-α levels, whereas anti-TNF-α Abs prevent SC myelin lesions and the increase in SC and CSF PrP^C levels. As it is known that both Cbl and EGF regulate SC PrP^C synthesis independently, and that Cbl regulates SC EGF synthesis, EGF may play both Cbl-independent and Cbl-dependent roles. When Cbl-D rats undergo Cbl replacement therapy, SC PrP^C levels are similar to those observed in Cbl-D rats. In rat frontal cortex (which is marginally affected by Cbl deficiency in histological terms), Cbl deficiency decreases PrP^C levels and the increase induced by Cbl replacement leads to their normalization. Increased nerve PrP^C levels are detected in the myelin lesions of the peripheral neuropathy of Cbl-D rats, and CSF PrP^C levels are also increased in Cbl-D patients (but not in patients with Cbl-unrelated neurological diseases). Various common steps in the downstream signaling pathway of Cbl, EGF, and PrP^C underlines the close relationship between the three molecules in keeping myelin normal.

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Abbreviations: Abs, antibodies; Akt, cytoplasmic serine-threonine kinase from Ak mouse strain thymoma; Cbl, cobalamin; Cbl-D, Cbl-deficient; CNS, central nervous system; CSF, cerebrospinal fluid; DMSO, dimethyl sulfoxide; Dpl, Doppel; EGF, epidermal growth factor; GFAP, glial fibrillary acidic protein; HCYS, homocysteine; i.c.v., intracerebroventricular; IL, interleukin; KO, knock-out; L, ligand; MMA, methylmalonic acid; mo, month; mTOR, mammalian target of rapamycin; NF, nuclear factor; NGF, nerve growth factor; NTR, neurotrophin receptor; ODC, oligodendrocyte; ON, otherwise normal; OR, octapeptide repeat; PNS, peripheral nervous system; PrP, prion; PrPC, normal PrP; PrP^{SC}, scrapie PrP; s, soluble; SC, spinal cord; SCD, subacute combined degeneration; Tg, transgenic; TNF, tumor necrosis factor.

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1. Introduction

At first glance, vitamin B_{12} (also called cobalamin (Cbl)) and prions (PrPs) seem to have nothing in common. It is enough to remember here that most human PrP-related diseases (here collectively called prionopathies *lato sensu*) are fatal (Frost and Diamond, 2010; Knight, 2013; Prusiner, 1999), whereas this is very seldom true of human diseases due to acquired deficiency or inherited defects in the metabolism and/or transport of Cbl (here collectively called cobalaminopathies, albeit imprecisely in some respects) (Scalabrino, 2009). However, if we look more closely, we can see that they have a number of similarities. First of all, most PrP-related and Cbl-related diseases seriously damage the myelin of the central nervous system (CNS) and/or peripheral nervous system (PNS) (Onodera et al., 2013; Prusiner, 1999; Scalabrino, 2009), thus suggesting that Cbl and normal prions (PrP^Cs) are both required for myelin maintenance, even though the underlying mechanisms are far from clear. Secondly, prionopathies and cobalaminopathies have two forms of different etiology: acquired and inherited (no transmitted form of human Cbl deficiency-related diseases is known) (Knight, 2013; Scalabrino et al., 2008; Wadsworth et al., 2010). Thirdly, acquired Cbl-deficient (Cbl-D) neuropathy (also called subacute combined degeneration (SCD)) and most prionopathies have a long latency period before manifesting themselves clinically and, accordingly, have their onset in middle and/or even old age (Andrès et al., 2004; Lachner et al., 2012; Prusiner, 2001; Scalabrino, 2009).

Cobalaminopathies and prionopathies also have some common neuropathological features. CNS reactive astrocytosis and microglial activation are common to SCD and most prionopathies (Brown, 2001; Marella and Chabry, 2004; Ransohoff and Perry, 2009; Rezaie and Lantos, 2001): reactive astrocytosis is a universal and heterogeneous CNS response to CNS injuries (Zamanian et al., 2012). Classically, glial fibrillary acidic protein (GFAP) upregulation is considered a marker of reactive astrocytes, although GFAP is also the main intermediate filament protein of quiescent astrocytes (Eng et al., 2000; Zamanian et al., 2012). It is still unclear whether reactive astrocytes play a beneficial or detrimental role (or both) in CNS lesions (Eng et al., 2000; Zamanian et al., 2012), and increased GFAP positivity is not a sufficient criterion for deciding whether the reactive astrocytosis associated with some cobalaminopathies and most prionopathies is identical or distinct. Nonetheless, reactive astrocytosis seems to be involved in the pathogenesis of both diseases (Raeber et al., 1997; Scalabrino et al., 2008), whereas oligodendrocytes (ODCs) do not (Prinz et al., 2004; Scalabrino, 2009), which is in line with the fact that both cobalaminopathies and prionopathies do not show any morphological signs of remyelination and therefore do not belong to the group of demyelinating diseases (DeArmond et al., 2002; Ironside et al., 2008; Scalabrino, 2009).

Other similarities are that peripheral neuropathy is observed in SCD patients and adult Cbl-D rats (Saperstein and Barohn, 2002; Scalabrino, 2009) as well as in some strains of PrP^C knock-out (KO) mice (Bremer et al., 2010; DeArmond et al., 2002; Ironside et al., 2008), and neither cobalaminopathies nor prionopathies show any histopathological signs of an inflammatory response.

Spongy vacuolation preferentially affects the CNS gray matter in animals and humans with prionopathies, although it may also affect the CNS white matter in some strains of PrP KO mice with SCD-like characteristics (DeArmond and Ironside, 1999; Ironside et al., 2008; Nazor et al., 2007; Radovanovic et al., 2005; Steele et al., 2007; Westaway et al., 1994). The intramyelinic and interstitial edema observable at electron microscopy accounts for SCD spongy vacuolation of the CNS white matter (especially the spinal cord (SC)), but it does not affect the axons (Scalabrino et al., 2008; Scalabrino, 2009). Furthermore, amyloid plaques and dendritic atrophy are observed in the CNS of some human patients and animals with prionopathies (Caughey et al., 2009; DeArmond et al., 2002; Ironside et al., 2008), but never in the CNS of cobalaminopathy patients and/or Cbl-D rats (Scalabrino, 2009).

We will begin by recapitulating the known effects of Cbl, epidermal growth factor (EGF) and PrP^Cs on CNS and PNS myelins as logical prolegomena, before discussing: (*i*) the finding that the Cbl deficiency-mediated abnormalities in CNS PrP^C levels play a role in the pathogenesis of CNS myelin damage; (*ii*) the finding that the Cbl deficiency-induced decrease in CNS EGF levels and synthesis plays a role in the pathogenesis of the PrP^C abnormalities and myelin damage; and (*iii*) the relationship between Cbl, EGF and PrP^Cs in maintaining CNS and PNS myelin.

2. The complex and multi-faceted basis of Cbl myelinotrophism

2.1. ODCs, astrocytes, and SC white matter

Labeled Cbl is avidly uptaken by SC ODCs isolated from newborn rats (*i.e.* when myelination is still incomplete, as demonstrated by their vacuolated SC white matter), but only in tiny amounts if the ODCs are isolated from the SC of adult rats (Scalabrino et al., 2008). It has been shown that activated SC astrocytes contribute to cause white matter myelin damage during Cbl deficiency and those isolated from the SC of adult Cbl-D rats also uptake labeled Cbl greatly