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Normal Cellular Prions: Friends and Foes towards Human CNS Myelin? The Role of Cobalamin

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It is well-known that normal cellular prions (PrPCs) have a fundamental role in maintaining the structure and functions of normal CNS myelin, although they are not alone in doing this, and their task is far from being fully elucidated. Important evidence of PrPC role in CNS myelin maintenance comes from studies of PrPC knock-out (KO) mice lacking one or more parts of the PrPC molecule. Furthermore, transgenic (Tg) mice expressing PrPC point mutations, insertions or deletions develop a spectrum of neuropathological pictures reminiscent those of transmissible spongiform encephalopathies. More in detail, mouse strains lacking or overexpressing the PrPC octapeptide repeated (OR) region show CNS myelin lesion. The presence of redundant OR regions in the PrPC molecule is causally related to some human prionopathies whose histopathological pictures include CNS spongiform vacuolation and astrocytic proliferation. All of the above studies highlighted that CNS myelin lesions may also be caused merely by local quantitative PrPC abnormalities.

We demonstrated that the severity of lesions in the spinal cord (SC) white matter of cobalamin-deficient (Cbl-D) rats does not correlate with the accumulation of methilmalonic acid and homocysteine (i.e. the two metabolites which accumulate when Cbl is lacking) in their SCs and sera, because no substantial increase in the severity of Cbl deficiency-induced lesions in the SC white matter was observed as methilmalonic acid and homocysteine accumulated in the SC [1,2]. Thereafter, we have identified new pathogenetic mechanisms of the myelin lesion of central Cbl-D neuropathy by demonstrating that the SC myelin lesions are caused not by mere Cbl withdrawal but the Cbl deficiency-induced abnormalities in the SC and cerebrospinal fluid (CSF) of some myelin-related cytokines and growth factors. Briefly, local tumor necrosis factor(TNF)-ϒ levels and/or synthesis are abnormally high and local epidermal growth factor (EGF) levels and/or synthesis abnormally low in SC of Cbl-D rats. In other words, TNF-α excess becomes myelinotoxic and simultaneous EGF lack deprives CNS of its myelintrophic action. Most of our findings concerning cytokine and growth factor derangements in CNS of Cbl-D rats were confirmed by us in human CSF of patients with subacute combined degeneration. The Cbl replacement treatment substantially corrected the above abnormalities in Cbl-D patients and Cbl-D rats.

On the basis of all the above, I posited the working hypothesis that there may be a link between Cbl and PrPCs and that this link is deranged in Cbl-D neuropathy because of the Cbl deficiency-induced imbalance in CNS cythokine and/or growth factor network. In particular, it should be emphasized that: i) PrPC synthesis has been shown to be regulated in vitro by TNF-ϒ and EGF; ii) TNF-ϒ levels are markedly increased in the brain of scrapie-infected mice; and iii) myelin vacuolation, reactive astrocytosis, and microglial activation are neuropathological features common to Cbl-D central neuropathy and the CNS of most prionopathies.

SC PrPC levels had increased by the time local myelin lesions appeared. This increase was mediated by excess myelinotoxic TNF-ϒ and prevented by repeated intracerebroventricular (i.c.v.) injections of EGF, which proved to be as effective as Cbl in preventing Cbl deficiency-induced SC myelin lesions. Repeated i.c.v. injections of anti-OR region antibodies prevented the Cbl deficiency-induced lesions of SC myelin. In vivo Cbl or EGF treatment significantly increased SC PrPC mRNA levels in Cbl-D rats.

I have always considered our studies of equivalent animal models of acquired Cbl-D neuropathy as prolegomena to our studies of adult patients with clinically confirmed severe Cbl deficiency. We demonstrated that: i) CSF PrPC levels were significantly higher in the therapy-free Cbl-D patients (i.e. with subacute combined degeneration) than in neurological controls; ii) CSF PrPC levels correlated significantly with CSF Cbl levels, and iii) CSF PrPC levels were normal in the patients with amyotrophic lateral sclerosis or Alzheimer's disease. Instead, we found significantly decreased CSF PrPC levels in patients with multiple sclerosis (MS) (regardless of its clinical course) [3,4]. The PrPC levels of post-mortem SC samples of MS patients were also decreased. The decreased PrPC availability in MS SC surely represents one of the causes of the remyelination failure in MS.

In conclusion, we were the first to demonstrate that an experimental myelinolytic neuropathy (Cbl-D central neuropathy) is also caused by a local excess of PrPCs that do not show any conformational change like in the case of PrPSCs. Conversely, PrPC levels are very low in CNS of a typical demyelinating disease, MS. It should be also noted that SC is the CNS part most severely affected by Cbl deficiency and in MS. In other words, our findings are in agreement with the results of PrPC KO-or PrPC Tg-mice showing that any deregulation (excess or deficiency) in CNS PrPC levels jeopardizes CNS normal myelin maintenance. Finally, we demonstrated for the first time that the Cbl and EGF buffering of SC PrPC levels is crucial for keeping SC myelin normal, because Cbl and EGF protect SC myelin against the myelin-damaging excess or lowering of SC PrPC levels [5,6].

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