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Abstract

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The Peripheral Nervous System and the Pathogenesis of Prion Diseases

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Keywords: Prions; Creutzfeldt-Jakob disease; lymphoreticular system; peripheral nervous system; peripheral pathogenesis.

INTRODUCTION

Prion diseases, or transmissible spongiform encephalopathies (TSEs), are neurological disorders caused by transmissible pathogens termed prions [1]. According to available evidence, prions are devoid of informational nucleic acids and consist of an “infectious” protein capable of converting a normal host protein called PrPC into a pathogenic isoform of itself termed PrPSc [2].

Prions can find their way through the body to the brain of their host, and colonize various extracerebral organs including the lymphoreticular system and skeletal muscles. However histopathological changes have not been identified in organs other than the central nervous system (CNS). The process by which prions travel through the body to the CNS is termed neuroinvasion and comprises two phases [7]. A primary phase of prion accumulation and replication in organs of the lymphoreticular system (LRS) is followed by a secondary phase which is initiated once the agent has gained access to peripheral nerves. It may be argued that this model oversimplifies the complex mechanisms of prion neuroinvasion, and indeed there are exceptions: some studies have shown that prion neuroinvasion along peripheral nerves can occur independently of lymphoid prion replication [8], and not all lymphoid organs are always colonized by prions [9]. However, we maintain that the vast majority of experimental
data can be explained on the basis of the two-step model of prion neuroinvasion.

**PRIONS REPLICATE IN LYMPHOID ORGANS**

The lymphoreticular system (LRS) is an early site of prion replication. In experimental models of prion diseases, PrPSc and prion-infectivity can be detected in the LRS as early as five days following prion challenge [10]. Which cell type is responsible for replication and accumulation of prions in the LRS? By separating stromal and non-stromal compartments of the spleen, it was soon realized that prion infectivity resides mainly in the stromal compartment. Stromal cells such as follicular dendritic cells (FDCs) were suspected to be the cell type responsible for prion replication. Subsequently, a number of studies strengthened this assumption. In the 1980ies it could be shown that prion replication in lymphoid organs is unaffected by whole-body ionizing radiation, FDCs are known to be resistant to ionizing radiation [11]. Further evidence that FDCs accumulate PrPSc came from investigations demonstrating PrPSc accumulation on FDCs in experimentally prion infected mice [12]. In addition, intraperitoneal infection does not lead to replication of prions in the spleen of mice with functionally impaired FDCs [13]. Ultrastructural studies employing immuno electron microscopy have shown that disease-associated PrP (presumably identical to PrPSc) is situated on the plasmalemma of FDCs [14]. Meanwhile it became obvious that the development and maintenance of secondary lymphoid organs and of FDCs is dependent on tumor necrosis factor, lymphotoxin alpha, and lymphotoxin beta signaling components [15]. Blocking of this pathway by administration of a lymphotoxin beta receptor-immunoglobulin fusion protein leads to the disappearance of mature, functional FDCs and to a significant reduction of prion infectivity in the spleen [16, 17].

**HOW DO PRIONS EXPLOIT PERIPHERAL NERVES**

Following intraperitoneal administration and replication in organs of the LRS, it is believed that prions gain access to peripheral nerves [7]. Considering the fact that PrPSc is localized on the plasmalemma of FDCs, one could presume that peripheral nerve entry occurs in the immediate neighborhood of FDCs. Indeed studies looking at the innervation pattern of lymphoid organs have shown close vicinity of FDCs with nerve fibers [18]. How transport from cells belonging to the LRS to peripheral nerves is accomplished is still a matter of discussion. Access to peripheral nerves may be facilitated if myelination of the nerves is reduced or absent [19]. Considering this, the mantle zone of the lymph follicles, which is innervated by terminal unmyelinated nerve fibers, could be the entry point of prions. A recently published study demonstrates that relocalization of FDCs to highly innervated regions within the LRS leads to accelerated prion neuroinvasion. This provides further support of the hypothesis that the distance between sites of prion accumulation and nerve endings may control the efficiency of neuroinvasion [20].

The possibility that prions may directly enter peripheral nerves omitting the need for replication of infectivity in lymphoid organs was raised by a study showing neuroinvasion in mice in which PrPc expression is limited to neuronal cells [8]. This possibility was further highlighted by investigations demonstrating direct prion neuroinvasion via a defined nerve if prions are applied to corresponding nerve endings [21].

**HOW ARE PRIONS TRANSPORTED ALONG PERIPHERAL NERVES?**

Once invasion of the peripheral nervous system (PNS) has taken place, the agent travels along peripheral nerves to the CNS. There is substantial evidence suggesting that prion transport in peripheral nerves occurs in a PrPC dependent fashion [7, 22, 23]. The exact mode of transport within the PNS remains to be discovered: in principle both axonal and non-axonal modes of transport are conceivable. For PrPc transport in the fast axonal pathway was shown [24]. For PrPSc the mode of transport has been studied indirectly by comparing the incubation times of mice inoculated in distal and proximal portions of peripheral nerves or by comparing incubation times of mice inoculated in...
Figure 2. Sympathetic innervation of lymphoreticular organs is rate limiting for prion neuroinvasion

Spinal cord histology showing pronounced gliosis in untreated (A) but not in sympathectomized (B) mice peripherally challenged with prions. Sympathetic innervation of untreated (C) and sympathectomized (D) mouse spleens visualised by anti-tyrosine hydroxylase immunostain.

Peripheral nerves to mice that were inoculated intracerebrally Figure 1 [19, 23]. The actual rate of spread within the PNS was calculated to be around 1 to 2 mm/day. Obviously this rate of spread does not correspond to the fast axonal transport. This contention is supported by a study proving that prion transport is unaltered in genetically modified mice that harbour a defect in fast axonal transport [25]. The lack of experimental evidence for axonal modes of prion transport in conjunction with several indirect lines of evidence supporting non-axonal prion transport led us to propose a “domino stone” mechanism, by which incoming PrPSc converts resident PrPC on the axolemmal surface, thereby propagating spatially the infection [7]. Yet, until experiments that provide us with an unambiguous answer to this problem, such as direct visualization of PrPSc transport in nerves, are nonexistent, this mechanism remains purely hypothetical.

WHICH SUBSETS OF PERIPHERAL NERVES TRANSPORT PRIONS?

The PNS is, like the immune system, made up of several anatomically and functionally distinct subcompartments. A part of the PNS is the autonomous nervous system, which comprises the sympathetic and parasympathetic nervous system,
has been the focus of various studies on prion neuroinvasion [26]. The first hints that prions might invade the CNS using nerve fibers of the autonomous nervous system came from studies looking at pathological changes and prion replication in various portions of the spinal cord [27]. This study demonstrated that, following intraperitoneal inoculation of prions, pathological changes typical of prion diseases and prion replication first appear in the mid-thoracic spinal cord. Involvement of sympathetic nerves was suggested due to the fact that nerve fibers, belonging to the sympathetic nervous system, enter the spinal cord at identical sites. Direct evidence that sympathetic nerve fibers seem to constitute the interface between organs of the LRS and the CNS came from studies employing various strategies of sympathectomy which lead to impaired prion transport from lymphoid organs to the CNS Figure 2 [28]. Conversely, transgenic mice overexpressing nerve growth factor, whose spleens are hyperinnervated, show accelerated prion neuroinvasion [28]. The surprising finding that prion infectivity titers seem to be elevated in hyperinnervated spleens when compared to mice with regular innervation patterns suggests that sympathetic nerves, besides being involved in the transport of prions, may also accumulate and replicate prions in lymphatic organs [28, 29].

A recently published study, demonstrating PrPSc in sympathetic ganglia of patients suffering from vCJD, provides evidence that the model of neuroinvasion established in genetically modified mice might also apply to humans [30]. Further studies established the existence of an additional access route to the CNS that bypasses the spinal cord, using nerves of the parasympathetic nervous system namely the vagal nerve [31]. This alternative route via the vagal nerve seems to be of paramount importance when animals are infected via the oral route. On the other hand, PrPSc can also be detected in sympathetic ganglia of animals infected by the oral route.

CONCLUSIONS

Prion neuroinvasion proceeds by complex mechanisms. It is quite remarkable that such baroque pathways of spread have been developed by an agent which – according to all available evidence – consists exclusively of one single proteic moiety. In order to reach the CNS, prions need intact lymphoreticular compartments of the immune system, and seem to replicate within germinal centers, possibly within mature FDCs. Further transport is provided by distinct subsets of peripheral nerves. Although considerable progress has been made in deciphering mechanisms underlying lymphoid prion replication and prion transport along peripheral nerves, numerous mechanisms await elucidation. A non-exhaustive list of unresolved questions would include the following:

- How are prions transferred from FDCs to nerve endings? Are additional cell types other than FDCs involved?
- How are prions transported within peripheral nerves? Why is expression of PrPC required for efficient prion transport?
- How does prion infectivity and/or PrPSc travel across synapses?

Answering these questions will not be an easy task, yet investigation of these subjects might yield fundamental insights into the characteristics of these novel and essentially mysterious agents, and may yield useful leads for the diagnosis and therapy of prion diseases.

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REFERENCES


