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Why are prions and amyloid structures immune suppressive and other intriguing questions facing neuroimmunologists in the future

Pourquoi les prions, les structures amyloïdes immunosuppressives et d'autres curieuses questions se poseront aux neuro-immunologistes de demain ?

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ABSTRACT

The immune system plays a major role in certain diseases of the brain like multiple sclerosis and neuromyelitis optica, while the brain may play a major role in modulating certain immunologic diseases of the periphery like inflammatory bowel disease. The most significant developments in neuroimmunology will involve explorations of the roles for the immune system in neurodegenerative conditions often associated with the presence of amyloid deposits. Here I present my personal perspectives on four of the most intriguing challenges that we face in the future of neuroimmunology: (1) Why are the traditional hallmarks of innate and adaptive inflammation conspicuously absent from brains of individuals with prion disease and amyloid pathology? (2) What is the role of adaptive and innate immunity in progressive forms of multiple sclerosis? (3) Is molecular mimicry an adequate explanation for the initiation of neuroinflammatory disease and for exacerbations in conditions like multiple sclerosis, narcolepsy, and neuromyelitis optica? (4) Do neural pathways regulate inflammatory diseases outside the nervous system?

RÉSUMÉ

Le système immunitaire joue un rôle majeur dans certaines maladies du système nerveux central comme la sclérose en plaques et la neuromyélite optique alors que le système nerveux central joue un rôle majeur en modulant certaines maladies immunologiques périphériques telles que les maladies inflammatoires de l'intestin. Les développements les plus significatifs en neuro-immunologie concerneront l'exploration du rôle du système immunitaire dans les maladies neuro-dégénératives souvent associées à la présence de dépôts amyloïdes. Je présente ici mes perspectives personnelles pour quatre des défis les plus intrigants auxquels la neuro-immunologie devra faire face dans le futur. (1) Pourquoi

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les marqueurs habituels de l'inflammation innée et adaptative sont-ils si évidemment absents du cerveau d'individus atteints de maladie à prion ou d'une pathologie amyloïde ? (2) Quel est le rôle de l'immunité innée et adaptative dans les formes progressives de sclérose en plaques ? (3) Le mimétisme moléculaire est-il une explication adéquate à l'initiation de maladies neuro-inflammatoires et à la possibilité d'exacerbation dans des circonstances comme la sclérose en plaques, la narcolepsie ou la neuromyélite optique ? (4) Les voies neuronales contrôlent-elles les maladies inflammatoires en dehors du système nerveux ?

''It's tough to make predictions, especially about the future'', is a humorous quote often attributed to the American sports legend Yogi Berra [1], yet this aphorism epitomizes my challenge. Lecturing here in Paris, I provide a relevant example, perhaps, of the difficulties in predicting the futre developments in our speciality (neuroimmunology). Who would have imagined that Cezanne's still life depictions of bowls of fruit, might lead to cubism in the next century (Fig. 1)?

So predicting the future of neuroimmunology is formidable, ''*c'est vraiment formidable*''. Given your kind invitation to speak at the French Society for Neurology, I shall try nonetheless with your forbearance to make predictions via posing four questions. It is perhaps safest to make predictions via self-interrogation.

1. Why are the traditional hallmarks of innate and adaptive inflammation conspicuously absent from brains of individuals with prion diseases and diseases with amyloid pathology?

Stan Prusiner writes in his magnificent autobiography, *Madness and Memory*, that prion diseases show very little evidence of a traditional immune response: ''[. . .]the literature was replete with reports on the lack of an immune response to infection with the scrapie agent. Sheep, goats, rats, mice and hamsters all developed the scrapie disease without provoking any reaction in their immune system. The same is true for kuru and Creutzfeldt-Jakob disease (CJD) in humans. Not only were there no antibody deposits in the brains of animals with scrapie, but there was also no evidence of a cellular immune response involving lymphocytes. Nor did the interferon system, which is activated by viruses, respond to scrapie proteins.'' [2] Prusiner continues, ''One of the features shared by scrapie and CJD that intrigued me was the quiescence of the host defense systems. My CJD patient had died without ever developing a fever. She never showed an elevated white blood cell (WBC), either in her blood or cerebrospinal fluid (CSF). At autopsy her brain showed no evidence of antibody deposits or WBC infiltration. She died of a 'prion infection', but her defense systems were silent'' [2].

On deeper examination, a modest immune response to prions in experimental transmissible spongiform encephalopathy and in CJD is detectable [3]: ''Six brains from well-studied CJD patients were reevaluated for T-cell infiltration. As before, no T-cell infiltration was apparent by light microscopy. However, the application of antibody to human cluster of differentiation 3 (CD3) showed that T cells accumulated predominantly near or around blood vessels but also in the central nervous system (CNS) parenchyma in five of the six brains studied.'' [3]. It is clear that an adaptive humoral or cellular immune response is largely quiescent in prion diseases, compared to what we see in multiple sclerosis, the quintessential neuroinflammatory disease of the brain. In multiple sclerosis (MS) there is net synthesis of immunoglobulin within the CNS and all the elements of the adaptive immune system are present with the CNS parenchyma. The adaptive immune system is also largely quiescent in diseases with marked amyloid pathology. The stark differences in the inflammatory response in MS and Alzheimer's Disease (AD) are described in Fig. 2 [4].

One of the most surprising findings from our own research was the discovery that amyloid forming proteins are immune suppressive [5–8]. We first described that aB crystallin (cryab) ameliorated ongoing experimental autoimmune encephalomyelitis (EAE) and down regulated antigen specific Th1 and Th17 responses. We had become interested in cryab following van Noort's pioneering work showing that aB crystallin was a target of the immune response in MS [9,10]. Expecting to find that cryab, an abundant component of MS lesions [11,12] exacerbated EAE, our experiments indicated that it suppressed disease and impacted key inflammatory pathways such as NF-κB and p38MAPK. Moreover inducing EAE in a Cryab$^{-/-}$ mouse, revealed that the disease was more intense and that the pathology was more widespread.

Surprisingly we learned from the work of Eisenberg and colleagues that cryab is a protein that forms amyloid, and has served as a model for a slow forming amyloid protein [13]. However, cryab has properties that allow for its polydispersity. Present in amyloid deposits in various prion and amyloid diseases ranging from CJD, to Lewy body disease, Alzheimer's, Parkinson's and Alexander's diseases, cryab may prevent initial unfolding of proteins and even amyloid fibril formation [14].

Based on these pioneering studies from Eisenberg's group at UCLA we engineered a set of hexapeptides from a variety of notorious amyloid proteins including prion protein (PrP), tau, amyloid-β, amylin, serum amyloid A, cryab and insulin. We found that these hexapeptides could attenuate ongoing EAE, and that they could bind to inflammatory mediators in plasma [7,8]. Earlier work had shown that cryab not only attenuated EAE, but was beneficial in models of myocardial infarction [15], stroke [16], and optic nerve ischemia [17].

While gain of function experiments with these self-assembling amyloid forming hexapeptides suppressed disease, loss of function of the parent amyloid forming protein, including PrP [18], amyloid precursor protein [6], tau [19], or