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Introductory Chapter: Prions

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1. Introduction

The cellular prion protein (PrP^C) is expressed as a cell surface protein mainly in the central and peripheral nervous system, as well as in some cells and organs of the immune system (leukocytes and the spleen), the reproductive system (the testes and ovaries), and others, such as Peyer's patches in the intestinal tract, heart, lungs, and skeletal muscles, spreading to almost all parts of the body [1]. Prions were only relatively recently revealed to act as infectious agents although the diseases they cause have been known for a long time—initially attributed to toxic, genetic, and psychological factors and “unconventional viruses”—as our understanding of their mechanism evolved together with the methodological advancements.

The discovery that prions are infectious agents changed the concept of protein synthesis in modern biology and built a bridge between the genesis of infectious and genetic diseases.

The normal distribution of PrP^C in certain organs correlates with the pathogenesis route of some prion diseases, such as scrapie, Kuru, bovine spongiform encephalopathy (BSE), new variant Creutzfeldt-Jakob disease (vCJD), chronic wasting disease (CWD), and feline spongiform encephalopathy (FSE), probably acting as a “transformer and conductor” of the infectious isoform.

From a historical perspective, scrapie—as a disease of sheep—was a subject of discussion in the British parliament back in 1755; however, it was not until 1936 that Cullie and Chelle proved its contagious character by experimental infection [2]. Studies demonstrated genetic predisposition to development of the disease [3].

The disease bovine spongiform encephalopathy (BSE) was first identified and reproduced in 1986 in the United Kingdom [4]. It resulted from an incinerating technology introduced in the 1970s that worked at a lower disposal temperature and the supplementation of calf feed mixtures with meat-bone meal from scrapie sheep.

In Wisconsin, USA, in 1947, the disease transmissible mink encephalopathy (TME) was reported, arising from the use of sheep carcasses for food. Due to the cannibalism existing among minks and the passages through them, the etiological agent has undergone changes (e.g., it is nonpathogenic to mice) [2]. Another prion disease in animals is chronic wasting disease (CWD), which affects cervids including deer, elk, and moose. It was described by Williams and Young in 1980 [5], and no genetic determinant was detected for its development.

Feline spongiform encephalopathy (FSE) was first reported as a disease in members of family Felidae in a zoo in the UK [6] and in other carnivorous animals. Eventually, the infection was demonstrated to originate from BSE [7], the source of infection being contaminated food. BSE is also the etiological agent of diseases in Nyala, Kudu—exotic ungulate encephalopathy (EUE)—and Lemurs (NHP—BSE in nonhuman primates) [6, 8].

There is a direct relationship between the prion diseases in animals and humans due to the ability of BSE to jump the barrier between species (via contaminated

food) and the emergence of a new variant of CJD in the UK in 1996 [9, 10] affecting mainly young people aged 27–35 years. The prions isolated from these patients are glycosylated at two sites (like BSE), and their gene encoding PrP has a characteristic homozygosity at codon 129 (methionine-methionine) [2].

Creutzfeldt–Jakob disease (CJD) was reported back in 1920 [11], and the elucidation of the etiology of Kuru (see below) prompted Gajdusek and coworkers to prove the infectious nature of this disease (CJD) by successfully transmitting it to chimpanzees and other species of monkeys. The disease may be manifested in several epidemic forms: iatrogenic CJD (iCJD) [12] resulting from surgical interventions (corneal grafting), use of contaminated electrodes in encephalography, sporadic CJD (sCJD) resulting from spontaneous mutations [11], and other TSE diseases associated with mutations in the coding gene, for example, familial or genetic f/gCJD [13], Gerstmann-Sträussler-Scheinker syndrome (GSS) [14], fatal familial insomnia (FFI) [15], sporadic fatal insomnia (sFI) [16], and variably protease-sensitive prionopathy (VPSPr) [17].

Kuru is an interesting form spread among the natives of the Fore linguistic group inhabiting the mountainous regions of Papua New Guinea. The disease was studied by Gajdusek and coworkers in the 1960s. Based on its similarity to scrapie and epidemiological, clinical, and pathohistological features [18], Gajdusek managed to reproduce the disease in chimpanzees [19]. The research proved that the disease is noncontagious but transmitted by a tribal funeral ritual in which the deceased one's relatives pay their respect by eating his/her undercooked brain [2].

In one way or another, all prion diseases in animals and humans are of social and economic importance. It is alarming that human activity—guided by economic, ritual, or other considerations—could trigger the evolution of a pathogen so that it progressively crosses the barrier between two species within just a few decades or turns into a strain characteristic of a specific species or ethnic group. This comes to demonstrate, in a negative perspective, how deep and strong an effect can unconscious human interference have on biological processes. The mechanisms underlying these processes, however, still remain largely unknown. That is why, to correctly unravel the pathogenic processes, it is also important to gain a deeper understanding of the normal role of the prion protein and the processes that accompany it. Hence, this book discusses the normal function of the prion protein (PrP^C) and its modulatory role in synaptic mechanisms. It describes the pathophysiological processes that accompany TSE, such as neurotoxicity, loss of anti-inflammatory protective function, and the mechanisms of neuronal death including prion-induced autophagy and apoptosis. In TSE, specifically there is accumulation of an isoform of the normal protein (PrP^{Sc}) in the cytoplasm of neurons. Thus, it is important to understand the mechanism underlying this process, which is also reviewed in this book. Another aspect outlined here is that some prion diseases show strain variations, which determine their development, demonstrating their key role in the development and progression of TSE.

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