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EDİZ DEMİRPENÇE

FİLİZ AKBIYIK

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Understanding The Infectious Agent in nvCJD: Role of Copper

Ediz DEMİRPEŇE, Filiz AKBIYIK

Hacettepe University, Faculty of Medicine, Department of Biochemistry, Ankara - TURKEY

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Protease-resistant prion protein (Prp^{Sc}) has been identified as the infectious agent in a group of neurodegenerative diseases called transmissible spongiform encephalopathies (TSEs) or prion diseases (1). One of the TSEs, Creutzfeldt-Jakob disease (CJD), is of particular interest, because it has been the cause of a food-originated epidemic in Europe. CJD was formerly described as a sporadic or iatrogenic disease and its interspecies transmissibility was known to be limited due to the species barrier (2). However, this new variant form of CJD (nvCJD) seems to be easily transmissible from cattle, to humans through the diet; therefore extensive research has been going on to define the structure, toxicity and propagation mechanism of this infectious agent.

The infectious Prp^{Sc} protein has a normal cellular counterpart, Prp^C, which is a sialoglycoprotein anchored to the cellular membrane through a glycosylphosphatidylinositol moiety (3). The dominant secondary structure of Prp^C is α -helix, whereas Prp^{Sc} is rich in β -sheet (4). In fact, there is no difference between the primary structures of Prp^C and Prp^{Sc}, and transgenic mice devoid of normal Prp^C are resistant to infection with Prp^{Sc}. Therefore, it has been proposed that Prp^{Sc} behaves as a template that promotes the conformational transition of Prp^C to Prp^{Sc} (1-4). Thus, prion diseases are mainly considered protein folding disorders.

Prp^{Sc} is detergent insoluble, resistant to proteolytic digestion and has a very high tendency to aggregate. Pathologic changes that occur in the brain due to the accumulation of Prp^{Sc} are florid plaques surrounded by spongiform change, neuronal loss and astrocytosis (5). Different hypotheses have been proposed to explain the neurodegenerative effects of Prp^{Sc}. Data suggest the involvement of transition metals in the mechanism but the functional consequences of the interaction of Prp^{Sc} with metals are still debated. The N-terminal domain of

the prion protein includes octapeptide motifs whose general sequence is P(H/G)GG(G/S)WGQ and these motifs are involved in copper (Cu⁺²) binding (6). Prp^C contains four Cu⁺² ions coordinated with four histidine imidazol nitrogens (7). Recent data indicate that only two of these Cu⁺² ions are bound with an affinity similar to other authentic cuproproteins (8). Cu⁺² binding has been shown to have diverse effects on Prp^C. It has been shown to stimulate the endocytosis of the prion protein from the cell surface of neuroblastoma cells (9). Cu⁺² also causes Prp^C to assume a protease-resistant and detergent-insoluble form (10). This species of prion protein is similar to Prp^{Sc}, but its conformation is different (6,10). Moreover, the addition of Cu⁺² facilitates the renaturation of denatured Prp^{Sc}, restoring its protease resistance and infectivity (11). The metal binding property of the prion protein seems to be important in understanding the function of Prp^C. Metal binding proteins are usually implicated in the oxidative metabolism of cells and oxidative stress is involved in a variety of neurodegenerative diseases (12). By using infected cell lines, it has been shown that infection with Prp^{Sc} impaired the defense of the cell against oxidative stress (13). In a similar study, neurons that were devoid of normal prion protein showed lower glutathione reductase activity and increased susceptibility to hydrogen peroxide toxicity (14). It has also been proposed that Prp^{Sc} increased the incorporation of Cu⁺² into the Cu/Zn superoxide dismutase (SOD) and it even had an activity like that of SOD (15). The presence of Cu⁺² ions renders the prion protein susceptible to metal-catalyzed oxidation, and the oxidation is accompanied by extensive aggregation and precipitation of the protein (16).

In an attempt to identify the smallest fragment of Prp^{Sc} that can be infectious and neurotoxic, a fragment corresponding to residues 106-126 of human Prp^C (PrP106-126) has been identified (17-19). This sequence corresponds to a highly conserved region of the protein

and is susceptible to conformational transition. It is capable of aggregating into amyloid-like fibrils and has a tendency to take a β -sheet structure (17). Prp106-126 has been shown to exert a neurotoxic effect in a number of cultured nerve cells by inducing apoptosis (18,19). It also inhibits the function of Prp^C through binding to it (20) and this inhibition prevents the uptake of copper into cells and the SOD-like activity of Prp^C.

In the last 20 years, a growing body of information has been accumulated in the field of prion research. There is no doubt that the infectious agent is a misfolded

protein, and it is capable of converting normal prion protein molecules into infectious ones. However, the molecular details of the mechanism remain to be elucidated. It is interesting to note that the implication of Cu⁺² ions in the formation of spongiform encephalopathies was proposed about 30 years ago (21). Recent findings also indicate the role of metal ions in the mechanism and provide new pieces for the puzzle. However, further research is necessary for us to be able to see the whole picture.

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