Abstract

Knowledge of structural and dynamical properties of prion protein is important for understanding of its biological role, structural conversion and transmissibility in prion biology. Appearance of rare and devastating prion diseases of humans such as Creutzfeldt-Jakob disease, kuru, fatal familial insomnia and Gerstmann-Straussler-Scheinker syndrome are related to structural conversion of cellular isoform of prion protein (PrP^{C}) to misfolded, toxic one (PrP^{Sc}). Beside human prion diseases are also known animal prion diseases such as scrapie, mad cow disease and chronic wasting disease. Little is known about mechanism of prion conversion, his physiological role and biological partners. Nuclear magnetic resonance spectroscopy enabled structural determination, examination of dynamical properties and study of molecular complexes. It is very useful method for characterization of mammalian prion proteins, that are composed of flexible N-terminal and well-defined C-terminal domain. Recent findings suggest that cellular prion protein is a multifunctional protein that participates in several biological processes. In this thesis we have examined interactions between human prion protein (huPrP) and the neuronal cell adhesion molecule (NCAM) by NMR spectroscopy. Structural investigation of interaction between NCAM and huPrP was performed using a recombinant second module of fibronectin type-3 (FNIII2) domain of NCAM and huPrP peptides of different lengths originating from its intrinsically disordered N-terminus. Our data provide evidence for interaction between N-terminal of huPrP and FNIII2 domain. Findings from this study implicate that PrP^{C} could interact with a pallet of bindings partners that consisted of similar fibronectin type domains.

Chronic wasting disease is a highly infectious prion disease of cervids that is widespread on the big area of North America. Additionally, first cases of CWD appeared in the Europe in 2016. The possible risk of CWD transmission from cervid to human present a global treat and big concern for public health. Analysis of PrP^{C} sequence of subfamilies Cervinae (elk) and Capreolinae (mule and white-tailed deer) revealed the existence of a polymorphism in amino acid sequence at position 226, in which elk PrP contains glutamate (E), while deer PrP contains glutamine (Q). In this study, we highlight the importance of PrP structure in prion susceptibility, and how single amino acid differences might influence prion transmissibility and pathogenesis. We have determined high-resolution structure of the mule deer prion protein (mdPrP). Although the overall structures of the mammalian prion proteins are similar, we have detected several local structural variations between compared structures. The most remarkable differences between compared PrP structures of cevids are located at the beginning of well-defined C-terminal domain, at the β2-α2 loop, at the N-terminal of α1 helix, at the α2-α3 loop and in the C-terminal of α3 helix. We have found that a single amino acid polymorphism can alter the PrP structure and could have important consequences on the different pathogenesis of CWD prions.

Key words: prion protein, prion diseases, chronic wasting disease, nuclear magnetic resonance.