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Titel des Beitrags: Globular domain of the prion protein needs to be unlocked by domain swapping to support prion protein conversion.

Abstract: Prion diseases are fatal transmissible neurodegenerative diseases affecting many mammalian species. The normal prion protein (PrP) converts into a pathological aggregated form, PrP(Sc), which is enriched in the ?-sheet structure. Although the high resolution structure of the normal PrP was determined, the structure of the converted form of PrP remains inaccessible to high resolution techniques. To map the PrP conversion process we introduced disulfide bridges into different positions within the globular domain of PrP, tethering selected secondary structure elements. The majority of tethered PrP mutants exhibited increased thermodynamic stability, nevertheless, they converted efficiently. Only the disulfides that tether subdomain B1-H1-B2 to subdomain H2-H3 prevented PrP conversion in vitro and in prion-infected cell cultures. Reduction of disulfides recovered the ability of these mutants to convert, demonstrating that the separation of subdomains is an essential step in conversion. Formation of disulfide-linked proteinase K-resistant dimers in fibrils composed of a pair of single cysteine mutants supports the model based on domain-swapped dimers as the building blocks of prion fibrils. In contrast to previously proposed structural models of PrP(Sc)
suggesting conversion of large secondary structural segments, we provide evidence for the
conservation of secondary structural elements of the globular domain upon PrP conversion. Previous
studies already showed that dimerization is the rate-limiting step in PrP conversion. We show that
separation and swapping of subdomains of the globular domain is necessary for conversion.
Therefore, we propose that the domain-swapped dimer of PrP precedes amyloid formation and
represents a potential target for therapeutic intervention.