Pattern recognition with a fibril-specific antibody fragment reveals the surface variability of natural amyloid fibrils.

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Abstract

Amyloid immunotherapy has led to the rise of antibodies, which target amyloid fibrils or structural precursors of fibrils, based on their specific conformational properties. Recently, we reported the biotechnological generation of the B10 antibody fragment, which provides conformation-specific binding to amyloid fibrils. B10 strongly interacts with fibrils from Alzheimer's β amyloid (Aβ) peptide, while disaggregated Aβ peptide or Aβ oligomers are not explicitly recognized. B10 also enables poly-amyloid-specific binding and recognizes amyloid fibrils derived from different types of amyloidosis or different polypeptide chains. Based on our current data, however, we find that B10 does not recognize all tested amyloid fibrils and amyloid tissue deposits. It also does not specifically interact with intrinsically unfolded polypeptide chains or globular proteins even if the latter encompass high β-sheet content or β-solenoid domains. By contrast, B10 binds amyloid fibrils from d-amino acid or l-amino acid peptides and non-proteinaceous biopolymers with highly regular and anionic surface properties, such as heparin and DNA. These data establish that B10 binding does not depend on an amyloid-specific or protein-specific backbone structure. Instead, it

involves the recognition of a highly regular and anionic surface pattern. This specificity mechanism is conserved in nature and occurs also within a group of natural amyloid receptors from the innate immune system, the pattern recognition receptors. Our data illuminate the structural diversity of naturally occurring amyloid scaffolds and enable the discrimination of distinct fibril populations in vitro and within diseased tissues.

Beteiligte Forschungseinheiten

Molekulare und Angewandte Mikrobiologie Axel Brakhage Mehr erfahren

Biotechnikum Miriam Agler-Rosenbaum Mehr erfahren

Leibniz-HKI-Autor*innen

Magdalena Bereza

Details

Christian Haupt

Details

Uwe Horn

Details

Peter Hortschansky

Details

Themenfelder

Camelide VHH-Antikörper

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