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New and Notable

Antimicrobial Amyloids?

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The molecular mechanisms by which misfolded amyloid proteins cause disease would seem, at first, to have little to do with the workings of the innate immune system. However, the companion work of Jang et al. (1) showing the antimicrobial peptide protegrin forms amyloid fibrils leads us to that very conclusion. It would also seem unlikely that the extended amorphous deposits known as amyloid seen in pathological specimens of human disease would have any similar biophysical properties to the relatively short cytotoxic peptides responsible for host defense. Yet, this, too, is the implication of recent research.

The role of amyloid proteins in disease has been at issue for over a century. Rudolf Virchow first described the Congo red-staining deposits seen in disease tissue and mistook them for carbohydrates. It later became clear that the main constituent of these deposits was a single protein in a misfolded state. The unique protein varies from the beta-amyloid peptide (BAP) of Alzheimer's disease (AD) to the prion protein (scrapie form PrPSc) of prion diseases, such as mad cow and Creutzfeldt-Jakob disease. Many years of painstaking research were required to dissect the true molecular nature of amyloid deposits, showing that the amyloid proteins were composed of stacked beta sheets in the form of extended fibrils. Their structure was eventually solved through biophysical techniques, such as x-ray diffraction and electron microscopy, but the role of these deposits remained obscure. For many years, the tombstone theory held sway, which regarded the amyloid deposits as a marker of some injurious event that had happened in the past, but was no longer an active process. In the 1990s, the amyloid cascade hypothesis (2), proposed that BAP played an active role in the pathogenesis of AD. Evidence for this theory included the existence of inherited forms of the disease with mutations in or near BAP, and the fact that patients with Trisomy 21 (Down's Syndrome) carrying an extra copy of the BAP gene experience an early onset form of AD with cognitive deficits appearing as early as the third decade of life. A third line of evidence demonstrated that the BAP from humans could be inserted into a transgenic mouse, resulting in an Alzheimer's-like disease characterized by amyloid deposits and learning deficits. More recently it has been shown that most amyloid peptides do not seem to be toxic in the monomeric or fibrillar state, but rather in a relatively low aggregation state, usually referred to as oligomers or protofibrils. These smaller aggregates seem to possess virtually all the cytotoxic activity of amyloid peptides, and substantial evidence suggests that channel formation plays a key role in the cytotoxic effect.

Protegrins are a class of basic cysteine-rich beta-sheet antimicrobial peptides of ~18 residues which possess potent cytotoxic activities against bacteria, fungi, and enveloped viruses. They play an important role in the innate immune system and are a critical part of the armamentarium of neutrophils and macrophages. Protegrins kill by breaching target membrane permeability, although there remains some controversy as to whether membrane leakage is due to channel formation or a carpet mechanism. Protegrins are a mini version of the larger host defense peptides known as defensins, of which three major types have been described, alpha, beta, and theta. All of these antimicrobial molecules possess a similar size, basic amino acid content, several disulfide bonds, and high content of beta-sheet structure, and all these structural factors appear to play a key role in mediating cytotoxicity. In the companion work, Jang et al. (1) report that protegrin-1 forms fibrils with the biophysical properties of amyloid. This remarkable discovery confirms and extends the notion that it is the beta-sheet secondary structure that predisposes it to fibril formation. It provides further confirmation that the beta-sheet is a uniquely suited protein structure to allow aggregation of monomers into oligomers and into larger extended structures. The data are striking in that they show remarkable biophysical resemblances between the fibrils formed by protegrins and fibrils formed by more classic amyloid peptides. The authors use atomic force microscopy, Thioflavin T staining, and molecular dynamic simulations to show that the PG-1 fibrils grow relatively fast compared to those of BAP fibrils and, curiously, do not grow in the presence of lipid bilayers. Previously, lipid bilayers have been shown with other amyloids to inhibit fibril formation and to favor the formation of small oligomers capable of inserting into the bilayer.

If antimicrobials can form amyloid fibrils, can amyloid peptides form antimicrobials? The BAP itself possesses antimicrobial activity under the appropriate conditions (3). These conditions, it turns out, favor the formation of small oligomers of beta-amyloid peptide of the kind which would possess cytotoxic and channel-forming function.

Some bacteria seem to produce amyloids for structural purposes and to retard the growth of neighboring bacteria (4). The companion work seems to close the loop connecting protein misfolding, beta-sheet structure, membrane insertion, channel formation, and cytotoxicity, as well as the alternate pathway of monomer aggregation into

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extended amyloid fibrils which precipitate out of solution. Seen in this light, some have commented that fibril formation may, in fact, be protective, in that fibrils are relatively nontoxic compared to oligomers. Further research will be required to demonstrate the presence of oligomeric channels in disease tissue specimens and, ultimately, therapeutic research avenues may explore the viability of molecules that prevent membrane insertion of oligomers or block the toxic pores formed by oligomers. The intriguing question of whether amyloid peptides play a host defense role in vivo remains to be explored.

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