52b Identification of Inhibitory Binding Faces of ß-Amyloid Fibril Formation

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Alzheimer's disease (AD) is the leading cause of dementia in the elderly. The brains of AD patients are characterized by the deposition of amyloid plaques, composed primarily of the fibrillar from of the amyloid-ß protein (Aß). Aß deposited within plaques consists principally of the 40- or 42-residue form of the peptide derived by proteolysis of cellular amyloid precursor protein (APP). Monomeric Aß self-associates to form the fibrillar Aß that deposits within amyloid plaques. Initial aggregation of Aß monomer occurs via a rate-limiting nucleation step. Following nucleus formation, rapid growth ensues and proceeds through a soluble intermediate known as a protofibril. Two mechanisms of protofibril growth have been identified: elongation by monomer deposition and direct protofibril association. These mechanisms can be isolated *in vitro* by controlling monomer concentration and ionic strength.[1] Although the relationship between amyloid plaques and AD is still unclear, increasing evidence suggests a role for Aß assembly in the progression of AD, and what has become known as the amyloid hypothesis continues to gain support. Consequently, inhibition of Aß fibril formation has emerged as one therapeutic strategy for AD. Several compounds, including antibodies, peptides, and small molecules, have been identified as capable of inhibiting *in vitro* assembly of Aß. We investigate the effect of several fibril formation inhibitors on the *in vitro* assembly of Aß(1-40) fibrils via protofibril intermediates. Assays designed to isolate protofibril growth mechanisms are used to characterize inhibitors of protofibril growth. It is found that inhibitors can recognize different protofibril binding faces to prevent growth by different mechanisms. Inhibition results are correlated with inhibitor structure to identify effective binding faces and underscore the importance of discerning inhibition mechanisms. Understanding the mechanism of action of Aß fibril formation inhibitors will assist research efforts to design therapeutic agents targeted at inhibiting Aß fibril formation.

[1] Nichols MR, Moss MA, Reed DK, Lin W-L, Mukhopadhyay R, Hoh JH, and Rosenberry TL (2002) Growth of ß-amyloid(1-40) protofibrils by monomer elongation and lateral association. Characterization of distinct products by light scattering and atomic force microscopy. *Biochemistry* 42: 6115-6127.