Single-chain variable fragment antibodies targeting Alzheimer's disease-relevant particular Aβ oligomers

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ABSTRACT

Toxic soluble Aβ oligomers (ADDLs) accumulation is now widely accepted as a primary and necessary event in Alzheimer's disease (AD) pathology. Antibody-based therapies targeting ADDLs have been shown to reduce AD pathology in both animal models and AD patients. In particular, usage of antibodies targeting conformational epitopes on ADDL molecule has emerged as a promising approach to effectively rescue neural function in AD. Starting from a synthetic library of human single chain antibodies (scFv), we used phage display to isolate a unique set of scFv's that efficiently distinguished Aβ oligomers from either monomeric or fibrillar Aβ, as well as transgenic mouse models of AD from wild type brain extracts. ADDLs bound to neuronal surface in primary cultures were readily detected by anti-ADDLs scFv's. In addition, a purified, phage free form of one of these scFv's, NUsc1, blocked ADDLs neuronal binding by neutralizing oligomeric ligands in solution. Importantly, NUsc1 also recognized endogenously-produced Aβ oligomers in human AD brain extracts and tissues, indicating that ADDLs prepared *in vitro* assume a disease-relevant conformation. NUsc1-reactive Aβ oligomers in AD human brain sections and cultured neurons are partially distinct from Aβ species detected by previously characterized anti-ADDLs full length IgG's obtained using animal vaccination. Size-exclusion chromatography conjugated with NUsc1-based detection analysis revealed a novel Aβ oligomeric species of 30 kDa abundant in both synthetic ADDLs and AD human brain extract. These novel anti-ADDLs scFv's may help to decipher the conformation of the actual pathological assemblies of Aβ, highlighting their potential as more efficient diagnostic and therapeutic reagents for facing AD.