A bacteriophage-based platform for early diagnosis of Alzheimer's disease

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Alzheimer's disease (AD) is the most common neurodegenerative disease affecting a large proportion of the human population worldwide. One hallmark of AD is the increased deposition of plaques, which consist of amyloid-beta (AB) peptide, a key molecule to cause AD onset and progression. However, it is not AB immobilized in plaques, but in the still-soluble oligomeric/fibrillar form that impairs synaptic function and memory encoding. It is therefore important to develop tools that selectively target AB in oligomeric/fibrillar form, to diagnose and neutralize these detrimental AB-clusters during the early stages of the disease.

Homing peptides that selectively recognize AB-oligomers and fibrils have been described: AB30-39, reactive for AB fibrils and AB33-42, reactive to fibrils and oligomers [1]. However, these peptides are unable to cross the blood-brain barrier (BBB) by themselves. To overcome this limitation, viruses became a very interesting tool given their versatility to be modified through genetic or chemical manipulation. Bacteriophages (phages), are viruses that only infect bacteria (a major advantage in terms of safety when therapeutic use in humans is envisaged). M13KE is one of the most widely used phage which has been reported as capable to cross the BBB [2].

The present work describes the development of a phage-based system capable of diagnose AD at an early stage by shuttling amyloid-beta specific ligands across the BBB. M13 phages were genetically engineered with two peptide sequences to selectively recognize amyloid-beta oligomers in order to target and visualize amyloid-beta aggregates in the brain. Immunohistochemistry results successfully demonstrated that AB1-phages selectively target AB-protofibrils in brain slices from AD-model mice, but not in brain slices from age-matched wild-type littermate. In addition, control phage (carrying no AB-selective peptide) did not stain AD or WT tissue. Co-staining with both anti-M13 and 6E10 (an antibody reactive against all species of AB including plaques), confirm that AB1 phage target AB-protofibrils, but not plaques.

Future work will be devoted to test this system in AD-mouse and human models, first for diagnosis purposes at an early stage of the disease. Second, for therapeutic intervention, we will assess the inhibition of the oligomeric AB-mediated synaptic loss and memory impairment.

If successful, this approach will provide the neuroscience community with a faster, user-friendly and cheaper diagnostic/therapeutic tool for Alzheimer´s disease.

References

[1] Perchiacca, JM., *et al.*, Structure-based design of conformation- and sequence-specific antibodies against amyloid beta. *Proc Natl Acad Sci U S A*, 109(1), 84-89, 2012.

[2] Frenkel, D and Solomon, B, Filamentous phage as vector-mediated antibody delivery to the brain. *Proc Natl Acad Sci U S A*, 99(8), 5675-5679, 2002.