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Modifiers of amyloid beta toxicity in Alzheimer's disease

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One of the hallmarks of Alzheimer's disease is the formation of extracellular senile plaques, preferentially composed of Amyloid beta protein. Processing of Amyloid precursor protein leads to the production of two reservoirs of Aβ: a secreted pool and a non-secreted cytoplasmic pool. Secreted Aβ contributes to extracellular plaques but despite various studies, the role of cytoplasmic Aβ in AD pathogenesis remains unclear. Indeed, the degree to which Aβ penetrates from vesicles through to the cytoplasm is not clear, however, it is likely that there is a dynamic equilibrium between all these pools. In this study, we hypothesise that cytoplasmic Aβ contributes to the toxicity of secreted Aβ through specific transmembrane interactions in our fly model of AD. Our preliminary experiments show that expression of aggregation prone form of extracellular Aβ leads to a reduction in longevity, locomotor deficits and the deposition of plaques while that of cytoplasmic Aβ, on the other hand, is non-toxic. Interestingly, the co-expression of cytoplasmic Aβ enhances the plaque deposition and toxicity of extracellular Aβ. To investigate how extracellular and cytoplasmic Aβ may interact we undertook an RNAi modifier screen of 115 candidate genes in *Drosophila*. We measured the increase in longevity caused by RNAi in flies expressing extracellular and cytoplasmic Aβ. Only those RNAi constructs that did not also cause increased longevity in control flies (those expressing only extracellular Aβ and those not expressing Aβ) were retained. By doing so, thirteen genes are found to specifically rescue the combined toxicity of cytoplasmic with extracellular Aβ. *Flottilin-1* and ABCB8 (CG1356) are the best validated modifiers that we have detected. The longevity data is also supported by brain histology, gene and protein expression measurements. Obtained results suggest a synergistic interaction between two pools of Aβ and highlight the importance of transmembrane Aβ interactions in AD pathology.

Biography

Mayida Azhar is a 3rd year PhD student in department of Genetics, University of Cambridge.

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