

a mind astray

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He hadn't been able to dial the full number for some time. But he had told his family that the phone was out of order. Until one of his daughters realised that it was not the phone which was faulty but her father's memory. This is just one of the many manifestations of what could be the beginnings of Alzheimer's disease (AD). A disease which affects millions of people worldwide, and sends their families into a whirlpool of doubt, impatience, pain and disbelief. Slowly but surely, Alzheimer's takes a hold of the patient's brain, causing damage to its neuronal structure and hampering its cognitive faculties. In time, the patient fails to recognise his or her own family besides suffering from disturbed basic vital functions, and the family members have to learn to deal with the loss of someone dear who is still alive... With a little over 100 years of research into AD, scientists are now able to diagnose the affliction relatively early. Despite this, there is still no medication which can cure a patient, though researchers have ventured down many alleys. One of these alleys involves a protein known as immunophilin FKBP52 which may have a future in stalling the progression of Alzheimer's.



Alex, by Jeff Bowering

Courtesy of the artist

Over the past few decades, especially since the era of molecular biology, scientists have reached an understanding of AD at a very fine level. There seem to be different forms of the disease. A rare hereditary form. One form which may be caused by neuronal inflammation. And the more current sporadic form which occurs with the passing of the years. In this instance, neuritic plaques and neurofibrillary tangles are observed in the brain, both of which are the result of two different

proteins – amyloid- β and tau, respectively – that accumulate in an abnormal fashion. As a result, normal neuronal growth and function are hindered bringing on the characteristic symptoms.

Tau is abundant in neurons and binds to microtubulin where it has a pivotal role in microtubule growth and stability. And if it affects microtubule growth, then it affects not only cellular architecture but also cellular trafficking, since cells use microtubules as motorways to deliver nutrients and other molecules to different destinations. Without the assistance of tau, neurons are then neither able to elongate, nor to regenerate. In AD, tau structure is modified via hyperphosphorylation and instead of assisting microtubulin, it creates tangled clumps of fibres in the neurone's cytosol.

If such clumps could be dismantled one way or another, or at least their growth impeded, then that would leave free tau for the microtubules. Consequently, cognitive malfunctions caused by stunted microtubule elongation could either be restored or avoided. This is the exciting – albeit speculative – discovery that was announced at the beginning of the year. And where immunophilin FKBP52 comes into the picture.

FKBP52 is a large protein found in abundance in the brain – up to 50 times more than in the immune system in rats, for instance. To date, FKBP52 is thought to have at least three probable distinct roles. First, the protein can function as a peptidyl-prolyl *cis-trans* isomerase – also known as rotamase activity – in which it has a role in the folding and unfolding of other proteins. Second, it can bind to the heat shock protein Hsp90, by way of which it interacts with steroid receptor heterocomplexes and regulates steroid receptor signalling. Third, and here's the novelty, it binds to tau.

And, not only does it bind to tau, but it especially binds to tau in its hyperphosphorylated form, which is the form that creates the tangled clumps characteristic of AD. Subsequently, as the reasoning goes, if FKBP52 can bind to the hyperphosphorylated tau, then it could prevent tau from forming clumps, thus slowing down the progression of AD, or indeed anticipating it.

It all sounds very promising. Yet scientists are quick to point out that tau is only one component which is part of AD. There is also

amyloid- β , to name but one. What is more, everything is still very hypothetical since research has not extended further than the laboratory and no direct link has been made to AD. Besides, tau interacts with hosts of other proteins, and who says that FKBP52 has a “privileged” interaction with it?

Sometimes, research is like fumbling for an unknown object in the dark. And it is not surprising that a disease such as Alzheimer's, which taints something as intangible as personality and the very subtle chemical balance which makes it, is so difficult to fathom. AD, and similar dementias, is possibly one of the worst illnesses which can afflict a human being – and their surroundings – since it affects the very essence of who we are. And that is no doubt why such huge advances have been made on the medical front in the past years. AD is now diagnosed faster. Over the years, ways have been found to slow it down. Surely the next step will be some kind of cure.

N.B. Also read Protein Spotlight issue 83, “Tangled”

Cross-references to UniProt

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