Key Stage 5

Plaques and tangles

Student worksheet

What is Alzheimer’s Disease?

Alzheimer’s disease (AD) is named after the doctor who first described it (Alois Alzheimer). It is a type of dementia, and symptoms include difficulties with thinking, memory, problem-solving or language.

AD mainly affects people over 65, although younger people can develop it.

What causes it?

The root cause of AD is poorly understood, and may be a combination of aging, genetic susceptibility, and overall body health. These factors can contribute to toxic proteins building up in the brain. One of the proteins involved is called beta-amyloid, which forms plaques around brain cells. Another protein called tau forms tangles within brain cells.

Over time, neuron and brain cells die and areas of the brain shrink. The first areas usually affected are responsible for memories.

Can we cure AD?

Currently there are no drugs to treat the underlying causes of Alzheimer’s disease. However, at the ARUK Oxford Drug Discovery Institute (ARUK ODDI), scientists are collaborating with other laboratories to find new ways to tackle the disease.

Firstly, the ODDI biologists build biological models of AD in the lab, and create ways to test specific properties of the model. The ODDI chemists design and make experimental drugs, which the biologists add to their biological model and run the test. There are many rounds of designing, making and testing, and many molecules fall by the wayside. Slowly they are able to craft and refine the small molecules until a few have the desired effect. Having shown that the approach is likely to succeed, they then hand the small molecules to pharmaceutical companies, who continue refinement and testing to turn the small molecules into a drug. Only the single best small molecule will undergo safety testing and, if it passes, undergo clinical trials with patients.

Your task

A laboratory has come up with an initial idea for a treatment for AD. They have discovered a drug that will destroy microglia, a type of brain cell that performs innate immunity. Should the ODDI investigate further?

You should:

- Learn more about what causes AD by completing the ‘AD flowchart’.
- Critique the lab’s idea – should it be investigated further and why? You can use information from the ‘review conclusion’.
- Suggest another target for a drug that could treat AD. You should explain why you think it would work.

https://www.oxfordsparks.ox.ac.uk/content/discovering-life-changing-dementia-treatments
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AD Flowchart

Watch the video [https://goo.gl/tmGCLH](https://goo.gl/tmGCLH) and complete the flowchart to show the causes of AD.

[Diagram of AD flowchart]

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Microglia have recently emerged as crucial players in the pathogenesis of late onset AD, but exactly how they are involved in the disease mechanism is not settled. The preponderance of human genetics evidence, exemplified by the large effect of loss-of-function TREM2 mutations on AD risk and on microglial function, argues that microglia have a protective function that lowers the incidence of AD. Conversely, there is also considerable evidence that microglia are responsible for neuronal damage in AD (albeit mostly in mouse models). In particular, microglia may engulf and remove synapses via a complement-dependent mechanism, and the induction of a microglial proinflammatory state may correlate with severity of neurodegeneration. Transcriptional profiling of microglial gene expression suggests that different states of microglial activation may occur during the course of AD, but more precise characterization—temporal, anatomical, and functional—is needed.

To synthesize the findings from disparate approaches, we propose the following hypothesis: Microglial function is normally protective in the brain, with microglia acting as housekeeping phagocytes to maintain tissue homeostasis and keep the extracellular space clean of Aβ, thereby preventing AD. When Aβ levels accumulate, microglia phagocyte and clear Aβ aggregates, and when outstripped in this activity, microglia compact Aβ aggregates in dense core plaques and shield them off from neurons. These latter protective activities involve activation of microglia to a DAM state, depend on TREM2, and are aided by apoE. Sometimes, because of aging or genetic susceptibility, microglial function becomes inadequate to prevent the onset and progression of AD. As toxic amyloid species accumulate, tau pathology accrues in stressed or damaged neurons, inducing microglia into a nonconstructive and inflammatory state in which they eat synapses, secrete neurotoxic cytokines that injure neurons and abet in the spread of tau pathology. In such a model of disease pathogenesis, microglia have two faces, one beneficial and one harmful, with the detrimental microglia population appearing later in the disease course and coinciding with synapse loss and symptomatic decline. If true, the double-edged sword of microglial function in AD will complicate therapeutic approaches that target microglia, because stimulation of microglial activity may be helpful at an early stage, to prevent AD before it is established, but become detrimental later, when the disease has reached a highly inflamed, neurodegenerative stage.