Lay Summary

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Entrapment of lipoprotein particles in the brain drives Alzheimer's disease

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Cholesterol is essential to the maintenance and function of the nerve cells. It is delivered to the cells via particles called lipoprotein. The space that the particles have to go through is a narrow cleft between cells in the brain, barely wider than the lipoprotein particles themselves. The particles have to navigate to perform their crucial cholesterol-transporting function through this tight space. We think that this extracellular space becomes compromised as it gets older, trapping the particles. This means that the amount of cholesterol being delivered to the nerve cells is reduced. This leads to learning and memory problems. We propose that the trapped particles which also carry Aβ, release their Aβ forming plaques, provoking inflammation, and that tangles form in the nerve cells due to reduced cholesterol delivery. All of these players have been known for many years to be important in the development of Alzheimer's disease but a single unifying mechanism to explain how they are linked is missing. One of the challenges to exploring this hypothesis is that these particles are very small, too small for conventional microscopes. Therefore, we wish to develop novel 3-dimensional microscopy methods to identify the particles in the human brain. If successful, the findings may point our understanding of the development of Alzheimer's disease in a new direction.