

Defeating Alzheimer's Disease with New Gene Therapies

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Most of us have known someone trapped by the deterioration of Alzheimer's disease. Although Alzheimer's disease (AD) is primarily a disease of the elderly, it has a widespread impact on society because the average age of our population is increasing. From the outside, we see Alzheimer's as a disease of memory loss: first little things, then loved ones, and eventually even the most basic tasks of self-care are forgotten. It has a huge impact on friends and family, who often become caregivers. Overall, care for those with Alzheimer's disease costs the United States 172 billion dollars a year, and that number will only increase in the coming years (Alzheimer's Association, 2010).

While we see memory loss as the major change that occurs in Alzheimer's disease, there are visible changes going on at the cellular level in the brain. If you were to look under the microscope at a slide of brain tissue from an Alzheimer's affected brain, you would see the two biological hallmarks of AD. The first hallmark is the presence of amyloid beta plaques outside of the neurons. Proteins are cut by chemical "scissors" called secretases (Hardy and Selkoe, 2002). These plaques are created when a protein called APP is cut in half in the wrong place. The second hallmark is the presence of tangles made of tau protein inside of the cells. In healthy cells, tau acts as a glue to hold the skeleton of a cell together (Lee et al., 2001). When phosphorus molecules are attached to tau by kinases, the tau becomes "sticky" and has self-adhesive properties (Buee, 2000). Both of these pathologies develop when particular proteins, amyloid beta or tau, aggregate and form clumps. Cells affected by these aggregates die, leaving behind non-functional areas of the brain that are full of dead neurons. Scientists still do not know what part of this process actually damages the neurons. Currently, there are no effective treatments to prevent or reverse the effects of tau tangles or amyloid beta plaques. This is one of the greatest tasks for the scientific community because Alzheimer's is such a painful problem for our society. An exciting new study by Zhang et al., (2009) has come out with a discovery that shows promise as a potential therapy. Senior study author Dr. Huaxi Xu said, "Identification of new genes involved in these processes will be instrumental in developing novel AD therapeutics (Cell Press, 2009)."

In the search for a cure, scientists have faced many obstacles. Zhang et al.'s (2009) article, "A Functional Mouse Retroposed Gene Rps23r1 Reduces Alzheimer's Beta-Amyloid Levels and Tau Phosphorylation," introduced a possible solution to this critical problem. In order to find a gene that was related to amyloid beta, Zhang et al., (2009) used a computer program, similar to a search engine, that looks for genes based on their functions. They found a gene in mice called Rps23r1, which we can call the "R gene" for the sake of this article. This gene was interesting because, as opposed to other areas of the body, it was very active in the brain, especially in the hippocampus. The hippocampus is the area of the brain in which neurons first start to die in Alzheimer's disease.

Zhang et al., (2009) then investigated whether this gene had any effect on the two hallmarks of Alzheimer's disease: amyloid plaques and tau tangles. To do this, they made the R gene more active in mouse cells that were affected by plaques and tangles. They found that the plaques and tangles decreased in these treated cells. This was an exciting finding because it showed that the R gene somehow controls the major pathologies in Alzheimer's disease. However, there is no gene like the R gene in humans, so they were uncertain whether putting this gene in human cells would have any effect at all. Using the same process as before, but in human cells, they found that the R gene reduced tau and amyloid beta in human cells. With this potential hurdle cleared, the researchers then went on to learn more about the R gene and how it controls Alzheimer's pathologies.

After several hypotheses explaining how this gene was controlling plaques and tangles did not pan out, Zhang et al., (2009) finally found success. They discovered that this gene controlled an important cellular pathway called the GSK-3 cAMP pKA pathway. This pathway controls many cellular functions such as cell division and the replication of DNA (Frame and Cohen, 2001). Essentially, this pathway is a series of steps that carry out cellular functions. Previous studies have shown that GSK-3 is one of the kinases that stick phosphorus molecules onto tau, making it able to form clumps (Flaherty et al., 2000). Their findings support the idea that the R gene decreases tau aggregation by inhibiting the kinase, GSK-3. Thus, they uncovered why the R gene decreases the tau tangles, but the pathway they identified had not been previously linked to amyloid beta levels. For this gene to be an effective therapy, they would have to figure out how it decreased amyloid beta levels along with tau tangles (Phiel et al., 2003).

They found their answer when they looked closely at the pathway that they had connected to the R gene. Since amyloid beta is created by secretases slicing APP in the wrong place, they looked at what part of this process was being disrupted. They found that when they put a lot of the R gene into cells, more of the "good cuts" of APP were made and fewer of the "bad" amyloid beta cuts were made. The pathway they associated with the R gene is also responsible for the control of PKA. The golgi apparatus is an organelle that is responsible for transporting materials from inside the cell to the membrane of the cell, like a cellular highway. The materials are transported in bubbles made up of the same substance as the cell membrane. The researchers discovered that the PKA pathway was increasing the amount of APP being transported in these bubbles to the places where it would be cut correctly (Xu, 1997). Basically, the R gene is causing a decrease in the amyloid beta plaques by increasing the amount of APP that is being cut correctly.

While these findings were quite exciting, the researchers still needed to show that the R gene could decrease Alzheimer's disease in living organisms. If they succeeded, it would be an indication that the R gene has real potential as a therapeutic agent. They found that mice with the equivalent of Alzheimer's disease, which also had the R gene in high levels, showed fewer plaques and tangles than mice without the R gene. Another promising sign was that the mice with high levels of the R gene did not show any

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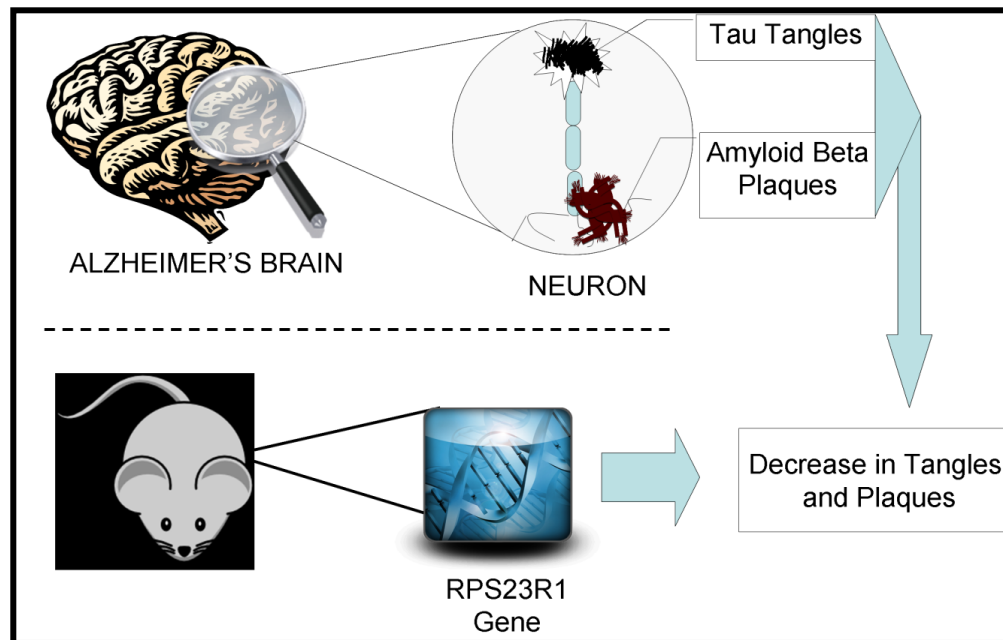


Figure 1: Alzheimer's disease is characterized by tau tangles and amyloid beta plaques in the neurons of the brain. A new gene discovered in mice, RPS23R1, decreases plaques and tangles in human cells. This indicates that it could be useful as a gene therapy for this previously untreatable disease.

behavioral disturbances. This is a sign that the R gene increase is not harming any other brain processes like movement or sensory perception. Obviously, a lot more research is needed before therapy with the R gene can be tested in people. However, these findings give us a glimmer of hope that one day treatments may be available to treat Alzheimer's disease.

The outcomes of this study help bridge the gap in knowledge regarding Alzheimer's treatment. The fact that this gene can work in human cells and that this gene works in animal models to reduce pathologies indicates that it could possibly be a gene therapy agent. Perhaps, soon, we will be able to look forward to a future free of the fear that we will be unable to recognize our loved ones or feed ourselves. Then we will also be free from the sadness of seeing our loved ones disappear before our eyes. Keep an eye on this gene, because it could be coming soon to a pharmacy near you!

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