MARK4 leaves its mark on your brain

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Abstract
Although a single mutation can seem inconsequential, Toshiya Oba and colleagues conducted a study in which the effect of an AD related mutation on a Microtubule affinity-regulating kinase 4 (MARK4) gene revealed that it can drastically worsen neurodegeneration and promote tau protein accumulation.

Imagine the effect of misplacing a single step in a recipe. The final dish will not taste appetizing, as it originally would. Similarly, a single change of a nucleotide base in the DNA of an organism can drastically change the function of an entire protein. Toshiya Oba and colleagues explore microtubule affinity-regulating kinase 4 (MARK4) with an Alzheimer's disease (AD) related mutation, ΔG316E317D. They track the enzyme with the mutation and observe the effects that it has on tau accumulation and neurodegeneration.

The researchers use a Drosophila model to compare the effects of the MARK4 mutation on wild type and Alzheimer's models. The method was made to have flies model the neurodegenerative disorder system in humans. Tauopathy fly models are made by modifying the flies so that one can express the wild type (WT) for MARK4 and the other can show MARK4 with the mutation. Researchers also used immunoblotting, also known as western blotting, an assay for detection of proteins that work by expressing the specific protein that one is looking for on the fly. Lastly, histological analysis was used to observe the neurodegeneration of the fly's retina.

The presence of the Alzheimer's mutation is similar to that of a misstep in a recipe, as it alters the final product. MARK4 is responsible for in-cell transport, division, structure, and phosphorylation of tau. The mutation, ΔG316E317D alters the function of MARK4 which leads to abnormal phosphorylation of an insoluble tau species. This mutation is associated with AD because abnormal amounts of insoluble tau can form tangles, which lead to neurodegeneration, or the death of neurons (Lund et al., 2014). The Drosophila model allows for the observation of the products formed by this mechanism.

Past studies have identified that phosphorylation by kinases may cause tau irregularities. Yet, the mechanism by which this occurs is unknown (Nishimura et al., 2004; Engel et al., 2006). They were focusing on picking apart tau accumulation and studying the different sources for the tau tangles. Studies that worked with the Drosophila models previously found that many enzyme kinases were associated with abnormal tau toxicity (Nishimura et al., 2004). By this same notion, researchers can reasonably assume that because phosphorylation promotes tau toxicity, it is related to neurodegenerative diseases such as Alzheimer's disease, and contributes to its synaptic dysfunction.

Moreover, with the introduction of an overexpressed enzyme, PAR-1 which enhances cancer cell invasiveness, fly stocks modeled tau toxicity (Nishimura et al., 2004). Using the histology method, researchers observed that the dysregulation of the enzyme GSK-3 was also a key mediator of AD pathogenesis in mice. In all of these studies, the hippocampal area had a greater number of tau accumulation than the rest of the brain (Engel et al., 2006; Shahani et al., 2006; Hooper et al., 2008). Thus, the overexpression of enzymes that phosphorylate tau can begin to do so abnormally, resulting in neurodegeneration (Nishimura et al., 2004; Shahani et al., 2006). Oba and Saito explain the results for such revelations.

Researchers choose Drosophila as their model to manipulate the DNA of the fly by adding the mutated MARK4 and wild type MARK4 to another fly (Langer-Safer et al., 1982). The duration of the study is not prolonged because flies have shorter lifespans than humans. The study presented a great model of the human brain and its neurodegenerative properties by showing the actions of the targeted mechanism (Nishimura et al., 2004).

Oba and colleagues find that the AD mutant MARK4 increases tau accumulation and promotes tau toxicity. They observe the Drosophila retina, a part of the eye, which is sensitive to light, in three important conditions: tau, tau with the wild type MARK4, and tau with the mutant MARK4. Researchers find that the retina with tau and the AD mutant MARK4 fly has the greatest accumulation compared to other conditions.

Findings show the AD mutant MARK4 increases tau toxicity in locations other than where kinases typically phosphorylate. This means that the AD mutant MARK4 can increase tau levels in different locations. The second observation consists of S2A mutant tau which is less toxic than the wild type of tau (Chatterjee et al., 2009). The S2A tau and AD mutant MARK4, experience an increase in vacuole area of 8 μm2 whereas the others are not significant (2-3μm).

Mutant MARK4 further promotes the accumulation of insoluble types of tau. Insoluble tau is formed through aggregates, which are groups of proteins. These aggregates are highly present in many neurodegenerative diseases such as Alzheimer's disease (Hanger et al., 2009). AD mutant MARK4 had the greatest levels of tau when forming oligomers and monomers, increasing the severity of the tau.

The work of these researchers aimed to unravel the behavior of mutated MARK4 on Alzheimer's disease and tau phosphorylation. They found that MARK4 worsens neurodegeneration by increasing the amount of tau tangles in the brain. This revelation raises questions about potential treatments for Alzheimer's disease (Sun et al., 2016). This study suggests a treatment targeting tau kinases can potentially aim to prevent or halt neurodegeneration, thus combating the disease as a whole.

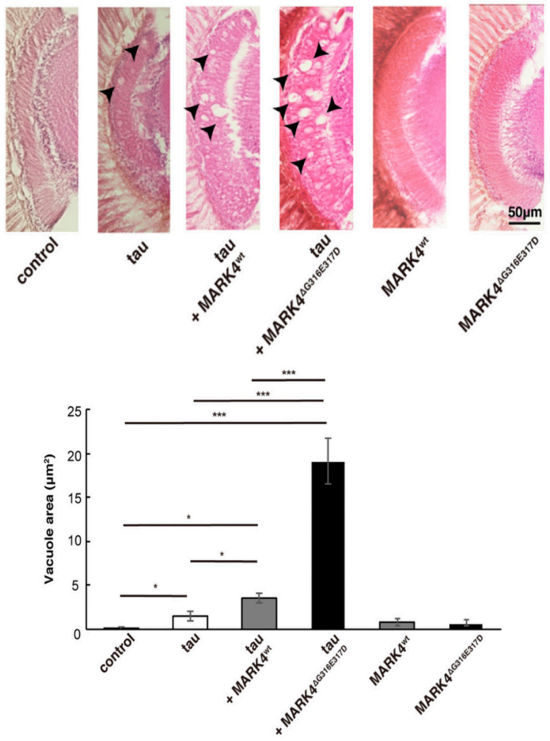

Figure 1. The mutated MARK4 increased tau toxicity to a greater extent than wild type MARK4. The image on the top of the figure contains a visual of the tau-induced neurodegeneration in the retina of the drosophila, as well as the controls. The image on the bottom shows the quantification of the total area of tau neurodegeneration in the retina of the drosophila.

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