Axolotl regeneration and Alzheimer's disease: A conceptual model

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Alzheimer's disease is a progressive neurodegenerative disease that causes memory loss and cognitive decline (Centers for Disease Control and Prevention, 2024). We can analyze Alzheimer's disease in different ways. The number of people living with Alzheimer's disease is expected to double by 2060; it is estimated that at that time, there will be 14.4 million people in America living with Alzheimer's disease (Centers for Disease Control and Prevention, 2024).

First, it is important to understand how Alzheimer's disease forms. It first forms with the accumulation of tau tangles and amyloid plaques. Over time, neurons die due to inflammation and oxidative stress (Maity et al., 2021; Parhizkar & Holtzman, 2022). Alzheimer's disease typically starts in the temporal lobes, specifically the entorhinal cortex of the hippocampus. Then, it spreads out to other cortical areas (Centers for Disease Control and Prevention, 2024).

Scientists have discovered that the APOE gene, APP gene, PSEN1 and PSEN2 genes, and EOFAD gene affect the risk of developing Alzheimer's disease. Therefore, Alzheimer's disease can also be studied as an inherited condition (National Institute on Aging, 2023). We will briefly describe the primary genes associated with Alzheimer's disease. APOE is an Alzheimer's disease-related gene. It is a type of lipoprotein. In the central nervous system, it can deliver cholesterol to neurons (cholesterol, a type of lipid, which can be carried by proteins and forms lipoproteins), and help with amyloid processing (National Institute on Aging, 2023; Parhizkar & Holtzman, 2022). The APOE gene includes 4 variants: E1, E2, E3, and E4. The APOE4 variant is associated with an increased risk of developing Alzheimer's disease (National Institute on Aging, 2023). APP is another gene related to Alzheimer's disease. It is the source of beta amyloid peptide, which can be aggregated into plaque in the brain. This gene can help with neuron growth and neurons' signaling. It also provides instructions for making amyloid precursor protein (Aydin et al., 2012; National Institute on Aging, 2023).

The development of gene-modifying drugs requires suitable animal models before the treatments can be tested in humans. One interesting and understudied potential animal model is the axolotl, or ambystoma mexicanum. Based on this concept of neurogenesis, we propose a new conceptual model of axolotl, based on their regenerative ability, in order to see if there is a potential relationship with Alzheimer's disease. Gene-modifying therapy is a potential target based on similarities between Alzheimer's disease and axolotl. One of the most important genes causing Alzheimer's disease is the APOE 4 gene (National Institute on Aging, 2023; Parhizkar & Holtzman, 2022).

Axolotls, a type of salamander native to Mexico, are considered an ideal model for studying Alzheimer's disease because of their regenerative abilities (Arenas Gómez & Echeverri, 2021). Axolotls can regenerate lost or damaged tissue, including parts of the brain. (Arenas Gómez & Echeverri, 2021; Amamoto et al., 2016)This unique skill may be translated to Alzheimer's disease, as it provides insights into regenerating brain cells, the final goal for treating Alzheimer's disease. In this article, we are going to describe a new conceptual model and potential mechanisms involving axolotls that could help treat Alzheimer's disease. In terms of organ level regeneration, axolotl can regenerate entire limbs, parts of the heart, spinal cord and even parts of the brain (Arenas Gómez & Echeverri, 2021; Del Moral-Morales et al., 2024). A juvenile axolotl can regenerate a limb within 40-50 days and regenerate the same limb multiple times (Del Moral-Morales et al., 2024). At the cell-level, axolotl can regenerate limbs using different kinds of cells, including neural, epidermal and connective cells (Arenas Gómez &

Echeverri, 2021). SOX2, ZIC1 and ZIC2 are the primary genes that affect brain cell regeneration in axolotl (Fei et al., 2014; Del Moral-Morales et al., 2024).

SOX2

SOX2 is a transcription factor; it controls the working of neural stem cells. It can be reactivated during CNS regeneration (Fei et al., 2014). Unlike mammals, axolotls maintain high SOX2 activity in adults. It specifically can be used in neural stem cell regeneration (Fei et al., 2014). In some of the recent findings, scientists used the CRISPR-Cas 9 gene editing technology to delete the SOX2 gene in order to study the significance of the SOX2 gene in axolotl regeneration. When SOX2 was deleted, many problems appeared. For example, when scientists cut the axolotl tails including the spinal cord, regeneration failed. This provided evidence that SOX2 is one of the most important genes in axolotl regeneration (Fei et al., 2014).

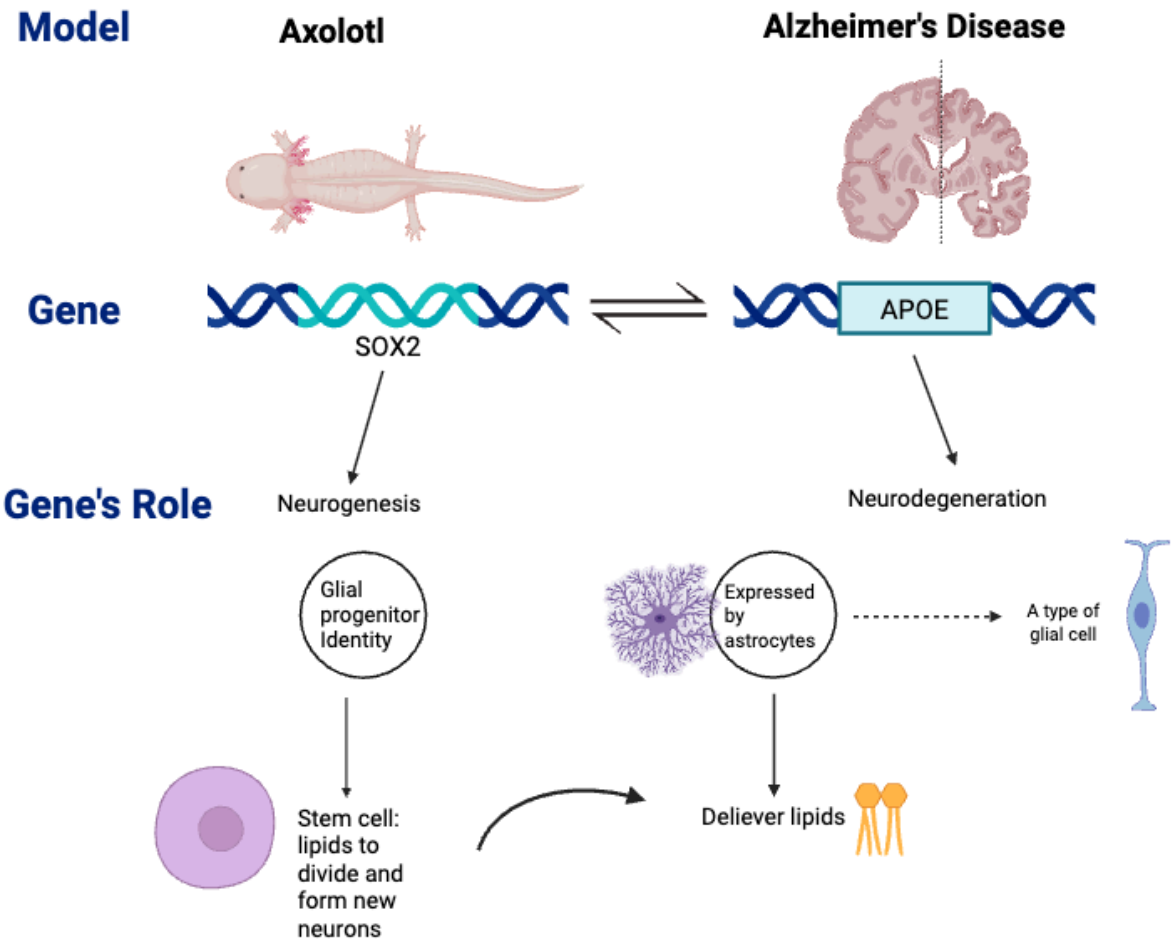
ZIC 1 & ZIC 2

ZIC 1 and ZIC 2 are the most important transcription factors in axolotl regeneration. They help control neuronal tube patterns, useful for cerebellum development. ZIC 1 and ZIC 2 genes also help with embryonic brain development (Arenas Gómez & Echeverri, 2021; Del Moral-Morales et al., 2024). Interestingly, ZIC 1 and ZIC 2 genes may act as preparatory in cell development, similar to APP and APOE acting as precursors to later gene processes (Aydin et al., 2012; National Institute on Aging, 2023).

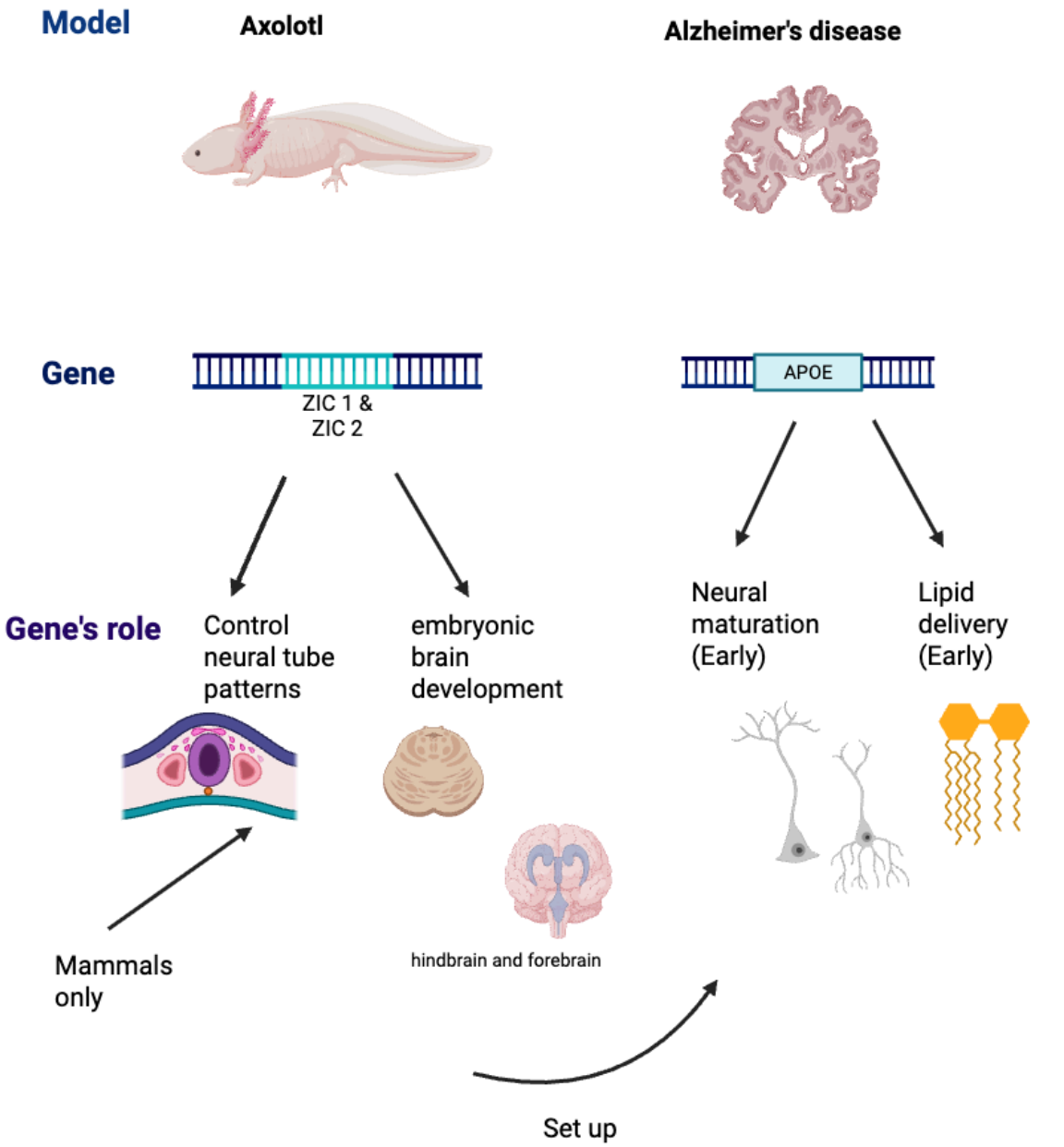
Conceptual Model

To our knowledge, only three papers have examined the potential of axolotl to serve as a suitable animal model for Alzheimer's disease research. We will briefly describe the significant findings from those papers. Benwood et al. (2023) found that they could use the bioprinting model to regenerate cells by inducing pluripotent stem cells (hiPSCs). As a result, researchers successfully regenerate them to neural progenitor cells, which the cells also survive for a long time from both population's cells. James et al. (2024) found there are some similarities between axolotl encoded proteins and human microtubules proteins (tau, APP and BACE1), which are involved in Alzheimer's disease process. Lastly, Phelps et al. (2025) found that proteins in axolotl have the similarities to human's tau tangled proteins, amyloid precursor protein and beta securase 1, which have the important roles in Alzheimer's disease.

To build this work, it is important to have a detailed conceptual model of these related genes' functions and developmental structures between axolotl and humans who have Alzheimer's disease. In Figure 1, it shows the SOX 2 gene might have the relationship with APOE gene in Alzheimer's disease: they all contain the similar glial cells identity (Fei et al., 2014; Parhizkar & Holtzman, 2022). SOX 2, the gene included in axolotl, is supposed to be the neurogenesis gene and stem cells, which can help lipids to divide. APOE gene, including in Alzheimer's disease, has the function of delivering lipids (National Institute on Aging, 2023; Parhizkar & Holtzman, 2022). In Figure 2, ZIC 1 and ZIC 2 genes which are contained in Axolotl and some mammals are available for setting up the early stage of brains. They may also connect with the APOE gene in Alzheimer's patients as they are all useful in the early stage setting process.



Takeaway:
Comparing SOX2-mediated regeneration in axolotls with APOE-driven lipid and glial signaling in Alzheimer's disease highlights conserved pathways that may enable lifelong neural repair and/or neurogenesis.



Takeaway
Axolotl ZIC genes may show how early brain development and neural patterning mechanisms intersect with APOE pathways implicated in Alzheimer's disease.

This adds potential pathways that axolotl could be used to better understand and treat Alzheimer's disease. Although this model might propose an idea of the relationship between Axolotl and Alzheimer's disease, there are still several limitations for this model. Can amphibian characteristics actually be applied to humans? We still don't know about it. In the future, our goal is to investigate more related genes between axolotl and humans and to see if axolotl's regeneration skills can be used in humans.

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