Paper #2: The Longevity Factor Foxo3

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BIOL 293: Cell Biology

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Mar 21, 2025

In this research article, researchers from Osaka University discovered a potential solution as treatment for cancer, congenital disorders, and aging through cell competition. They discovered a protein called Foxo3, that eliminates “unfit” cells. They used the spinal cord and muscle tissue to visualize specific cell patterns and see how they work on many test trials using the zebrafish. They developed this experiment because they wanted to find out how the cells use cell competition to get rid of the genetic material, creating those “unfit cells” and keeping them on track for cell dividing and replicating to make copies of themselves. Doing this experiment, the Japanese researchers made remarkable discoveries. This research was done on December 17, 2024 at Osaka University.

In one of their trials, they blocked apoptosis, which is a type of programmed cell death, and then started to see irregular cell patterns happening in the zebrafish’s spinal cord and muscle tissue. With the irregular cell patterns, this emphasized how important the apoptosis was to the zebrafish when it comes down to removing unfit cells. Now the next question the researchers wanted to know was: How does it sense the unfit cells and remove them? Their next move is to study a protein called Sonic Hedgehog (Shh) which develops in the zebrafish tissue. According to the research article, “*Sonic Hedgehog Promotes Tumor Cell Survival by Inhibiting CDON Pro-Apoptosis Activity*,” Sonic Hedgehog is a crucial morphogen with diverse functions, playing vital roles in both embryonic development and adult life (1). However if it becomes abnormal it can develop diseases such as cancer. It develops in front of the brain and the spinal cord. The researchers now uncovered that high level displayed apoptotic markers showed a lot of abnormal Shh activity. When they blocked the apoptosis, they saw the recurrent abundant amount of Shh activity for their location. They also put together that when the abundant unfit cells come about,

they undergo cell death. This created more curiosity of "How do the cells communicate on their level of Shh activity?"

With this leading question, they found out that a specific membrane protein, N-cadherin, exchange signals for the cells to respond to abnormal Shh activity that lead to the pathway removal of unfit cells like Smad/Foxo3 and oxygen species Bcl2 pathway. In the article *"The mystery of BCL2 family: Bcl-2 proteins and apoptosis: an update"* Bc-l2 serves as one of the two major pathways to apoptosis, the mitochondrial pathway. Bc-l2 served as a vital role to whether the cell lived or died (2). With this discovery, it led to the finding of Foxo3, a protein mediator to the cell competition. They tested their hypothesis of if Foxo3 can be the leading factor to removing unfit cells by using zebrafish and mice. According to Tohru Ishitani, senior author of the study, "Foxo3-mediated physiological cell competition is required to eliminate naturally generated unfit cells and for the consequent precise development of embryonic, spinal cord, and muscle tissues. (3)" However they found out that reduced Foxo3 is associated with age-related disease that can also be cancerous as well as development issues.

Even with these potential risks, this discovery can lead to outstanding possibilities for treatments to fight off cancer, age-related disease, and even improving health and life span. With the help of studying the zebrafish and mice, Foxo3 could be seen as the potential universal marker of cell competition. Narrowing down the unfit cells, this could help us find out how we can stop the abnormality of unfit cells and ultimately give us a better understanding of how cell competition works in this field.

References

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