SUMMERY OF THE LONGEVITY FACTOR

FOXO3

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The longevity factor Foxo3 mediates 'unfit' cell elimination to ensure healthy body construction is a paper released by Science Daily in 2024 which reviews a study done at Osaka university. This study focused mainly on what would happen if apoptosis were blocked in zebrafish, as well as the methods of cellular competition. The study concluded that blocking apoptosis in zebrafish would lead to a higher rate of mutations in their cells, pinpointed a protein which they were able to monitor in order to monitor cellular health, and even identified a protein and its pathway that they believe is used for cellular communication and to initiate apoptosis.

The paper starts by reviewing the first part of the study done at Osaka university. "The research team from Osaka university used zebrafish... By blocking or inhibiting apoptosis -- a type of programmed cell death -- they discovered altered cell patterns in these tissues" (1). Apoptosis is the process by which one's body eliminates cells that it sees as unfit due to either mutations or ineffectiveness due to old age. Without this process, there would be a large buildup of mutated or ineffective cells. However, this appears to be exactly what the researchers at Osaka university wanted [1].

Next, the article delves into the second stage of the study ""This finding emphasized the importance of apoptosis for eliminating unfit cells via competition, but it also raised a crucial question: how are these cells sensed and removed?"" (1). In this part of the study, researchers at Osaka used "sophisticated imaging techniques" (1) to identify a protein known as Sonic hedgehog, a protein which regulates the morphogenesis of most organ cells and is mainly found during the embryonic stage [2]. Sonic hedgehog is a protein which is common among most cells within zebrafish. This protein also has a normal activity level for each type of cell. It was shown that cells which had an abnormal level of Sonic hedgehog activity, either high or low,

were the cells most often marked for apoptosis. This is one method by which cellular competition takes place. “Cell competition is a cell fitness-sensing mechanism conserved from insects to mammals that eliminates those cells that, although viable, are less fit than their neighbors.” (3) this likely means that cells with normal Sonic hedgehog levels were seen as fit and were allowed to survive while those whose levels of Sonic hedgehog activity differed from the mean were marked for apoptosis.

This identification of Sonic hedgehog “begged another question: how do cells communicate their Shh activity levels to one another?” (1). This question led to the third stage of the study. Through continued use of the imaging techniques, the researchers were able to discover that information was shared about Sonic hedgehog from one cell to another via N-cadherin. N-cadherin is a cellular membrane protein which is able to present and receive information about the amount of Sonic hedgehog activity, allowing the immune system to direct apoptosis within the cells which are seen as unfit. Also during this stage of the study, researchers discovered that “the removal of unfit cells occurs via a specific pathway -- the Smad/Foxo3/reactive oxygen species/Bcl2 pathway.” (1). Foxo3 is a protein linked with extreme longevity and large amounts of apoptosis [4], these large amounts of apoptosis caused by Foxo3 help to keep the body healthy and increase longevity and has also led to is being called a “mediator of cell competition” (1). Foxo3 also uses the same pathway as Smad, ROS, and BCL2, which are all regulatory proteins in their own regard, leading to the name of the pathway.

All in all, the study was a success in that it found a useful protein marker which could be used to monitor the possibility of age-related diseases. It also opens new avenues for research and understanding which could lead to a million possibilities. This could lead to new

types of health and risk screening, new kinds of medication, and new information about how to live the healthiest lives we can. [1]

References

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