The longevity Factor Foxo3

Austin Dodd

Biomedical Science

Cell Biology Biol 293

March 21, 2025

The longevity Factor Foxo3

A study involving zebrafish led by Japanese researchers at Osaka University was done to uncover core mechanics in physiological cell competition. Cell competition is an important homeostatic process that removes viable but undesired cells within the body. The zebrafish were used to visualize cell patterns in spinal and muscle tissue (3). Inhibiting apoptosis, they discovered an altered cell pattern within the tissues. Apoptosis is an important process within the body where cells self-destruct in an orderly manner which removes unwanted or damaged cells. When apoptosis was blocked during development, abnormal growth patterns were observed in the spinal cord and muscle (3). The findings were crucial to understanding the importance of apoptosis in its role of eliminating unfit cells in cell competition. During the study, the question was raised as to how any damaged cells were sensed and then eliminated. To figure this out the team pulled their focus on a protein called Sonic Hedgehog (SHH). After observing SHH, the question arose: how are cells able to communicate the level of SHH activity to each other (3)? The researchers at Osaka University found that N-cadherin was primarily responsible for letting cells respond to others with a different SHH activity level.

The Pathway of Cell Destruction

The pathway through which unfit cells are eliminated involves Smad, Foxo3, ROS, and Bcl2, ultimately leading to the identification of Foxo3 (3). The signaling pathways leading to cell death are well implemented in animal cells. As such the investigation into apoptosis as a form of therapeutic treatment for cancers became a realistic approach (1). The therapeutic features of apoptosis were explored and used to purposefully target and induce cell death. The result would be the release of cytochrome c from the mitochondria, and a downstream activation of proteins from the caspase family (1). The activation of caspases can lead to the formation of apoptosomes, which contain APAF1 and caspase 9. The apoptosome is a protein complex formed within the process of apoptosis and activates APAF1 and caspase 9, leading to cell

destruction (1). The apoptotic process involves a breakdown of nuclear membrane via caspase 6 as well as a breakdown of DNA into nucleosomal structures (1).

During apoptosis, damaged cells must first be sensed and recognized to begin the process of apoptosis. Thus, the researchers diverted their attention to SHH which was perfect since it had a clear activation gradient within developing zebrafish tissue (3). The SHH pathway is necessary in regulating cell migration, proliferation, and apoptosis. It was found that cells that displayed abnormal SHH activity levels had higher levels of apoptotic markers (6). SSH also plays a role in signaling for the protection against hypoxia/reoxygenation-induced apoptosis. SSH is also capable of restoring oxidative damage induced by H/R-induced apoptosis (6). According to the data collected, when apoptosis was blocked the number of damaged cells increased which disrupted the SHH gradient. As such it was concluded that cells with abnormal levels of SHH undergo apoptosis (3).

The pathway starts with TGF-β activation as well as Smad protein signaling. TGF-β functions as an immunosuppressor which is like what was discussed in class involving cancer cells increasing production of TGF-β which causes immunosuppression and angiogenesis. by controlling the proliferation and survival of various immune cells. A key aspect of its homeostatic role is inducing apoptosis in a cell type-specific manner (7). Within the TGF-β signaling pathway, Smad2 and 3 function as receptor-regulated effector proteins. Upon activation, TβRI phosphorylates will lead to the nuclear accumulation of R-Smads (7). Endocytosis promotes TGF-β signaling by providing a platform for R-Smad phosphorylation. Phosphorylation can help with the formation of active Smad signaling complexes (7). The next part of the pathway involves Foxo3 activation and transcriptional regulation. The Smad proteins upregulate Foxo3, leading to its nuclear translocation. The next part of the pathway for the removal of cells is the Foxo3 activation. Foxo transcription factors are downstream targets of

PI3K. These will have proapoptotic and antimitogenic effects of different cell types (4). Foxo3 has been found to play a role in B cell development. Additionally, during activation of B cells by BCR, PI3K signaling downregulates Foxo function. However, BCR cross-linking can block PI3K activation which results in nuclear localization of Foxo3 (4). Foxo3 has the role of promoting Apoptosis in BCR-stimulated B cells. Foxo3 is capable of sustaining tissue homeostasis through the cell competition process. A reduction in Foxo activity could potentially lead to an increase in unfit cells (4;3).

The pathway then leads to reactive oxygen species (ROS) accumulation within the cell which can cause damage to the cell triggering apoptosis. ROS can modify the cell-signaling proteins and can be generated through many different extracellular and intracellular actions (2). Additionally, ROS plays other roles besides cell death including growth and differentiation. ROS is comprised of highly reactive oxygen free radicals which damage cellular components such as lipids, proteins, and nucleic acids (2). This makes ROS accumulation necessary during apoptosis. ROS plays a crucial role as second messengers in determining cell fate and modifying various signaling molecules (2). The last step in cell apoptosis is B-cell lymphoma 2 (BCL2) regulation. The BCL2 family of proteins is comprised of key regulators of apoptosis. When there is DNA damage or cell stress and the apoptotic pathway is initiated, there is a loss of mitochondrial membrane potential (5). The membrane potential loss is regulated by the BCL2 protein. The BCL2 family is comprised of anti-apoptotic and pro-apoptotic multi-domain (5). For apoptosis to occur the multi-domain pro-apoptotic proteins are activated by facilitated oligomerization within the outer mitochondrial membrane with ensuing loss of membrane potential (5).

Conclusion

It was found that low Foxo3 activity is associated with disorders of development, cancer, and other age-related diseases. Cell competition can eliminate undesired cells which include those with abnormal Wnt and Shh activity. Wnt as discussed in class are essential for brain development, limb patterning, and organogenesis. However, hyperactive Wnt signaling is seen in the progression of many cancers. Foxo3 is a common mediator in unfit cell destruction as observed when blocking apoptosis in mice and zebrafish. Foxo 3 expression is crucial in understanding how cells are eliminated via cell competition and is seen as a potential indicator of cell competition. The research using both zebrafish and mice produced results that hinted Foxo3 as being pivotal in the understanding of cell competition within the body and can help to make clear the cause of cell abnormalities.

References

1. Carneiro, B. A., & El-Deiry, W. S. (2020). Targeting apoptosis in cancer therapy. *Nature Reviews. Clinical Oncology*, *17*(7), 395–417. https://doi.org/10.1038/s41571-020-0341-y

2. Dong, W., Wu, D., Ye, Q., Vikash, V., Wang, X., Zhang, J., Liu, Y., & Egea, J. (2016). ROS and ROS-Mediated Cellular Signaling. *Oxidative Medicine and Cellular Longevity*, *2016*(2016), 1–18. https://doi.org/10.1155/2016/4350965.

3. Osaka University. (2024, December 17). The longevity factor Foxo3 mediates 'unfit' cell elimination to ensure healthy body construction. *ScienceDaily*. Retrieved March 21, 2025, from www.sciencedaily.com/releases/2024/12/241217131237.htm.

4. Ottens, K., Hinman, R. M., Barrios, E., Skaug, B., Davis, L. S., Li, Q.-Z., Castrillon, D. H., & Satterthwaite, A. B. (2018). Foxo3 Promotes Apoptosis of B Cell Receptor-Stimulated Immature B Cells, Thus Limiting the Window for Receptor Editing. *The Journal of Immunology (1950)*, *201*(3), 940–949. https://doi.org/10.4049/jimmunol.1701070.

5. Vogler, M., Walter, H. S., & Dyer, M. J. S. (2017). Targeting anti-apoptotic BCL2 family proteins in haematological malignancies – from pathogenesis to treatment. *British Journal of Haematology*, *178*(3), 364–379. https://doi.org/10.1111/bjh.14684.

6. Zhang, R.-Y., Qiao, Z.-Y., Liu, H.-J., & Ma, J.-W. (2018). Sonic hedgehog signaling regulates hypoxia/reoxygenation-induced H9C2 myocardial cell apoptosis. *Experimental and Therapeutic Medicine*, *16*(5), 4193–4200. https://doi.org/10.3892/etm.2018.6678.

7. Zi, Z., Chapnick, D. A., & Liu, X. (2012). Dynamics of TGF-β/Smad signaling. *FEBS Letters*, *586*(14), 1921–1928. https://doi.org/10.1016/j.febslet.2012.03.063.