The Role of Foxo3-Driven Apoptosis in Healthy Body Construction

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A recent study conducted by Osaka University describes the crucial role of the longevity factor Foxo3 in maintaining the health of an organism and its body construction. In this study, researchers analyzed the mechanisms driving cell competition through a series of experiments on live Zebrafish and tissue samples. They concluded that Foxo3 is a key factor in the controlled culling of damaged, stressed, or otherwise functionally compromised cells, which enables the proper construction of tissues and organs and prevents further gene expression errors (1). The study focuses on the importance of the interactions of Smad proteins, Foxo3, Reactive Oxygen Species, and Bcl2, and their effect on programmed cell death, also known as apoptosis.

Foxo3, short for forkhead box O-3, is a type of forkhead transcription factor well known for its role in the regulation of genes associated with longevity, metabolism, and stress (3). This protein has been found to promote the survival of healthy cells during development by facilitating the destruction of damaged or malignant cells in tissues. This corroborates the concept discussed in class that an organism's health is not only dependent on its ability to tolerate or even repair damaged cells, but also to actively seek out and eliminate them to maintain the health of organs and tissue. Foxo3 collaborates with various other factors to create a pathway that regulates molecular events relating to targeted apoptosis, including Smad proteins. Smads are intracellular molecules that regulate gene expression by transmitting signals from the Transforming growth factor beta (or TGF-β) family of cytokines, which regulate cell proliferation, apoptosis, and immune responses. The research team at Osaka University found that the cellular stress response in the zebrafish tissue samples showed co-expression of Smad proteins and Foxo3, which suggests that the proteins can collaborate to express

genes that trigger apoptosis in cells marked unfit as part of a cellular “quality control” mechanism (4). One key signal for marking damaged cells is the presence of Reactive Oxygen Species (ROS). Although ROS is a natural byproduct of cellular metabolism, excessive production of it will cause oxidation that damages DNA, proteins, and lipids within cells. The Osaka team noticed that Foxo3 activation was triggered in cells with increased ROS levels, which initiated the processes necessary for their destruction (4). As we learned in Lecture 14, this makes ROS the signal in a genetic expression control pathway that activates the gene responsible for the expression of Foxo3. Another important type of protein in this pathway is B-cell lymphoma 2 (Bcl2), a family of regulatory proteins that are antiapoptotic, which means that they hinder programmed cell death, making Bcl2 a strong contributor to cancer development. Although Bcl2 and Foxo3 appear to have contradictory effects, the Osaka team observed that Foxo3 activity led to the suppression of Bcl2 production in damaged cells. This means that Foxo3 is likely involved with the regulation of Bcl2 levels, allowing for it to remove the barriers preventing cells from apoptosis and increasing the efficiency of its targeted cell-culling abilities (4). This targeting is aided by the Shh signaling pathway, a mechanism that features the Sonic hedgehog protein. Shh is a morphogen, which means it provides concentration-dependent instructions to cells that allow them to determine their position and role within developing tissues. The results of the study show that the controlled removal of non-functional cells regulated by Foxo3 is crucial for maintaining sensitive Shh concentration gradients that enable proper Shh signaling (4). Disruption of these gradients through the proliferation of unfit cells could lead to tissue and organ developmental errors. The team of researchers at Osaka University attributes

the combination of apoptotic processes conducted by these factors to their own pathway, the Smad-Foxo3-ROS axis (1). This pathway's effects on the targeted apoptosis required to maintain healthy tissue development through suppression of antiapoptotic Bcl2 and maintenance of gradients required for Shh signaling make it a critical form of quality control in embryonic development. While our understanding of the Smad-Foxo3-ROS pathway is limited, further research could provide fundamental breakthroughs in the fields of cancer treatment and anti-aging therapy, making it one of the most exciting new developments in the field of biomedical sciences.

References:

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