

# The Longevity Factor Foxo3

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Japanese researchers at Osaka University studied zebrafish and by doing so, they discovered the main processes that drive developmental robustness and physiological cell competition. The experiments specifically looked at the cell patterns occurring in the zebrafishes' spinal cords and muscle tissues. In the first experiments, during the zebrafishes' embryonic development, the researchers blocked apoptosis, which is a process most body cells go through to maintain homeostasis (a constant, stable environment) by cell competition (1). It is a self-destruction that ensures the cell's deletion once it becomes old or dysfunctional (unfit) so that it does not introduce harm to the body (2). The zebrafishes' bodies responded as the researchers expected: alterations in the cell patterns of the tissues appeared. This observation highlighted the significance of apoptosis as well as made the researchers wonder how these "unfit cells" were identified and deleted (1).

To try to answer this new question, the researchers concentrated on observing the Sonic Hedgehog (Shh) protein via advanced visualization systems (1). This protein is encoded by the Sonic Hedgehog gene to establish the role of cells during embryonic development. It is especially important for the growth of the central nervous system and organization of the body map (3). While observing this protein, the researchers recognized that large amounts of apoptotic markers were located in cells with irregular proportions of Sonic Hedgehog activity. Additionally, with apoptosis being inhibited, there was a buildup of the unfit cells, which in turn interrupts the gradient of the Shh protein (3). With these findings, the researchers deduced that unfit cells with irregular Shh activity are programmed for apoptosis. They also pondered another matter: how cells convey their own Sonic Hedgehog protein activity to each other (1).

It was discovered that cells have a membrane protein called N-cadherin that allows cells to perceive adjacent cells with irregular proportions of Sonic Hedgehog activity and

acknowledging them by inducing apoptosis in them via the following pathway: Smad, Foxo3, reactive oxidation species, and Bcl2 (1). Smad proteins regulate gene transcription and expression by transmitting signals from activated transforming growth factor-beta (TGF- $\beta$ ) receptors to the nucleus from the surface of the cell (6). Foxo3 is also a protein that regulates gene expression, specifically affecting cell resistance to stress and cell metabolism. It is also highly associated with longevity and cellular homeostasis (5). Reactive oxygen species (ROS) are very reactive molecules which are comprised of Oxygen and the byproducts of oxygen metabolism in cells. These molecules play a role as signalers for cell growth and immune response; however, an excess of ROS can cause oxidative stress in cells and damage them (4). Bcl2 proteins are regulators which control the activation or deactivation of caspases, the proteases that carry out apoptosis, to signal the mitochondria for cell death or not (2).

The finding of N-cadherin helped the researchers identify the Foxo3 protein, as the moderator for cell competition because of its “consequent precise development of embryonic, spinal cord, and muscle tissues.” However, little is still known about the process of cell competition. Another question the researchers wanted to figure out was if there are universal machineries which control different types of cell competition. The researchers know that if the gene pool of Foxo3 is varied, the protein can affiliate with longevity as well as if Foxo3 activity is significantly low, the protein can be associated with more age-related problems. If scientists are able to achieve the full understanding of cell competition’s role in apoptosis, new medical treatments could be produced. The expression of the protein was also found in unfit cells of mice and zebrafish, indicating the protein’s prospective capacity to be a universal marker of cell competition, which would allow scientists to accurately recognize generated unfit cells (1).

## References

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