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Our cell's “protein factory” can decrease fats to promote lifespan

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ABSTRACT

Aging is a shared phenomenon amongst all organisms, and it’s well understood that stress hastens aging. However, the knowledge of how aging affects our capacity to deal with stress is less widespread. It turns out that our ability to deal with stress loses function in aging, and hyperactivating stress responses that usually decline during aging can extend lifespan.

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Organisms face stress daily, and generally, these stressors have some form of negative effect on our physiology. For example, exposure to thermal stress (elevated heat) increases body temperatures, causes loss of cognitive function, and mood changes. Humans have adapted several different methods for dealing with stress, such as exercise, decadent foods, and alcoholic beverages. Similarly, each cell in the human body experiences stresses daily. Stress can affect any part of the cell. Each compartment of the cell has a dedicated stress response responsible for protecting its integrity and function when exposed to stress.

One of the primary organelles (compartments) of the cell is the endoplasmic reticulum. The endoplasmic reticulum is commonly called the "factory" of the cell, as most of the synthesis of proteins and lipids (fats) occurs within the endoplasmic reticulum. Since the endoplasmic reticulum serves as the "factory," it is unsurprising that many specific stress response types of machinery exist to protect it. One of these quality control mechanisms is called the unfolded protein response. This mechanism is the primary method of preserving the proteins of the endoplasmic reticulum.

A key characteristic that needs to first be understood is that all stress responses – including the unfolded protein response – decline during the aging process. As the functional output of the unfolded protein response declines, the cell's capacity to deal with endoplasmic reticulum stress also decreases, and this leads to the physiological consequences of aging. As an analogy, a young person can deal with heat stress very well, but an older person may succumb to

deadly overheating due to decreased capacity to deal with heat stress. This same concept applies to our cells.

We've found that we can hijack stress response types of machinery, hyperactivate them, and extend lifespan by preventing the deterioration of the cell. That is, we can hyperactive the unfolded protein response and promote lifespan by preserving the endoplasmic reticulum's function. If we go back to our analogy above, this would be like allowing the elderly to be robustly resistant to heat as a teenager.

As stated above, the unfolded protein response's primary function was previously described as preserving proteins in the endoplasmic reticulum. However, we found that hyperactivating the unfolded protein response could actually drive a depletion of lipids to promote lifespan – and it's pretty clear that decreasing fat is generally a good thing.

Perhaps most astounding is that in a whole organism, unfolded protein response only has to be hyperactivated in neurons to deplete lipids in the entire organism and extend lifespan. Our study was performed in the model organism, Caenorhabditis elegans, a microscopic worm that shares many of the molecular mechanisms humans have. We found that overexpressing a single gene in neurons leads to a massive increase in lifespan by protecting the function of the endoplasmic reticulum. This occurs because neurons can actually signal to the rest of the body to also activate a beneficial unfolded protein response. This makes sense, as we would want our brains to be able to signal to the rest of our bodies that a specific stress is present. This would be like if the manager of a faculty saw that there was a fire, he could communicate to the entire staff to evacuate, whether the employees saw the fire or not. In a very analogous manner, neurons can use neurotransmitters to signal to other cells to communicate endoplasmic reticulum stress.

Finally, we found that the beneficial effects of unfolded protein response on decreasing lipids were completely independent of the historically described function of unfolded protein response in maintaining proteins. That is, merely driving the depletion of lipids was sufficient to extend lifespan, even in the absence of protecting the cell's proteins. While all this work was performed in worms, it is likely that a highly similar phenomenon also occurs in our bodies. And so, if we could train our bodies to preserve the function of our stress responses and prevent their deterioration over time, we could maintain the homeostatic function of our bodies and slow down aging.