Aging just is damage accumulation

Aging is the accumulation of damage and nothing more. As the level of damage rises, cells and the tissue made from them function poorly, and this in turn causes increased risk of disease and death. This is the garbage catastrophe of aging.

What causes this rising level of damage? If we can answer that, we know what causes aging.

(Note that this is a different question from asking whether aging is programmed by evolution or not.)

When we, or any organisms, are young, our cells can repair damage, but as we get older, the damage repair mechanism is itself damaged. This leads to rising levels of damage and an inability to fix it.

The main mechanism for damage repair is autophagy, from the Greek for “self-eating”. Autophagy is the cellular self-cleansing process in which cellular organelles such as mitochondria and proteins within the cell are broken down and their components recycled for making new organelles and proteins.

Autophagy is a daily occurrence – or should be – with peaks and troughs of activity. The absence of food strongly increases the rate of autophagy, so that in young organisms at least, its rate rises dramatically overnight. Fasting even longer than overnight further increases the rate of autophagy.

Other interventions besides fasting also increase autophagy, for instance, exercise and certain drugs and supplements.
But in older organisms, the capacity for increasing autophagy in response to fasting or other stimuli decreases. This leads to a rising level of damage that interferes with cell function and is characteristic of aging.

Autophagy is crucial for the organism. Treatments that prolong lifespan, for example calorie restriction, fasting, or even genetic manipulation of insulin signaling, require the organism to possess an intact autophagy mechanism to work.[1. Jia, Kailiang, and Beth Levine. “Autophagy is required for dietary restriction-mediated life span extension in C. elegans.” Autophagy 3.6 (2007): 597-599.]

No autophagy, no lifespan extension.

What leads to declining autophagy and a rising level of damage?

Accumulating damage itself leads to declining autophagy

When cellular organelles and proteins that are past their expiration date are broken down and recycled during autophagy, it turns out that some of the material cannot be completely disposed of. Much of this material is composed of lipofuscin, the toxic waste of aging.[2. Terman, Alexei. “Garbage catastrophe theory of aging: imperfect removal of oxidative damage?.” Redox Report (2013).]

Lipofuscin is all but non-degradable, and it accumulates with age.

Autophagy takes place inside cellular vesicles, called lysosomes, which are formed for that specific purpose. The inside of the lysosome is kept at an acidic pH, so that the autophagic enzymes will function optimally. These enzymes are inserted into the lysosome, along with the material that is to be broken down, and autophagy proceeds.

Some fraction of the material is impervious to breakdown, however, and this forms lipofuscin.

As lipofuscin builds up in the lysosomes, it impedes the process of autophagy. The cell continues to pour autophagic enzymes into the lysosome, but these are increasingly ineffective, as lipofuscin absorbs them and renders them useless. The entire process of autophagy becomes weaker.

Why autophagy is necessary

Most people understand that the constituents of our bodies turn over regularly, being broken down and rebuilt on a constant basis. Most of the cells and material in our bodies are not the same as they were earlier, so that it can be truthfully said that we literally are not the same person we were a few years before.

For example, red blood cells have a lifespan of about 120 days. If you were to take a blood sample from a person and determine the age of each red blood
cell, you would find few to none that were older than that.

All of the red blood cells in your body were created within the last four months.

Why does this happen, and why is it necessary?

The constituents – cells, their organelles, and structural proteins and lipids – are subject to wear and tear. The most important source of wear and tear is due to metabolism, i.e. life itself.

When cells burn energy sources in order to power the processes of life, this burning releases byproducts, called free radicals, and these can and do damage to surrounding cell components. Think of it as the exhaust from a power plant, the pollution of which can cause damage to the surrounding area.

Cells have developed ways of coping with the byproducts of burning cellular fuel. One way is to contain and control them with internal antioxidants, such as glutathione, catalase, and superoxide dismutase. These may be likened to scrubbers in the exhaust stacks of a power plant.

The other way that cells have developed to cope with the inevitable damage caused by fuel-burning is to periodically replace the damaged components. Hence the process of autophagy.

**Mitochondria and aging**

Mitochondria are the cellular organelles commonly called “the powerhouses of the cell”, because most of the fuel-burning takes place in them.

As such, mitochondria are subject to greater damage from oxidation – fuel-burning – than other cell components.

Mitochondria are critical in aging. Older organisms have larger and more poorly functioning mitochondria, which pour out greater amounts of oxidizing free radicals, causing more and more damage.[3. Weber, Tobias A., and Andreas S. Reichert. “Impaired quality control of mitochondria: aging from a new perspective.” *Experimental gerontology* 45.7 (2010): 503-511.]

Since mitochondria are so subject to damage, they wear out, and cells use autophagy to eliminate damaged mitochondria, which are then replaced with new ones. This process must proceed efficiently for the cell to retain its full youthful function. Quality control of mitochondria is essential.

So, as organisms age and autophagy declines, older and poorly functioning mitochondria become prevalent.

To maintain youthful, fully functional, and efficient mitochondria, autophagy must work properly. Yet as we’ve seen, autophagy declines with age.
Aging as a garbage catastrophe

The inefficient and incomplete breakdown of cellular organelles and other components leads to increasing amounts of waste inside lysosomes, and it never goes away. This is the garbage catastrophe of aging. (See reference 2.)

From this perspective, it might be predicted that:

(i) suppression of oxidative damage would enhance longevity;

(ii) accumulation of incompletely digested material (e.g. lipofuscin pigment) would interfere with cellular functions and increase probability of death;

(iii) rejuvenation during reproduction is mainly provided by dilution of undigested material associated with intensive growth of the developing organism; and

(iv) age-related damage starts to accumulate substantially when development is complete, and mainly affects postmitotic cells and extracellular matrix, not proliferating cells.

There is abundant support for all these predictions.

Prevention of the formation of lipofuscin, i.e. cellular garbage, and/or removal of it when it exists, is crucial to slowing or stopping aging. For that purpose, it may not only be necessary, but sufficient.

Consider that when a cell divides, any waste material inside that cell is now cut in half. This may be the mechanism by which stem cells, which can divide throughout the lifespan of an organism, maintain perpetual youth.

The dilution of waste material through cell division may also be the reason why even aged organisms always give birth to young progeny. By diluting the waste contents of gametes (sperm and eggs) continually, they’re maintained in a youthful state, with no aging damage.


Unfortunately for us, most of our cells do not divide continually. Heart cells and neurons, for example. So we’re stuck with cells that accumulate damage, because they can’t dilute it by passing it to numerous daughter cells.
**Lipofuscin**

What is lipofuscin anyway? If we can determine its composition, we may be able to understand how to prevent it and how to eliminate it.


Iron-containing proteins, such as ferritin, are subject to the normal turnover of cell components, and are broken down inside the lysosome. When this happens, free iron reacts with proteins and lipids, forming lipofuscin.

The enzymes that normally break down proteins and lipids inside the lysosome are not capable of breaking the chemical bonds formed in this reaction and that characterize lipofuscin.

Another important source of lipofuscin is so-called AGE, or advanced glycation end-products.[6. Yin, Dazhong. “Biochemical basis of lipofuscin, ceroid, and age pigment-like fluorophores.” Free Radical Biology and Medicine 21.6 (1996): 871-888.] AGEs are formed by the non-enzymatic reaction of sugars with proteins, and they can be broken down by the cell with difficulty or not at all. They occur in everyone but are higher in diabetes, which is characterized by high blood sugar.[7. Kalousova, M., J. Skrha, and T. Zima. “Advanced glycation end-products and advanced oxidation protein products in patients with diabetes mellitus.” Physiological Research 51.6 (2002): 597-604.]

Both iron and sugars are necessary for the formation of lipofuscin.

**The garbage catastrophe theory and the evidence**

Does everything outlined above agree with other evidence on aging and longevity? Consider the following.

1. Calorie restriction and fasting promote longevity, and they both are associated with increased autophagy.
2. Decreased insulin signaling promotes longevity, and it too is characterized by increased autophagy.
3. Substances that promote longevity also increase autophagy, for example resveratrol, metformin, berberine, curcumin, and lithium.
5. Some animals don’t age. The Hydra, a non-aging animal, continually renews its cells, i.e. it has no post-mitotic cells, thus diluting all its cellular damage, resulting in no aging.[9. Martinez, Daniel E. “Mortality patterns suggest lack of senescence in hydra.” Experimental gerontology 33.3 (1998): 217-225.]
The scientist Alexei Terman, of Linkoping University in Sweden, writes (reference 2):

Clearly, if all damaged structures were renewed with perfect accuracy, aging would not occur. But the inevitability of aging suggests that the biological mechanisms of removal and re-synthesis are not perfect. Of these two processes, the one most suspect in the progression of aging is that of inefficient removal.

Full understanding of the nature of aging, therefore, requires an explanation of the reasons why the renewal process is imperfect, even under the most favorable conditions. As argued here, the basis of this imperfection may be in the incomplete removal of damaged biological material, which is necessary to make room for newly synthesized structures. This, in turn, may derive from the unfortunate fact that some of these damaged products are difficult or impossible to digest, particularly by the lysosomal compartment.

**How to prevent and/or slow aging**

**Iron**

I’ve argued that iron is the primary driver of aging, and looking at aging from the standpoint of the garbage catastrophe lends new support to this idea. Why?

Because iron is required for the formation of lipofuscin, the cell’s toxic waste.

Therefore, to slow the formation of lipofuscin, keep iron levels in the low normal range. Ferritin is the body’s main iron-storage molecule, and the more you have of it, the more will be turned over on lysosomes and the more iron will be left there, creating lipofuscin and catalyzing chemical reactions that damage cell structures.

**Intermittent fasting**

Intermittent fasting (and calorie restriction, which few people are willing to do over the long term) activates autophagy potently. Therefore fasting increases the clearance of damage. In older people, whose cells are clogged with garbage that inhibits autophagy, fasting may bring the rate of autophagy back to youthful levels.

**Autophagy boosters**

Certain substances/drugs can boost autophagy. These include resveratrol, hydroxycitrate, curcumin.
Exercise

Exercise increases autophagy and thus the clearance of cellular damage.

Normal blood sugar

Keeping blood sugar in the low normal range will help to prevent the formation of advanced glycation end-products (AGE), one of the constituents of non-degradable cellular garbage.

Experimental treatments

There have been a few reports of substances that can clear lipofuscin from cells. If these were to pan out, they could turn out to be potent anti-aging interventions.

One such substance is a form of cyclodextrin, which is a cheap safe molecule that is already used as an excipient in medicines.[10. Song, Wensi, et al. “2-Hydroxypropyl-β-cyclodextrin Promotes Transcription Factor EB-mediated Activation of Autophagy IMPLICATIONS FOR THERAPY.” Journal of Biological Chemistry 289.14 (2014): 10211-10222.]


PS: You can read more about these issues in my books Dumping Iron and Stop the Clock.

Follow me on Twitter.

Check out my Supplements Buying Guide for Men, where you’ll find many of the anti-aging supplements mentioned in this article.