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Iron and not mTOR is the primary driver of aging

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The scientist Mikhail Blagosklonny is best-known for his advocacy of the "quasi-program" theory of aging. What this means is that aging is the continuation of the development program; certain genes that are absolutely necessary for organism development, when continued after maturity, cause aging. Therefore aging is quasi-programmed into the genome.

In a recent article in *Oncotarget* (of which he is one of the editors-in-chief), Blagosklonny sums up the evidence for what he believes is the triumph of his theory.[1] In this theory, the cellular nutrient-sensing pathway and growth promoter mTOR (mammalian target of rapamycin) plays a key role. Inhibition of mTOR can prolong life. The continued operation of mTOR pushes cells into the senescent state.

It was recently shown that an analog of the drug rapamycin, which inhibits mTOR, increased immunity in elderly human volunteers.[2]

How does rapamycin work? Well, as can be seen by its name, it works on the target of rapamycin (TOR), and inhibits it.

But how do cells become senescent? Is it really because mTOR pushes them into it? Lacking here is any mechanism or theory as to why more growth would make cells senescent.

On the other hand, iron causes damage even at minimal levels, and iron is a growth factor.

Consider the following facts.

Age-dependent mitochondrial accumulation of iron "may increase mitochondrial dysfunction and oxidative damage, thereby enhancing the susceptibility to apoptosis [cell suicide]".[3]

Oxidative stress induced by hydrogen peroxide can induce cell senescence[4] Iron is a well-known catalyst of oxidative damage and stress.

So, we know that iron can lead to damage and is associated with cellular senescence.

What about mTOR?

It turns out that iron chelators can inhibit mTOR.[5], [6]) The addition of iron to the medium prevented cancer cell death, showing either that iron activates mTOR or is a necessary cofactor for it.

Treatment of transplant patients with rapamycin (sirolimus) can cause iron deficiency anemia by interfering with iron homeostasis.[7]

> The reduction in iron levels [with rapamycin treatment] together with the

> stable ferritin serum concentrations may suggest a condition of functional iron deficiency, partially resembling that observed in the inflammation-related anemia.

Therefore, rapamycin may inhibit mTOR by modifying iron metabolism.

Iron has the hallmarks of a pro-aging function: it's necessary for growth and development, and it accumulates with age. It causes molecular / cellular damage, and is known to cause diseases such as cancer. (Which is characterized by high growth, mTOR activation, and iron accumulation.) Iron in lipofuscin is a major source of cell aging and damage and senescence.[8]

The lifelong accumulation of iron activates mTOR, causes cellular damage, and increases aging. Iron is intimately involved in both the growth and aging aspects of mTOR.

Calorie restriction extends life and results in far less iron accumulation.[9], [10] Inhibition of iron absorption from food extends lifespan.[11]

Addition of iron promotes aging in C. elegans.[12]

Iron promotes aging, and inhibition of iron slows aging.

Inhibition of iron accumulation or decreasing iron levels is just not a sexy scientific topic. Drugs like rapamycin and metformin garner attention from scientists and doctors alike - and from people, who want to pop a pill and make no further effort.

Yet iron comes from without - it's not a constituent of the cell in the same way thatmTOR is. Therefore, it's much easier to slow or prevent aging by dealing with iron.

Iron is a much better candidate for a prime driver of aging than ismTOR.

[Note: This paper was written and uploaded on April 2, 2016. Date on side of this page is wrong.]

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