Cellular & Anti-aging Biology

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Contributing Editor

Have humans finally discovered path to reverse aging: Synergistic interaction between cellular pathways is the new hope in combating old age

Quest for the pathway to reverse aging

Ever since times immemorial human beings have strived towards achieving immortality. Ancient texts, historical accounts, scriptures, and even fiction tales have often described magical potions that could make humans immortal and ever youthful. The ultimate hunt for 'ambrosia' may seem like a distant folklore but its essence is rooted in the minds of almost every living human being. Scientific and medical progress has allowed us to combat disease and illnesses and thus considerably extend the lifespan of individuals. Although, diseases expedite mortality but even healthy living beings gradually perish and die naturally. This slow yet potent biological phenomenon of gradual deterioration of health and senescence is popularly known as '**Aging**'. It was earlier believed that aging is an irreversible phenomena and once triggered will only progress with time. This concept rendered humans in a state of helplessness and instilled the idea of superficially masking the signs of aging. This led to a boom in the cosmetic industries which promise to camouflage and even mask traces of aging, although only superficially.

Science has explained that aging like all other natural biological processes has an underlying cellular and molecular mechanism which is complex in nature and is multi-factorial. However, certain medical conditions, diseases, unhealthy lifestyles, dietary habits and environmental factors may trigger premature aging. This topic has become a hotspot for research where researchers are not only trying to understand the mechanism but also find ways of reversing the process of aging. The biggest hurdle in human age related research is the choice of an accurate animal or cell model which can precisely serve as an alternative to human beings.

In this regard *Caenorhabditis elegans*, a free living nematode is widely used for development, genetic and aging studies. A

simple nervous system, genetic homology with mammals, a short life span of three weeks and a fully mapped connectome are some of the unique features that has enabled *C.elegans* to serve as a classical model organism. A recent study published in the journal 'Cell Reports' by scientists of the MDI Biological Laboratory, in collaboration with scientists from the Buck Institute for Research on Aging in Novato, Calif., and Nanjing University in China, has shed new light on the mechanism of aging. The team of scientists has identified cellular pathways that work in a synergistic manner for longevity in *C. elegans* and that amplify its lifespan fivefold than usual (1). Figure 1 summarizes the different regulatory pathways and their effects on the lifespan of *C. elegans.*

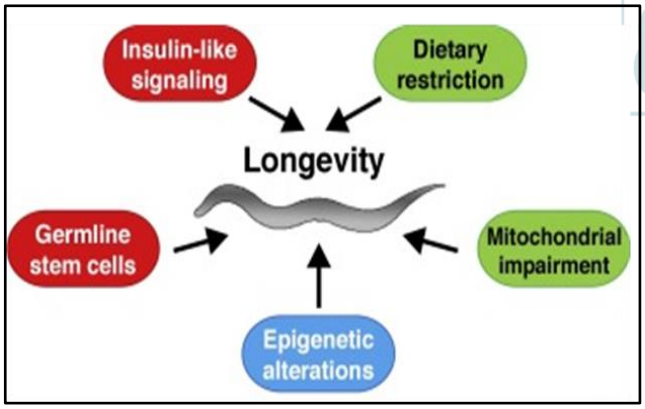

Figure 1: Graphical depiction of lifespan regulatory pathways in C. elegans. Green-pathways that promote longevity; Red-pathways that limit lifespan; Blue-pathways with variable effects on longevity. [***Source:*** *Drug Discovery Today: Disease Models, 2018*.]

The details and relevance of the study

Human based research is practically difficult because it is not possible to carry out experiments directly on human subjects and only few animal species can serve as representative animal models. Thus research based on age related aspects is further crucial owing to the long lifespan of humans and the complexities associated with the same. C. elegans has been considered a classical model organism and several aging studies and age associated disorder studies have been carried out on this simple nematode worm. The present research delves at the mechanistic aspect of two cellular pathways that majorly govern aging in C. elegans and how their interaction leads to increased longevity in the worm. Since the nematode worm has a short lifespan of only three to four weeks it is easier to assess and analyze the effects of environmental and genetic interventions to extend healthy lifespan in the organism. These are "conserved" pathways which have been passed down to humans through evolution and thus are being considered attractive targets for research.

These two pathways are the insulin-like signaling (IIS) and target of rapamycin (TOR) pathways and it is documented that perturbation of this pathways can help in the genetic modulation of aging (3). Further aging is associated with disrupted energy homeostasis and mitochondrial dysfunction (4). To carry out mechanistic studies on the nematodes researchers use mutant strains, these are genetically modified organisms in which only one gene or sometimes one pathway is altered precisely. Similarly a double mutant strain will carry alterations in two different genes/pathways. In this study scientists used a daf-2 rsks-1 double mutant strain of C.elegans. DAF-2 is the C.elegans ortholog of the insulin growth factor 1 (IGF-1)

receptor and its inhibition doubles the lifespan of the adult worm. RSKS-1 is the C. elegans ortholog of ribosomal S6 kinase (S6K) which plays a major role in TOR pathway and its alteration can alter the lifespan of the organism. Genes act at transcriptional and translational levels and have pivotal roles in several cellular pathways (5). It is further reported that reduction in mRNA translation can reduce aging but the underlying mechanism is not clear. In this study it was reported that an alteration in the IIS pathway increases the lifespan of the worm by 100 percent. An alteration in the TOR pathway increases the lifespan of the worm by 30 percent. So it was assumed that the double mutant should increase the lifespan by 130 percent. However, contrary to the assumption the lifespan in double mutants was amplified by 500 percent.

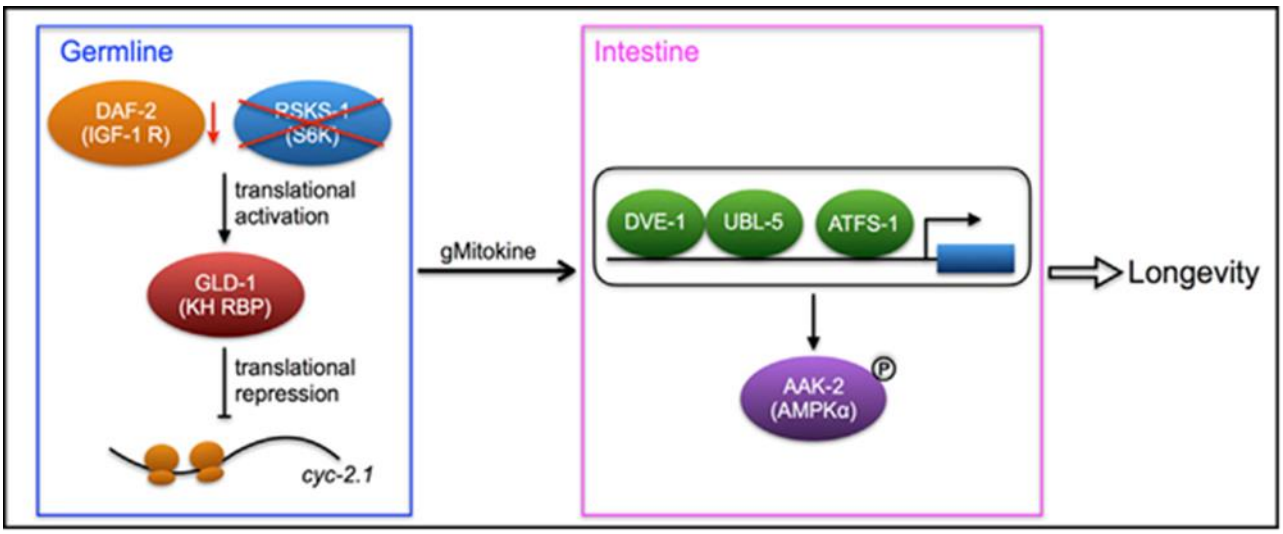

Figure 2: Graphical depiction of the synergistic interaction between cellular pathways. [Source: Cell reports, 2019]

This clearly shows that these two pathways have a synergistic effect on longevity and the research has elucidated the underlying mechanism and given us a clear picture of how the two different pathways interact via translational machinery to bring about the effect. To briefly summarize, polysomal profiling was performed to understand the role of translational regulation and cytochrome c (CYC-2.1) and ribosomal genes were identified as the key mediators of longevity. The knockdown of cyc-2.1 extends lifespan significantly by activating the intestinal mitochondrial unfolded protein response (UPRmt), AMP-activated kinase (AMPK) and mitochondrial fission. Further cyc-2.1's translational repression is mediated by RNA binding protein GLD-1 which is important for the non-autonomous activation of UPRmt and synergistic longevity of the daf-2 rsks-1 mutant. These results show translationally regulated nonautonomous mitochondrial stress response mechanism in the modulation of lifespan by insulin-like

signaling and S6K (1). The results have clearly shown that in order to study longevity and aging scientists have to investigate the roles of cellular networks and cross talk between different pathways instead of focusing on single individual pathways. The results showed that the effect of genetically altering pathways was not one plus one equals to two, instead one plus one equals to five. If the results are extrapolated in human beings the increase in lifespan would be equivalent to 400 to 500 years. Figure 2 summarizes the crux of the research graphically.

Future prospects and applications of the study

This study has unlocked new possibilities and revamped the concept of aging and longevity. It has given us a potent cue that if aging has to be targeted we will have to look into the complex cellular and genetic networks even if they are completely different from each other. Nature works in synergy with different elements to bring about order or chaos similarly synergistic interaction is responsible for the lifespan and aging of living beings. This study has also explained why scientists have not yet been able to identify a single gene or pinpoint a single pathway which is responsible for the potential of some humans to live to extraordinary old ages devoid of any major age-related diseases until shortly before their deaths. The study has further paved way for the experiment of combination therapies and molecular targets for drug development. This research is going to be pivotal in the development of drugs that would extend the healthy lifespan of individuals and help in combating the ill effects of old age. The research holds potential of bringing a revolution in the field of anti-aging therapies and medical treatments. Sustaining and extending the healthy lifespan of our fast aging population is the need of the hour and will help us build a pool of long living healthy humans instead of crippled aged individuals. The study has proven that combating old age is after all no longer a work of fiction but an act of research and medicine.

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