

Deregulated Nutrient Sensing and Altered Intercellular Communication

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Aging is an insidiously progressive deterioration in the physiological integrity of a cell resulting in impaired function. With an impetus to biomedical research and advances, it has come across a multitude of theories expatiated to reason aging. This article focuses on deregulated nutrient sensing and altered intercellular communication and their potential role in diminution of a cell's vigor, aging, and longevity of life.

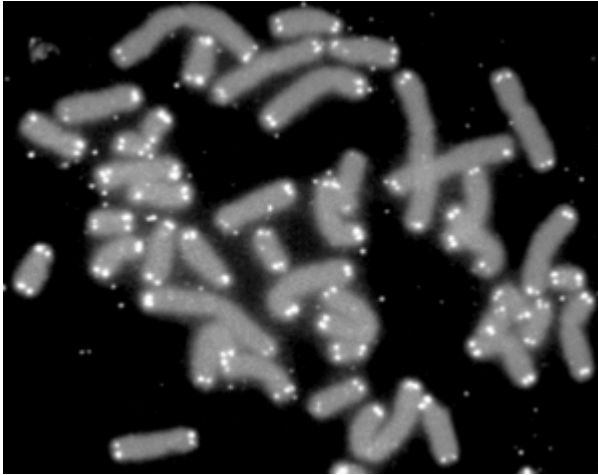


Introduction to Deregulated Nutrient Sensing and Altered Intercellular Communication

Aging is characterized by **temporal functional deterioration in the lifecycle of a cell**. It has tantalized many a curious mind throughout the history of mankind. Aging is defined as a diminished response to stress, escalation of homeostatic imbalance and an enhanced threat from aging-related pathologies.

There are various traits, theories, philosophies that try and unearth the mysterious origin of aging. Though none have been successful alone to expound aging explicitly, they have definitely escalated our understanding about aging.

The various physiological traits of aging can be summarized as follows:



[Image](http://science.nasa.gov/media/medialibrary/2006/03/16/22mar_telomeres_resources/caps.gif): "Telomere caps." by U.S. Department of Energy Human Genome Program - http://science.nasa.gov/media/medialibrary/2006/03/16/22mar_telomeres_resources/caps.gif. License: Public Domain

- Genomic instability
- [Mitochondrial dysfunction](#)
- [Telomere attrition](#)
- Epigenetic alterations
- [Loss of proteostasis](#)
- Altered intercellular communication
- Cellular senescence
- Deregulated nutrient sensing
- Stem cell exhaustion

We now cater to a detailed description of '**deregulated nutrient sensing**' and theory of '**altered intercellular communication**' keeping their role in aging as our prime prospect.

Deregulated Nutrient Sensing

Multiple nutrient-sensing pathways regulate intake to provide just the right amount of nutrition. **Decreased nutrient intake** can act to reduce the aging of cells because it slows the accumulation of damage due to reactive oxygen species (ROS).

Dietary restriction/calorie restriction leading to decelerated senescence as a mode of taming aging has fuelled fascination, interest, and research in the biomedical world. Also, as we age there is a decline in nutrient sensing, which in turn ages the cells. This is somewhat of a paradox.

Garinis et al. in 2008 in their humble attempt to decode this paradox proposed that IIS down-modulation portrays a defensive response targeted at truncating cell growth and cellular metabolism in the prospect of systemic damage. As per their theory, species with constitutively slowed IIS pathway have a longer lifespan.

Evidence generated so far strongly suggests that diminished nutrient signaling culminates in an extension of a cell's lifecycle. **Anabolic signaling (signals related to the formation of nutrients)** leads to a decline in the functional reserve of a cell and expedites aging. Deregulated nutrient sensing is an antagonistic hallmark of cellular

aging and represents a response to damage.

The different types of fat significant when dealing with nutrient sensing are:

- Free fatty acids
- Visceral adipose tissue
- Total body fat

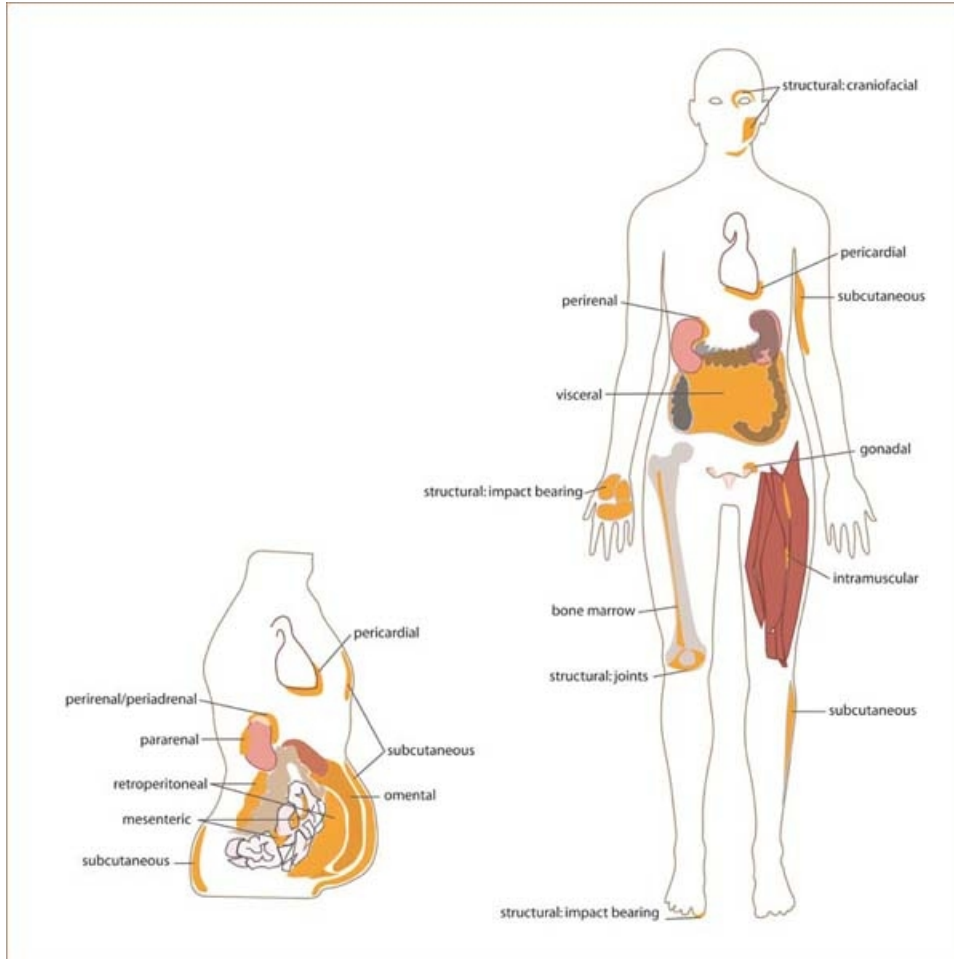


Image: "White adipose falls under two major classifications: visceral, or surrounding organs, and subcutaneous, under the skin." by Cook, A. and Cowan, C., Adipose (March 31, 2009), StemBook, ed. The Stem Cell Research Community, StemBook, doi/10.3824/stembook.1.40.1, <http://www.stembook.org>. - [1] Direct StemBook Figure 1 White adipose distribution in the body. Cook, A. and Cowan, C., Adipose (March 31, 2009), StemBook, ed. The Stem Cell Research Community, StemBook, doi/10.3824/stembook.1.40.1, <http://www.stembook.org>. License: [CC BY 3.0](https://creativecommons.org/licenses/by/3.0/)

Muscle and **liver** are the primary hosts for nutrient metabolite production and hence play a critical role in the maintenance of nutrient sensing. The chief processes associated with these organs can be summarized as follows:

Muscle	Fat oxidation, protein synthesis, muscle mass
Liver	LDL-C catabolism, VLDL output, hepatic fat content

There are 4 pathways extensively researched upon to study aging in light of deregulated nutrient sensing. These are:

- Insulin and Insulin-like growth factor (IGF-1) signaling pathway (IIS)
- mTOR pathway
- Pathway involving Sirtuins
- AMP Kinase (AMPK) pathway

A short description of each pathway is as follows:

Insulin and Insulin-like growth factor (IGF-1) signaling pathway (IIS)

Consistent with the role of nutrient-sensing in aging, **IIS pathway alteration** has reliably modulated the vigor and functionality of a cell in all investigated eukaryote organisms like worms, flies and mice. IIS pathway is the most preserved aging-modulating pathway described in the literature.

Anterior pituitary produced growth hormone (GH) and **its secondary mediator IGF-1** are the chief constituents of the **somatotrophic axis** in humans. This axis is prominently active in hepatocytes. The intracellular cascade activated once IGF-1 takes charge is the same as that for glucose metabolism management through insulin and IGF-1.

The major targets of the IIS pathway are the **FOXO family of transcription factors** and **mTOR complexes**.

Alteration and dysregulation of the IIS pathway are potentially possible at various junctures as:

- Genetic polymorphisms
- [Genetic mutations](#)
- Functional dysregulation of GH
- Defective IGF-1 receptor
- Altered insulin receptor
- Defunct downstream cascade check points
- Diminished intracellular effector response of molecules such as AKT, mTOR and FOXO

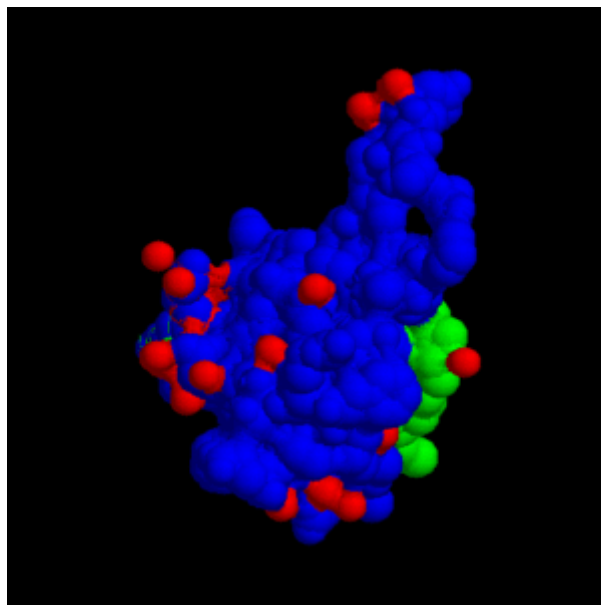


Image: "IGF-1." License: Public Domain

The attenuation of induction of downstream cascade through manipulation at various steps of IIS in experimental set ups has produced lengthening of cellular lifespan. However, GH and IGF-1 levels drop during normal aging and also in experimental models

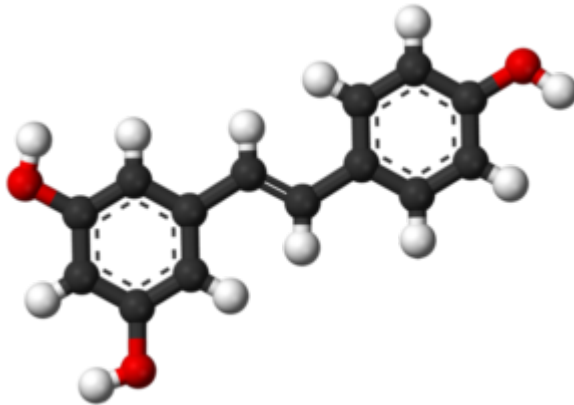
of **progeroid** mice with premature aging. While reduced IIS epitomizes physiological and expedited aging, a constitutively down-modulated IIS aggrandizes longevity.

It is concluded that decreased IIS pathway in a person can emphasize on reduction in damage at cellular level ,by reducing glucose accumulation in the body, thus delaying aging procedures.

The mTOR pathway

mTOR stands for **mechanistic target of Rapamycin**. The mTOR pathway deals with sensing of high amino acid concentration. Experts in this field are positive about the role of Rapamycin as a mechanistic target to modulate nutrient response pathway and substantially affect aging and age-related pathologies.mTOR signal nutrient abundance and anabolism thus prompting obesity and other fat-related pathologies in old age. They firmly believe it's a question of "when" rather than 'if'.

Pathway involving Sirtuins



[Image:](#) "Ball-and-stick model of the resveratrol molecule." by Jynto and Ben Mills – Derived from File:Benzene-aromatic-3D-balls.png, File:Hexahydroxybenzene-3D-balls-B.png and File:Benzene-non-aromatic-3D-balls.png. License: Public Domain

Sirtuin genes have been assigned anti-aging functions in yeast, *Caenorhabditis elegans*, and *Drosophila*. They are being extensively studied to determine the exact etiology of the role of dietary restriction and calorie restriction in aging. Regulation of mitochondrial biogenesis has been implicated. Indeed, the action of **Resveratrol**, a putative SIRT1 activator in delivering health benefits in treated mice by stimulation of mitochondrial biogenesis has been demonstrated in experimental circumstances. Sirtuins signal nutrient scarcity and catabolism just opposite to mTOR and IIS thus can be a boost antiaging.

AMP Kinase (AMPK) pathway

The AMPK protein acts as a **metabolic sensor**, more like a qualified cellular housekeeper to control energy homeostasis and resistance to stress. It thus curbs the attempts of many deleterious processes towards diminishing an individual's capacity for survival. The AMPK pathway is instrumental in aging-related processes such as [mitochondrial dysfunction](#), defective autophagy (self-killing of cells) and metabolic deregulation.

Thus, it is concluded that AMPK and sirtuins should act in opposition to the action of IIS

and mTOR to shut down the excess metabolic activities and nutrient reservation, thereby regulating aging.

Clinical implication

The fact that anabolic metabolism and increased nutrient-sensing accelerate aging has far-reaching clinical implications. **Pharmacological manipulation** of the cellular processes and pathways to induce a state of decreased nutrient availability thus has the theoretical potential of increasing the longevity of a cell's lifespan. Indeed, active research has revealed the extension of the lifespan in mice with Rapamycin through these mechanisms.

Altered Intercellular Communication

There is naïve evidence to propose that aging is not an exclusive cellular mechanism but involves defective intercellular communication. Intercellular communication plays an important factor in the progress of this essential definite phase in a cell's life by maintaining neurohormonal signaling.

Thus, there is a possibility that aging is controlled by alterations beyond the autonomy of an individual cell. Altered intracellular communication is an integrative hallmark of aging. It is an **expression of the culprit of the phenotype**.

Neuro-hormonal signaling becomes deregulated In aging proceeds. As **inflammatory reactions** increase, they deregulate intercellular signaling. The important pathways involved in intercellular communication are as follows:

- Inflammaging
- Adrenergic signaling
- Renin-angiotensin system
- Insulin-IGF signaling
- Immunosurveillance

Inflammaging

An insidiously progressive pro-inflammatory state predominates as a cell experiences aging. This smoldering aging-associated phenotype is '**Inflammaging**'. Inflammatory reactions enhanced by degenerative medical conditions such as type 2 diabetes, atherosclerosis, obesity correlate with aging. Different theories have been hypothesized to throw more light in this prospect. The same can be summarized as follows:

- A tendency towards secretion of pro-inflammatory cytokines by senescent cells
- Aggregation of pro-inflammatory tissue damage
- Failure of a defunct immune system in effective clearance of harmful organisms and dysfunctional cells of one's own self
- Defective autophagy
- Inhibition of epidermal stem cell function
- Enhanced production of IL-1 β , tumor necrosis factor, and interferons
- Escalated activation of NF- κ B transcription factor

Another upcoming terminology is "**Immunosenescence**". It epitomizes the aggravation of aging phenotype due to altered immune system function, diminished agility in curbing pathogens and in the clearance of defective host cells.

Nelson et al. in 2012 proposed the **Bystander effect**, also known as “**Contagious**” **aging**. Contagious aging refers to the alteration of neighboring cells by senescent cells through paracrine means via gap junctions.

Altered intercellular communication directly influences tissue homeostasis and function, resulting in cell damage accumulated in a long time frame.

Clinical implication

Various experimental modulations of inflammatory pathways, immune system, intercellular communication processes to delay aging have been attempted in different mouse models. Few have been successful in preventing age-associated features. Further research has been already stimulated to find a reliable way to bring these experiments into reality. Few promising approaches can be summarized as follows:

- **Dietary restrictions**
- **Rejuvenation strategies** based on the use of blood-borne systemic factors as revealed in parabiosis experiments
- Long term administration of **anti-inflammatory agents** such as aspirin
- **Manipulation of an intestinal bacterial ecosystem** of the human body to shape the function of the host immune system with subsequent systemic metabolic effects towards optimization of the cell's milieu interior.

Summary

Aging is defined as a diminished response to stress, escalation of homeostatic imbalance and an enhanced threat from aging-related pathologies. There are various physiological traits that characterize aging.

Multiple nutrient-sensing pathways suggest a regulated intake of nutrients is compulsory to provide just the right amount of nutrition. Decreased nutrient intake can act to reduce the aging of cells because it slows the accumulation of damage due to Reactive Oxygen Species (**ROS**). As we age there is a decline in nutrient sensing, which in turn ages the cells.

There are 4 predominantly important pathways implicated in deregulated nutrient sensing:

- IIS pathway
- mTOR pathway
- Pathway involving sirtuins
- AMPK pathway

The most important, well-studied and most preserved pathway consistently associated with aging is the IIS pathway.

Biomedical, cytogenic and molecular research has made various genetic and pharmacodynamic manipulations of these aging-associated pathways a potential possibility in the near future. The clinical implications of these manipulations cannot be underestimated.

Recent advances have questioned the existence of aging as an exclusive cell-associated autonomous process. Defective intercellular communication as a cause of aging is increasingly being appreciated. More specifically, defective neurohormonal signaling and dysregulated inflammatory pathways with a dysfunctional immune system have been

implicated in this vein.

- Smoldering pro-inflammatory phenotype which accelerates aging is termed as 'Inflammaging'.
- Immunosenescence stands for decreased longevity of the lifespan of a cell secondary to the dysfunctional immune system with decreased proactive behavior towards curbing infections, pathogens and diminished clearance of defective host cells.
- Contagious aging, also known as 'Bystander effect', epitomizes **paracrine** alteration of a cell by neighboring senescent cells to accelerate aging. It is mediated through gap junctions.

Various means of modulation of deregulated intercellular communication pathways are being actively sought in experimental setups. Long term administration of aspirin and manipulation of the intestinal ecosystem are primary triggers of the deregulation of communication pathways.

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Correct answers: 1A, 2D, 3A

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