

Systems Biology of Human Aging Network Model Wall Chart

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Summary

This network diagram is presented to aid in conceptualizing the many processes of aging, the causal chains of events, and the interactions among them. Contemplation of this network indicates promising intervention points for therapy development. This diagram is maintained on the Web as a reference for researchers and students. Content is updated as new information comes to light.

www.LegendaryPharma.com/chartbg.html

The many observable signs of human senescence have been hypothesized by various researchers to result from several primary causes. Inspection of the biochemical and physiological pathways associated with age-related changes and with the hypothesized causes reveals several parallel cascades of events that involve several important interactions and feedback loops. This network model includes both intracellular and extracellular processes. It ranges in scale from the molecular to the whole-body level. Environmental effects and proposed interventions are highlighted around the margins of the network.

Important pathways include:

Nuclear mutations, telomere shortening, chromosome breaks, chromatin alterations, and epigenetic DNA adducts change gene expression.

Extracellular proteins become damaged by glycation, oxidation, crosslinking, and lytic enzymes, resulting in mechanical stiffness, weakness, and inflammation.

Altered environmental niches for cells contribute to transdifferentiation, arrested cell division, cell death, cancer, stem cell depletion, tissue wasting, neurodegeneration, and organ malfunction. Stiffer blood vessels promote stroke and heart disease.

Lysosomes accumulate reactive, crosslinked *lipofuscin*, which impairs autophagic turnover of macromolecules and organelles, resulting in accumulation of dysfunctional macromolecules and organelles. This interferes with cell function. When lipofuscin leaks into the cytosol, it can trigger apoptosis of cells, which are not readily replaced.

Mitochondrial DNA mutates. Mutations are copied, resulting in altered cell physiology.

Lamin-A splice-variant, **progerin**, accumulates in the nuclear scaffold, impairing cell division.

Nuclear envelope pore proteins become oxidized, allowing inappropriate traffic of other proteins into and out of the nucleus.

Oxidized aggregates in cytoplasm become crosslinked, resist turnover, inhibit proteasome activity, increase redox poise, and physically interfere with intracellular transport, especially in axons. Inhibited proteasomes reduce turnover of damaged molecules and of expired molecular signals. Increased redox poise alters signaling and enzyme activities, and erodes telomeres. **Inflammatory cascades**, promoted by damaged molecules and sick cells, further damage tissues. **Neuroendocrine and immune systems** degrade. **ER stress**: Misfolded proteins accumulate in the ER.

Several researchers have proposed to adapt this network model's contents into an interactive website with hyperlinks to references and background materials. Others have proposed to create a machine learning computer model to find promising targets. A symposium to promote these developments was held at Arizona State University, December 2008; abstracts are at

http://legendarypharma.com/meetings/2008ASU_SysBioAging/aging.html

A second symposium was held 8-9 December 2009 at the National Institute on Aging Gerontology Research Center in Baltimore, Maryland.

A third meeting in this series was held in Philadelphia 6-7 Dec 2010.

<http://biomed.drexel.edu/SBHA/SBHA-2010.html>

Getting Started With This Network Diagram

At first glance this wall chart looks like a complicated web. However, as a *conceptual summary*, in one view, we can see how most biogerontological processes relate to each other. Importantly, examination of these relationships allows us to pick out reasonably plausible *causal chains of events*. Within these chains, we can see age-related changes or accumulations that appear to be promising targets for future therapy development. Especially harmful is damage to the body's regeneration and repair systems, because they normally repair damage to other structures and systems. *Repairing the repair systems* should receive high priority in planning the development of new therapies. An important example is age-associated accumulation of *lipofuscin* inside the lysosomes inside neurons. This can block autophagic removal of damaged structures inside the cells. In this chart, we can follow several important pathways from age-associated causes down through the age-associated pathologies that result.

This symbolic diagram is not really a picture of a cell. It changes in scale from molecular events at the top, through whole cell activities in the middle, to tissue, organ, and whole body diseases at the bottom.

Thick horizontal borders separate transitions in scale. Intracellular events are described on the top left. Extracellular matrix and blood are described on the top right.

Colors have meaning, as indicated in the "Color Key".

Shapes have meanings described in the "Shape Key".

Solid boxes represent physical materials.

Slanted-roof boxes represent increase or decrease in quantities during aging.

Hatched boxes represent activities or processes.

Thin arrows represent causal sequences of events.

Thick arrows represent physical transport or movement.

A **circle with an "X"** inside represents inhibition of the indicated process; this might mark a candidate target for therapeutic intervention.

Tags pointing in from the far left and right represent environmental factors or external interventions.

Abbreviations

| | |
|----------------------------|--|
| Aβ | = β -amyloid peptide 1-42 |
| AGEs | = Advanced Glycation Endproducts |
| ALEs | = Advanced Lipoxidation Endproducts |
| Aggs | = Aggregated, crosslinked Junk molecules, including Lipofuscin & similar aggregated material |
| Apgsm | = Autophagosome |
| Apsy | = Autophagy |
| Assy | = Assembly |
| BBB | = Blood-brain barrier |
| BM | = Basement Membrane |
| Ca | = Calcium |
| CCL11 | = Eotaxin, a chemokine in blood and CSF |
| CMA | = Chaperone-mediated Autophagy |
| CMV | = Cytomegalovirus |
| COPD | = Chronic Obstructive Pulmonary Disease |
| CR | = Calorie Restriction |
| CSF | = Cerebrospinal Fluid |
| Cu | = Copper |
| decr | = Decrease, Decreases, Decreased |
| Dev | = Developmental |
| Diffn | = Differentiation |
| EC | = Extracellular |
| ECM | = Extracellular Matrix |
| ETC | = Electron Transport Chain |
| eg. | = For example |
| exp | = Gene Expression |
| GDF11 | = Growth differentiation factor 11 |
| GnRH | = Gonadotropin-releasing hormone , also known as Luteinizing-hormone-releasing hormone (LHRH) and luliberin |
| GPx | = Glutathione Peroxidase |
| HDACs | = Histone deacetylases |
| Hg | = Mercury |

| | |
|---------------------------------|--|
| HO* | = Hydroxyl radical |
| Hypothal | = Hypothalamus, Hypothalamic |
| Ig | = Immunoglobulins |
| IL | = Interleukin |
| IMM | = Inner Mitochondrial Membrane |
| incr | = Increase, Increases, Increased |
| inflam | = Inflammation, Inflammatory |
| ISCs | = Iron-sulfur clusters |
| Junk | = Damaged Intracellular Structures, incl. oxidized proteins, lipid membranes, mitochondria, & proteasomes. |
| LDL | = Low Density Lipoprotein |
| LF | = Lipofuscin or ceroid. Heterogeneous, crosslinked, indigestible material. |
| Lysm | = Lysosome |
| memb pot | = membrane potential (mV) |
| mito | = mitochondrion |
| MMP | = matrix metalloproteinase |
| MSCs | = Mesenchymal Stem Cells, and derivatives, e.g. fibroblasts, osteoblasts. |
| mt | = mitochondrial |
| mtDNA | = mitochondrial DNA |
| nDNA | = nuclear DNA |
| O₂*- | = Superoxide ion |
| PARP | = Poly-ADP-ribose polymerase |
| Pb | = Lead |
| PFC | = Pre-Frontal Cortex of the brain |
| PGC-1α | = Peroxisome proliferator-activated receptor gamma coactivator 1-alpha |
| PHF | = Paired Helical Fibrils of tau protein |
| PM | = Post Mitotic tissues, non-dividing cells, especially CNS neurons, skeletal muscle, and cardiac muscle |
| RAGE | = Receptor of Advanced Glycation Endproducts |
| RBCs | = Red blood cells. Erythrocytes |
| ROS | = Reactive Oxygen Species. Free radicals, such as superoxide, or hydroxyl radical. |

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| | |
|--------------|---|
| SN | = Substantia nigra |
| SR | = Sarcoplasmic Reticulum of muscle fibers |
| Tase | = Telomerase |
| Tmere | = Telomere |
| TTR | = Transthyretin |
| Zn | = Zinc |

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Permalink to the latest version:

<http://www.LegendaryPharma.com/chartbg.html>

References and links to more information about these topics may be found at:

<http://LegendaryPharma.com/senescence.html>

Keywords may be searched at: **PubMed**, **scirus**, **Google Scholar**, or your favorite reference or search system.

A very good short review of aging mechanisms was published in the journal, **Nature** by Jan Vijg & Judith Campisi. (2008) Puzzles, promises and a cure for ageing. *Nature*, 454, 1065-1071.

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