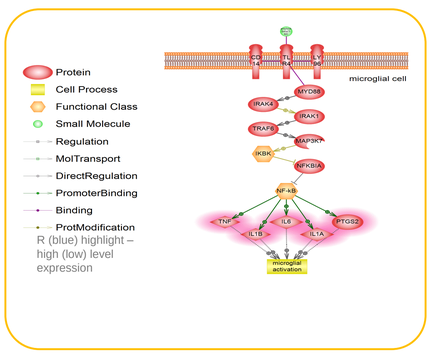
PATHWAYS TO UNDERSTANDING BRAIN AGING (DECIPHERING COMPLEX CELL PROCESSES)

ABSTRACT

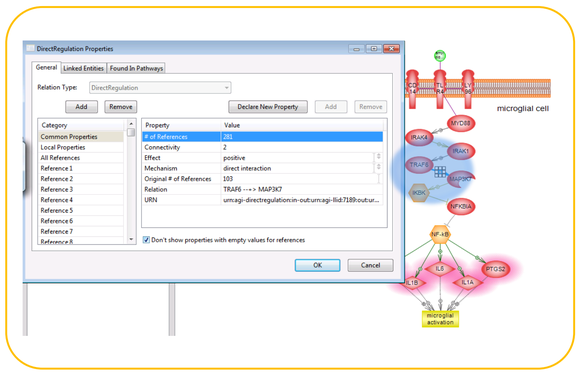
Genomics technologies have increased the quantities of data of aging and aging related disease. The ability to visual manipulate enormous biological data with help of interactive maps or pathways helps researchers to understand the complex conditions like disease onset and progression, and can help developing useful diagnostics and effective treatments.

Aging is the gradual process of destructive alterations in all structural levels of an organism, from genes and proteins to organ systems. We have reconstructed collections of interactive signaling pathways that describe general molecular mechanisms of aging at the cellular lever, as well as development of specific aging-related diseases such as Alzheimer or Parkinson's disease, and others.

To build the pathway collection for Aging related diseases, ResNet (the database of 100000+ relations), Pathway Studio (data visualization and analysis tool), and Elsevier Text Mining (text mining and search tool) were used.



The Pathway – is an interactive visual micro -database which contains information about proteins and relations



Each relation between proteins provides access to articles

CONCLUSION

Aging disease pathways collection is the catalog containing all currently known facts about molecular bases of aging-related processes in humans, arranged in accessible format for use in biomedical research. The pathways collection is a powerful tool that can help building and browsing networks of biological aging.

MOLECULAR SIGNALING OF INNATE CAUSES OF CELL AGING

Aging is the biological process that is initiated in each and every cell of an organism, but has its characteristic features specific to every differentiated tissue. The main difference between specific aging-related brain cells degeneration and common cell senescence seems to be a matter of the local expression: specific characteristics of differentiated tissue and cells (high number of synaptic terminals and mitochondria, unmyelinated axon) make them highly vulnerable to aging.

Subcelluar level

- persisted DNA repair
- epigenetic alterations
- telomere attrition
- hyperfunction of mTOR/INS/IGF
- proteome instability
- glyco/lipotoxicity
- sirtuins suppression

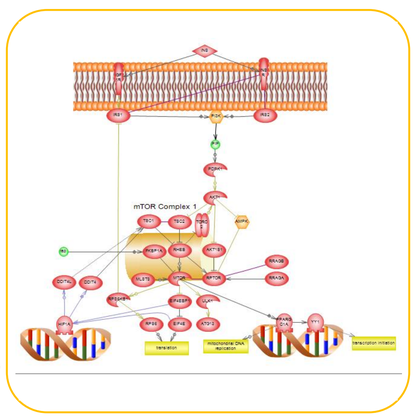
Cellular level

- stem cell exhaustion
- cell cycle arrest (cellular senescence)
- mitochondrial decline
- cell communications altering
- programmed cell death

Cell specific level

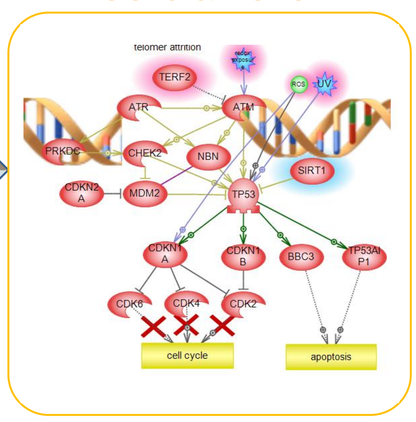
- neurons loss
- proteotoxicity: lipofuscin accumulation
- protein aggregation: Reelin deposits
- proteotoxicity: amyloid accumulation
- neuron's provoked inflammation

Subcellular level



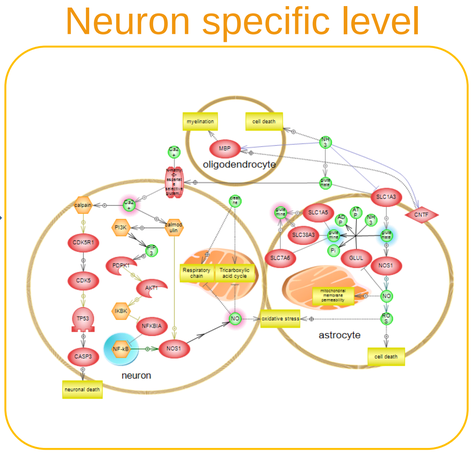
"Hyperfunction of mTOR signaling in Aging"

Cellular level



"Cell senescence in Aging"

Neuron specific level



"Effects of Ammonia on Neurons"

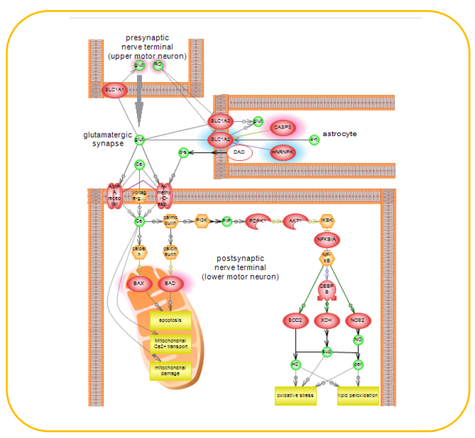
FUNCTIONAL LEVEL OF AGING PROGRESS

Complications (diseases) of aging

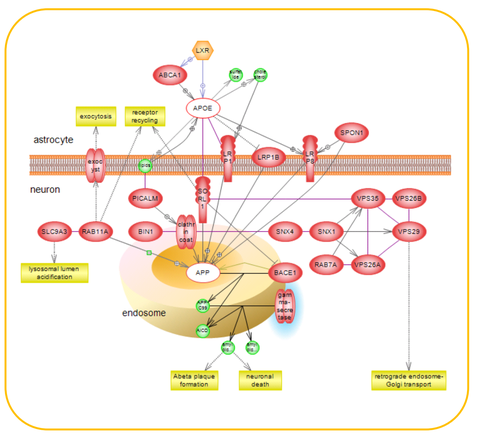
- ❑ Mild cognitive impairment
- ❑ Alzheimer's disease
- ❑ Cerebrovascular disease
- ❑ Parkinson's disease
- ❑ Lou Gehrig's disease
- ❑ Vascular dementia
- ❑ Primary progressive aphasia

Brain specific function impairment in aging

- ❑ Brain hormones alteration in aging
- ❑ Brain-blood barrier dysfunction
- ❑ Chronic neuroinflammation



Glutamate-Mediated Excitotoxicity in Amyotrophic Lateral Sclerosis



Amyloid beta and APP Intracellular Transport in Alzheimer's Disease

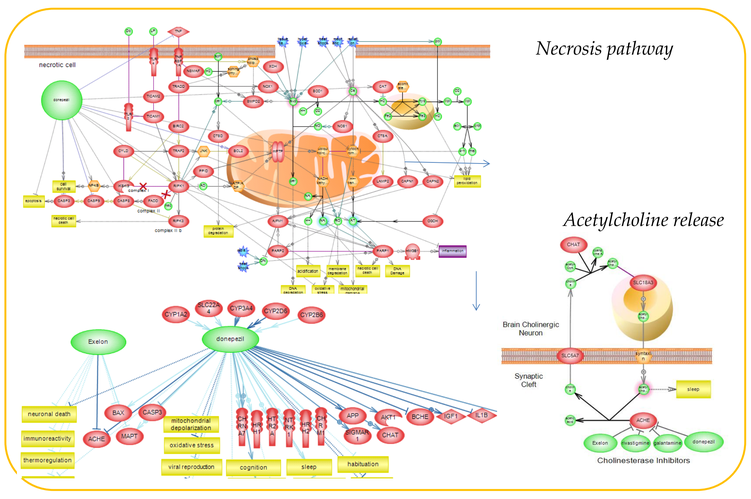
Alzheimer's disease Pathways from Aging collection :

- Amyloid beta and APP Intracellular Transport in Alzheimer's Disease
- Amyloid beta Formation
- APP and Glutamate Signaling-Related Neuronal Dysfunction in Alzheimer's Disease
- Complement Activation in Alzheimer's Disease
- Mechanism of Amyloid beta Clearance
- Metals and Amyloid beta Toxicity
- Microglia Activation in Alzheimer's Disease
- Multiple Functions of Estrogen in Mitochondria in Alzheimer's Disease
- Neurofibrillary Tangle Formation in Alzheimer's Disease
- Traffic and Degradation of Extracellular Amyloid beta in Alzheimer's Disease

PATHWAYS ANALYSIS

- ❑ Map patient experimental expression profile data to the pathways
- ❑ Map animal model experimental expression profile data to the pathways

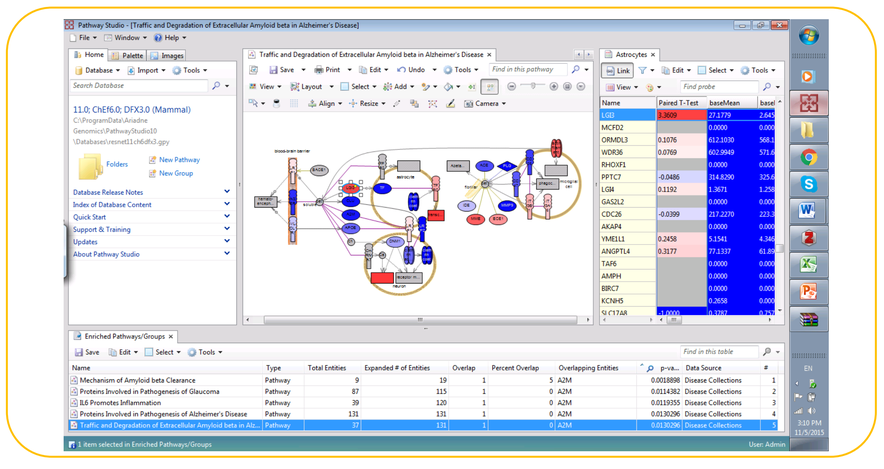
Looking for connections between drug and any pathway, you can easily outline the molecular mechanism of this drug action.
Like here, where we were looking for donepezil mechanism action.



By analyzing the differentially expressed genes of aging disease's animal models against our pathway collections, you can find human disease pathways which have over- or under-expressed animal genes to identify new human genes likely involved in the disease.

Like here, we find low and high expressed genes in 15-month-old mouse hippocampal formation on "Traffic and Degradation of Extracellular Amyloid beta in Alzheimer's Disease" pathway.

By analyzing expression data from patient tissue sample against our pathway collections, you can find up and down regulated genes in the disease related molecular mechanism, which could help thinking about the treatment corrections.



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