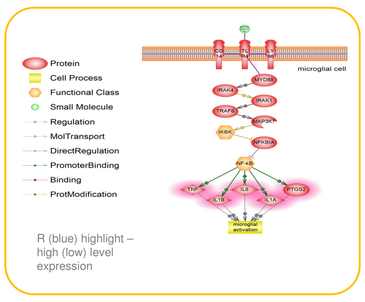
PATHWAYS TO UNDERSTANDING BRAIN AGING (DECIPHERING COMPLEX CELL PROCESSES)

ABSTRACT

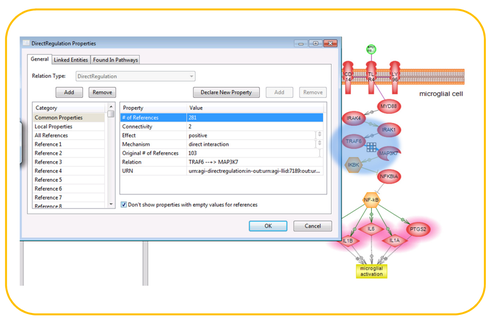
Genomics technologies have increased the quantities of data of aging and aging related disease. The ability to visual manipulate enormous biological data with help of interactive maps or pathways helps researchers to understand the complex conditions like disease onset and progression, and can help developing 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. It helps in analyzing experimental model animals and patients' data and in searching for relevant and specific scientific research results among big aging-related data for uncovering cause-effect relationships and integrating the facts. Even users unfamiliar with aging-related diseases can get a general idea: identify the proteins that are the major players, and see how potential drugs affect certain functions in the pathway and what the mechanism of action could be.

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 basis of observed age-related brain function impairment is the alterations in conservative molecular processes that are not cell specific, such as cell senescence which affect practically all cells in the body. 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.

Pathways from the collection for

Subcelluar level

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

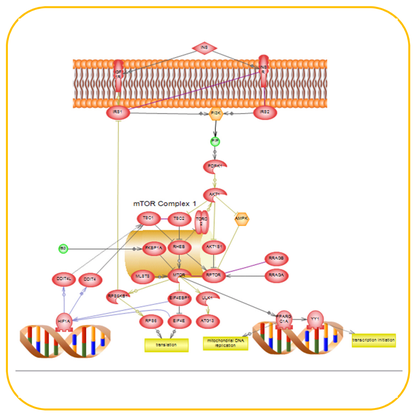
Cellular level

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

Cell specific level

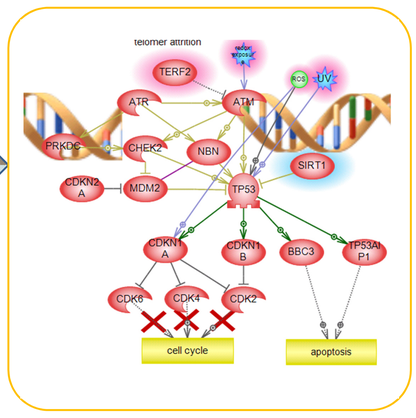
- neurons loss
- proteotoxicity: lipofuscin accumulation
- protein aggregation: Reelin deposits
- proteotoxicity: amyloid accumulation
- neuron's provoked inflammation

Subcellular level



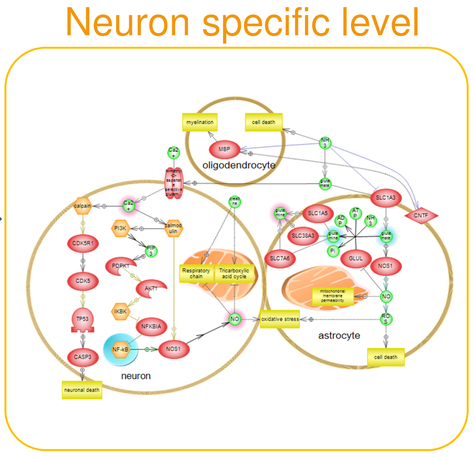
Pathway "Hyperfunction of mTOR signaling in Aging"

Cellular level



Pathway "Cell senescence in Aging"

Neuron specific level



Pathway "Effects of Ammonia on Neurons"

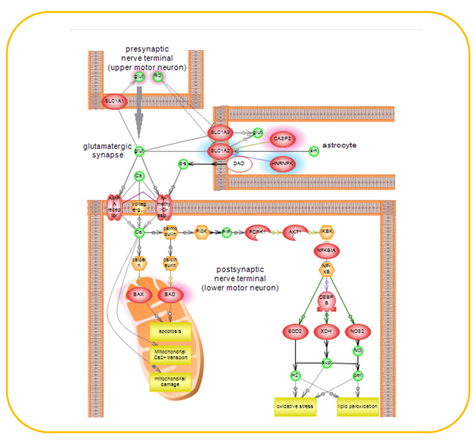
FUNCTIONAL LEVEL OF AGING PROGRESS

Complications (diseases) of aging

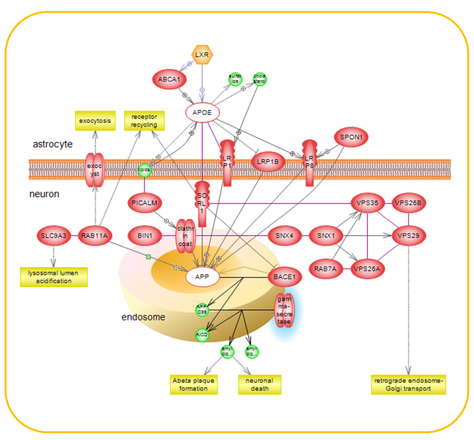
- ❑ Mild cognitive impairment
- ❑ Alzheimer's disease
- ❑ Cerebrovascular disease
- ❑ Parkinson's disease
- ❑ Lou Gehrig's disease
- ❑ Vascular dementia
- ❑ Primary progressive aphasia

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

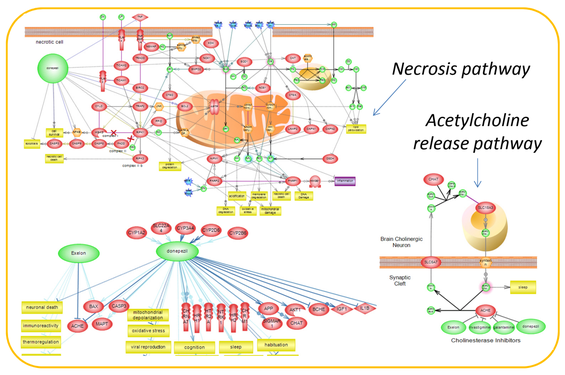
Alzheimer's disease Pathways from Aging collection :

- 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

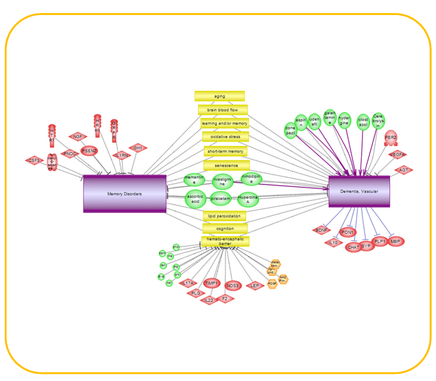
PATHWAYS ANALYSIS

Easy access to facts about aging related genes and cell processes

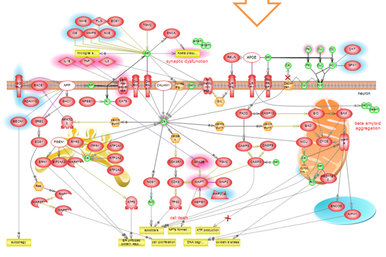
- ❑ Find new targets
- ❑ Look for mechanism of action of existing drugs
- ❑ Use pathway as a template. Add, subtract, and combine pathways for customized use.



Using pathways as a template, you can combine them to get one bigger and complex model. Such as "Alzheimer's Disease Overview" below.



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.



Exploring connections between point disease or cell process and proteins and small molecules in the database, you can find most of disease related biomarkers or targets in two-click action. Like here, we were looking for common interaction partners for both Memory Disorders and Vascular Dementia.

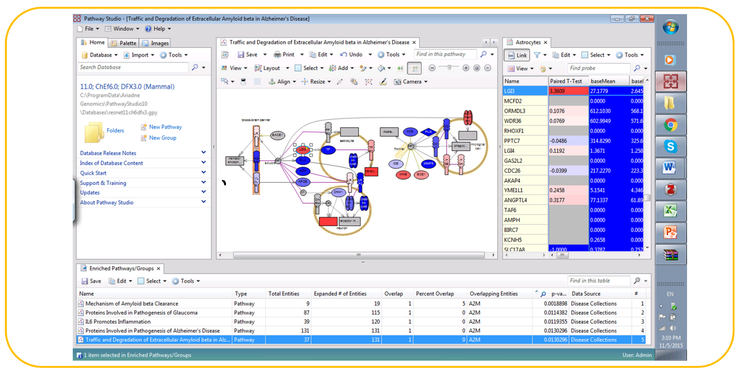
Experiment data analysis

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

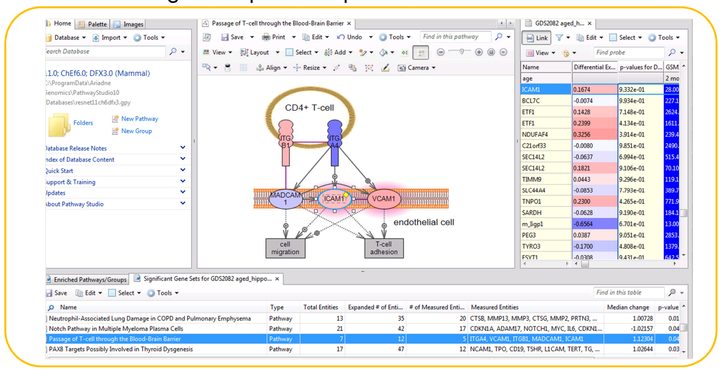
PathwayStudio's tools for pathway analysis
Find Groups/Pathways Enriched With Selected Entities
Find Similar Pathways/Groups
Find Sub-networks Enriched by Selected Entities
Gene Set Enrichment Analysis (GSEA)
Positional Gene Set Enrichment Analysis (PGSEA)
Sub-network Enrichment Analysis (SNEA)
Build Dense Expressed Networks
Find Genomics Positions Enriched with Selected Entities

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.



How pathway analysis applied to patient's gene expression profiles could look like



A. Nesterova, E. Klimov, M. Zharkova, V. Sobolev, S. Sozin, I. Teremetskaya, A. Anuchina
a.nesterova@elsevier.com, klimov_eugeney@mail.ru
Elsevier, Rockville, MD, USA, in collaboration with MSU, Moscow, Russia
www.elsevier.com/pathway-studio