Metabolic Network Analysis for Understanding the Biology of Aging

Sudharshan Ravi*[a,b] and Rudiyanto Gunawan[a,b,c]

[a] Institute for Chemical and Bioengineering, ETH Zurich, Switzerland

[b] Swiss Institute of Bioinformatics, Lausanne, Switzerland

[c] Department of Chemical and Biological Engineering, University at Buffalo, USA

*Email: ravis@chem.ethz.ch

Background and Motivation

- Aging is a complex and multifactorial process characterized by a progressive loss in physiological function, lowered ability to respond to stress and increased vulnerability to diseases. It is a major risk factor of a plethora of human diseases such as cancer, cardiovascular and neurodegenerative diseases[1].
- With increase in life expectancy and falling fertility rates, world population is aging. Thus, a better understanding of the biology of aging has the potential to delay the on-set of age-related diseases and is paramount in reducing the burden on the economy.
- A close connection between aging and metabolism is well documented[2,3]. Dietary restriction is the most robust and successful aging intervention strategy that has been confirmed in many model organisms (Fig. 2). However, specific metabolic pathways and genetic factors involved in aging process are still largely unknown.
- The identification of human metabolic alterations during the aging process and their phenotypes is crucial for formulating an intervention strategy.

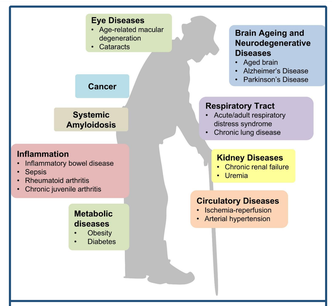

Figure 1: Age – related diseases

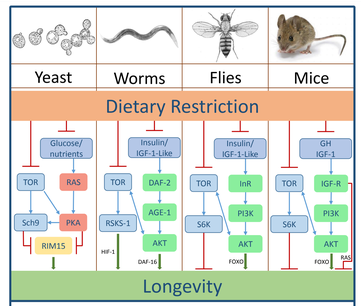

Figure 2: Dietary restriction in model organism

Methods

- We analyzed human transcriptomics data from the Genotype-Tissue Expression (GTEx) project to elucidate age-related changes in humans (see Fig. 3).
- A linear mixed effect model (LMM) was employed to determine age-related gene expression changes.

$$Y_{ijk} = \beta_i + \alpha_{ij} T_j + \gamma_{ik} Sex_k + \varepsilon_i Age_k + b_k + e_{ijk}$$

- Here, Y_{ijk} is the expression of gene *i* in tissue *j* belonging to the subject *k*, $\alpha_{ij} T_j$ and $\gamma_{ik} Sex_k$ denote the fixed effects of tissue (T_j) and sex, respectively, and b_k is the random effect associated with each subject. To analyse tissue-specific gene expression changes, the linear mixed effect model was applied on a subset of the transcriptomic data belonging to that particular tissue, without the term $\alpha_{ij} T_j$.
- Tissue and sex were treated as fixed effects. Individuals were taken as random effects.
- Dynamic changes in gene expressions and their effect sizes were studied using a 30-year moving window (MW) analysis. Normalized RNA-Seq read counts were compared between the age groups: 20s vs 40s, 30s vs 50s, 40s vs 60s and 50s vs 70s, using LMM.
- The age-related gene expression changes were mapped onto the human genome scale metabolic network (Recon – 3D)[4]. We identified over-represented metabolic subsystems among the 'aging' genes using a Fisher exact test.

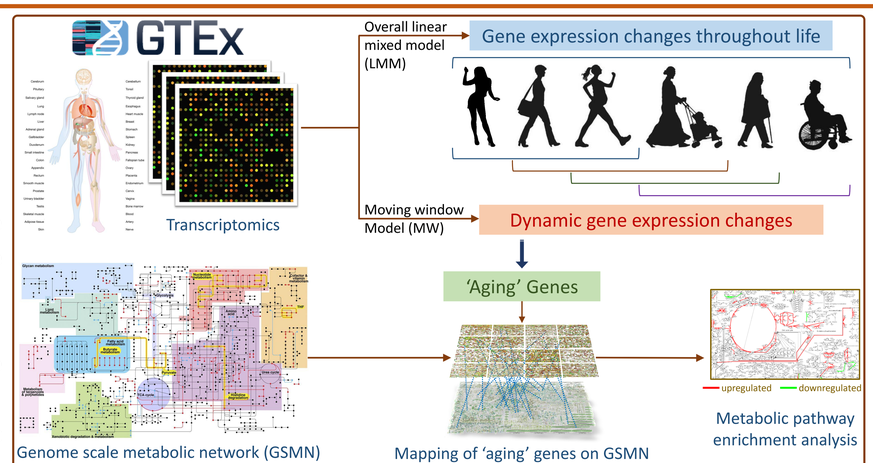

Figure 3: Schematic representation of curation of age – related metabolic pathway changes

Results

- While there exist tissue-specific alterations in metabolism during aging, our overall LMM analysis points to significant age-related metabolic changes in pathways pertaining to cellular energy generation. Oxidative phosphorylation (Oxphos) and tricarboxylic acid (TCA) cycle are over-represented among the set of downregulated aging genes across multiple tissues (Fig. 4A)
- Fatty acid synthesis and oxidation show marked downregulation overall. Impairment of these pathways have previously been implicated in mammalian aging[2].
- Many tissues display an upregulation of the inositol phosphate metabolism pathway (Fig. 4B). Members of this pathway regulate cell proliferation, migration and Akt signaling. They are shown to be frequently disrupted in neurodegenerative diseases and cancers.
- Moving window analysis shows that statistically significant changes in the gene expression related to metabolism have only moderate to weak effect sizes, as measured by Cohen's f^2 score.
- Metabolic pathways in cellular energy generation (TCA, Oxphos and fatty acid oxidation) are downregulated between 20s to 40s, which persist to late life (Fig 5A).
- Metabolites playing key roles in the inflammation process and xenobiotic response, including Arachidonic acid, Linoleic acid and Leukotrienes, are upregulated in early life (Fig 5B).
- Amino acid metabolisms are moderately downregulated in late life (Fig 5A). Metabolic changes in late life are associated with a lower level of chondroitin. Depletion of chondroitin results in a decrease in tissue hydration, a loss of fluid movement, functional and structural loss of adult neurons and cell apoptosis.

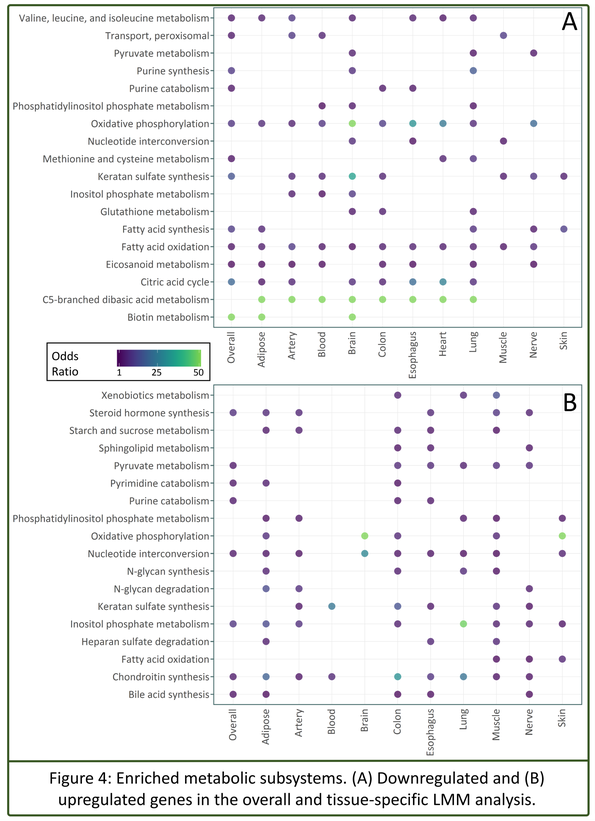

Figure 4: Enriched metabolic subsystems. (A) Downregulated and (B) upregulated genes in the overall and tissue-specific LMM analysis.

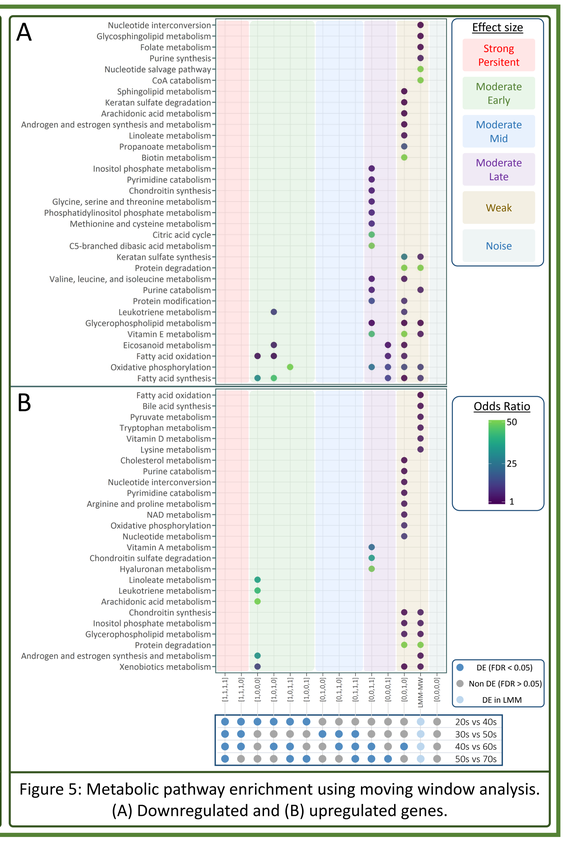

Figure 5: Metabolic pathway enrichment using moving window analysis. (A) Downregulated and (B) upregulated genes.

Summary

- The identification of metabolic pathways involved in aging is an important first step toward formulating a strategy for mitigating aging.
- Our LMM and moving window analyses of human gene expression show weak to moderate age-related alterations in the expression of enzymes involved in the metabolic pathways.
- Metabolic subsystems involved in cellular energy production (TCA, Oxphos and fatty acid oxidation) are moderately downregulated in early life, a change that persists to late life, albeit weakly.
- Metabolic pathways associated with the inflammation process and xenobiotic response are upregulated in early life.
- Moderate late life changes affect enzymes involved in amino acid and chondroitin sulfate metabolisms.
- There exist tissue-specific age-related changes in metabolisms. Notably, aging is associated predominantly with downregulation of cellular metabolism in the brain.

Acknowledgement

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References

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