Metabolic Network Analysis for Understanding the Biology of Ageing

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Background

- Ageing is a major risk factor of a plethora of human diseases such as cancer, cardiovascular and neurodegenerative diseases. Thus, a better understanding of the biology of ageing has the potential to delay the on-set of age-related diseases.
- A close connection between ageing and metabolism is well documented[1,2]. However, specific metabolic pathways that are involved in ageing process are still largely unknown.
- The understanding of human metabolic alterations during ageing and their phenotypes is crucial for formulating an intervention strategy.

Age-related changes

- In this study, we analyzed human transcriptomics data from the Genotype-Tissue Expression (GTEx) project to elucidate age-related changes in human metabolism (see Fig. 1).
- A linear mixed effect model was employed to determine age-related gene expression changes.

$$y_{ijk} = t_i + g_j + b_k + e_{ijk}$$

- y_{ijk} represents the *ijk*-th logarithmic gene expression (RNA – Seq) in the *i*-th tissue, for the *j*-th factor, e.g. age, and in the *k*-th individual. The variable *e* denotes the random error.
- Tissue was treated as a fixed effect, age was modeled as a continuous covariate, and individuals were taken as random effects.
- The age-related gene expression changes were mapped onto the human genome scale metabolic network (Recon – 2) [3].

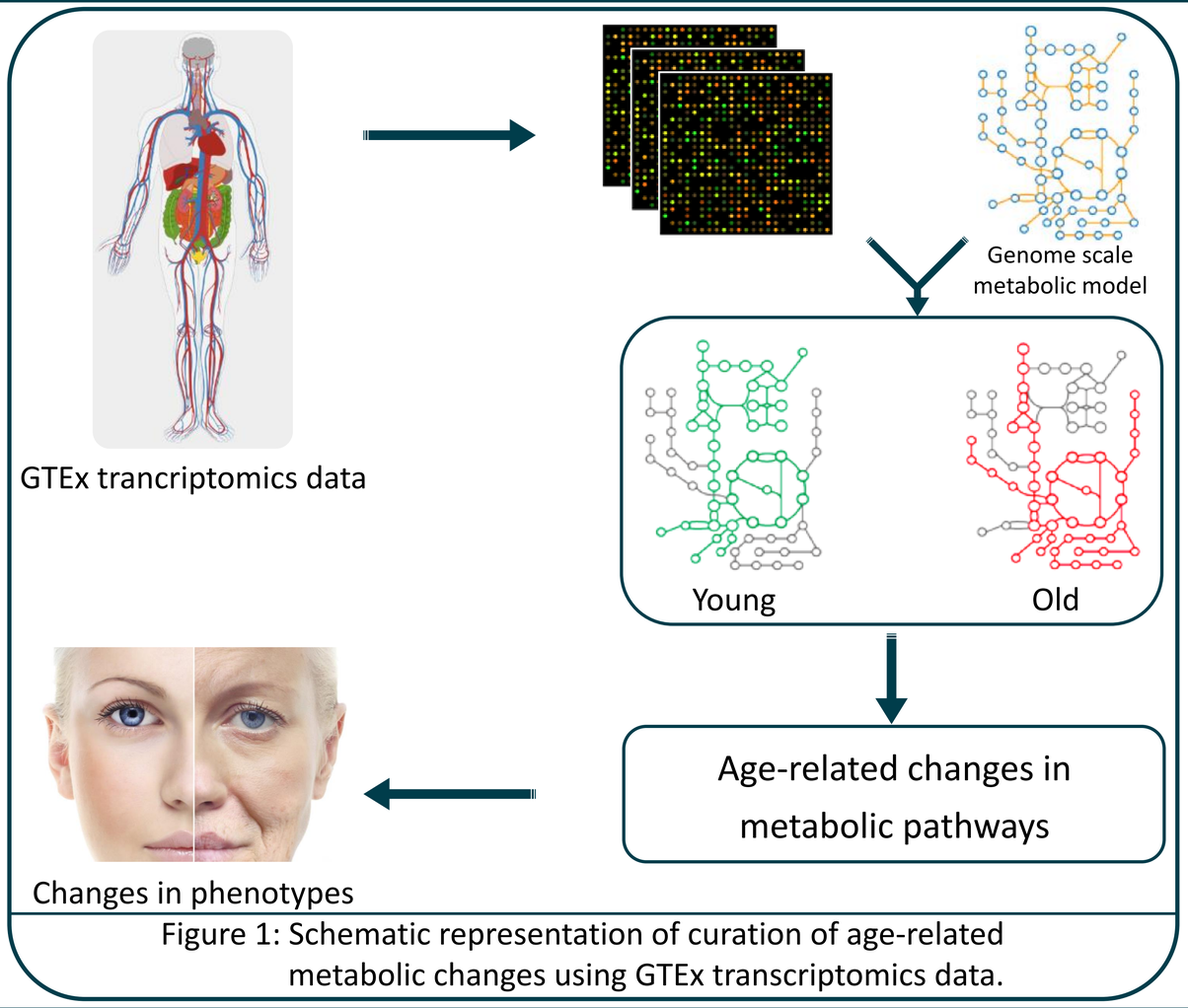

Figure 1: Schematic representation of curation of age-related metabolic changes using GTEx transcriptomics data.

Metabolic pathway alterations

- Age-related changes in human gene expression pointed to downregulation of TCA cycle, oxidative phosphorylation and other pathways related to energy production and catabolism (see Fig 2).

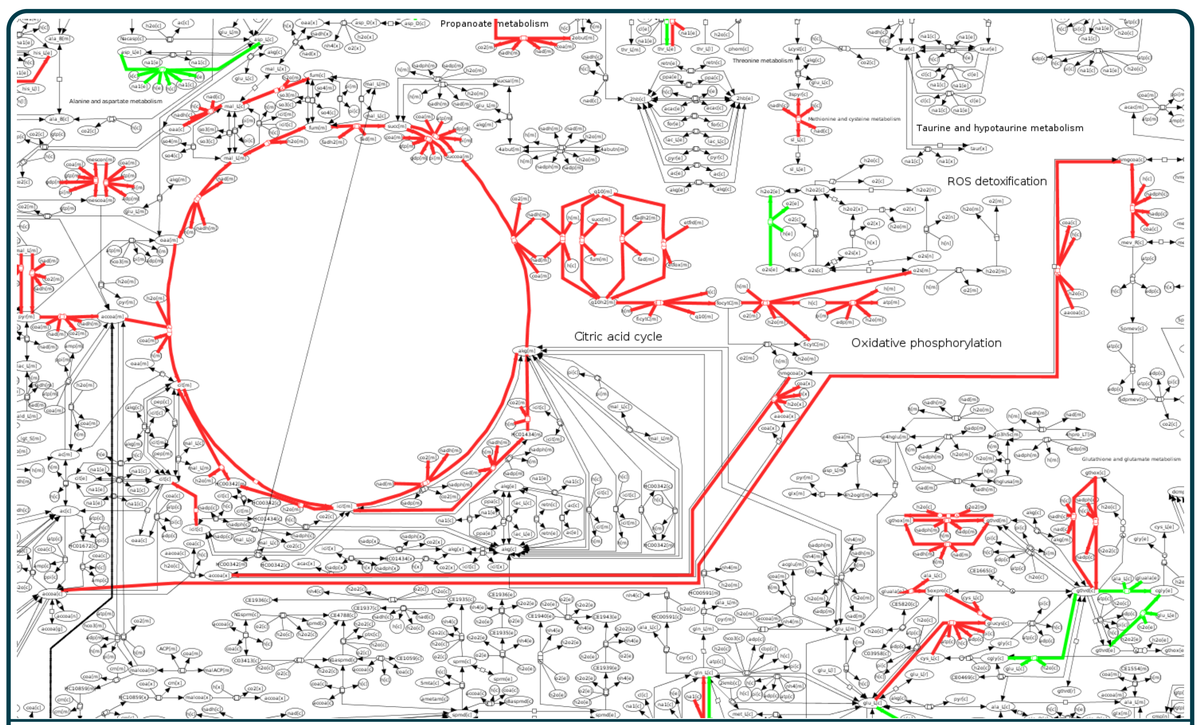

Figure 2: Mapping of age-related gene expression changes onto the human genome scale metabolic model.

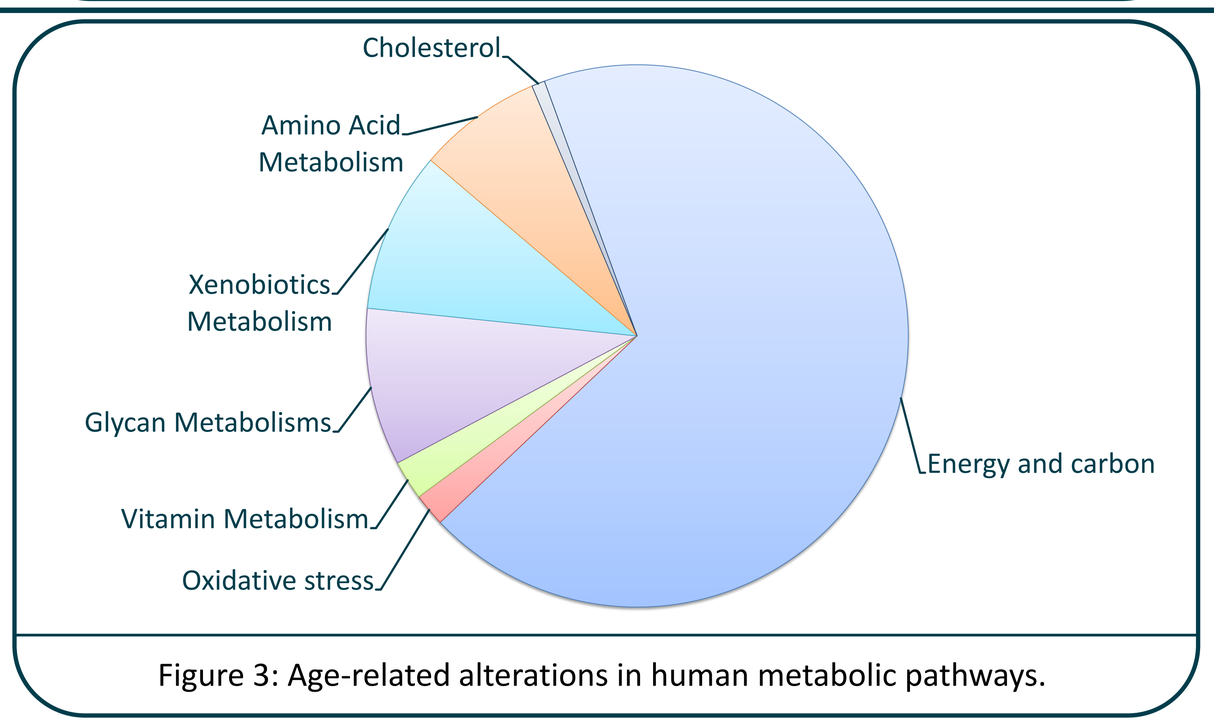

Figure 3: Age-related alterations in human metabolic pathways.

- Figure 3 shows the metabolic pathways with significant age-related alterations according to the gene expression changes.
- Besides energy generation, amino acid and glycan metabolism were prominently dysregulated with age.
- Finally, the response to foreign substances (xenobiotic) showed an upregulation with age.

Summary and Outlook

- The analysis of human gene expression implicated alterations in metabolic pathways, particularly those related to cellular energy generation, amino acid homeostasis and xenobiotics, in the ageing process.
- The identification of ageing metabolic pathways is an important first step toward formulating a strategy for mitigating ageing.
- In our continuing work, we will expand our analysis to data from dietary restricted animals, and formulate and validate metabolic targets for ageing using *Caenorhabditis elegans* as a model organism.

Acknowledgement

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References

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