Bioinformatics Analysis of Human Ageing From Transcriptomics to Phenomics

Rudiyanto Gunawan*[a,b] , Sudharshan Ravi[a,b] and Manuel Garcia-Albornoz[a]
[a]Institute for Chemical and Bioengineering, ETH Zurich, Zurich
[b]Swiss Institute of Bioinformatics, Lausanne, Switzerland

Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

Swiss Institute of Bioinformatics

*Email: rudi.gunawan@chem.ethz.ch

Background

- Ageing is a major risk factor of a plethora of human diseases such as cancer, cardiovascular and neurodegenerative diseases[1,2]. Thus, a better understanding of the biology of ageing has the potential to prevent or delay the on-set of age-related diseases.
- There is a general consensus that ageing results from the accumulation of "damage", but the specific molecular damages are still debated.
- The identification of specific molecular pathways and biological processes that are dysregulated during ageing and that are also relevant in human diseases and traits, may lead to a better understanding of the biology of human ageing.

Bioinformatics Pipeline

- We analyzed human transcriptomics data from the Genotype-Tissue Expression (GTEx) project to determines genes that are differentially expressed with age using a linear mixed effect model[3] (see Fig. 1).

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

- Here, y_{ijk} represents the *ijk*-th logarithmic gene expression (RNA – Seq) in the t_i tissue, at the g_j factor, e.g. age, and in the b_k individual. The variable *e* denotes the random error.
- A human phenotype – gene association dataset was manually curated from GWAS database and Mendelian mutations, comprising 3358 conceptual entities or traits and 7257 genes.
- Gene Ontology (GO) semantic similarity scores based on GO biological processes were calculated between the ageing genes and the genes associated with human phenotypes to identify a subset of human traits that are closely connected to ageing.

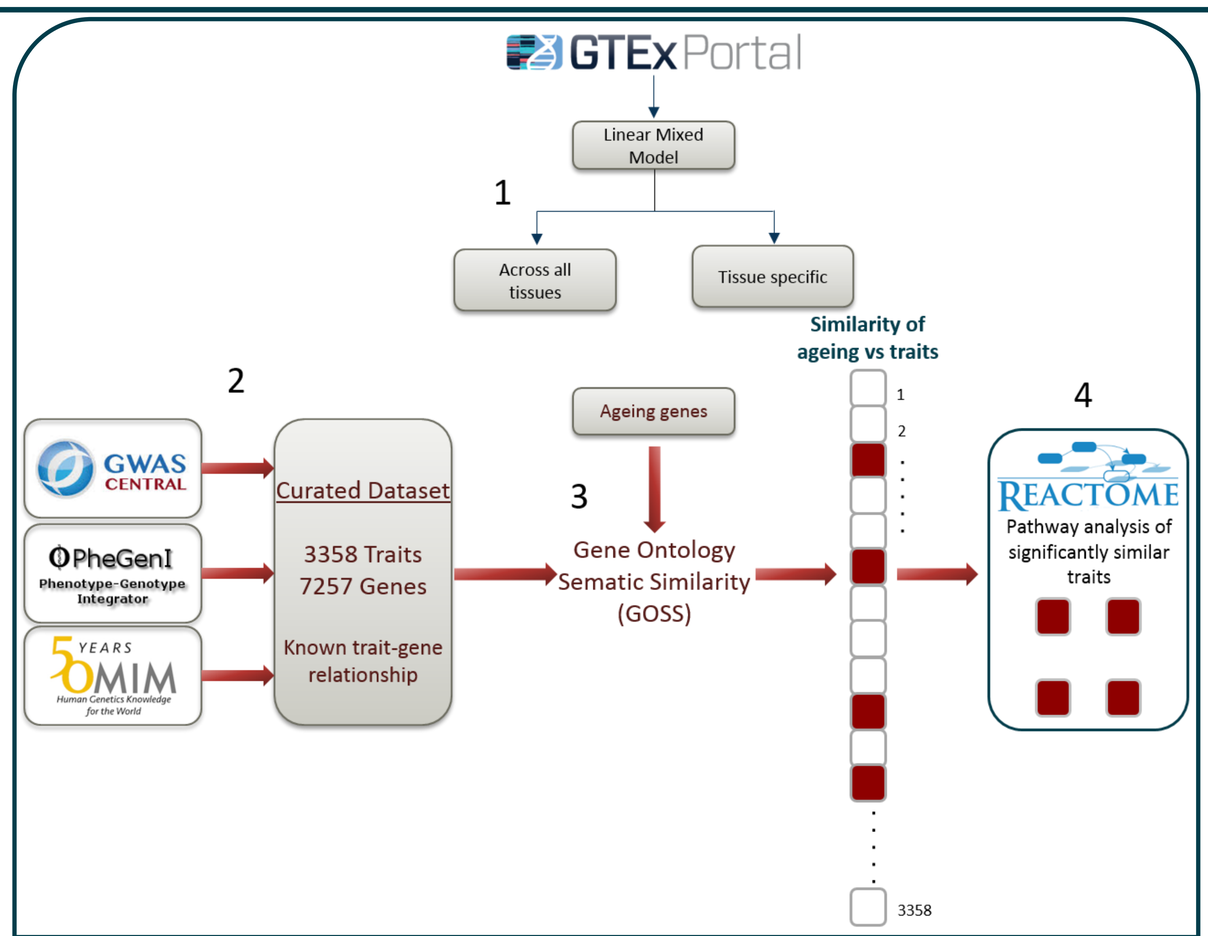
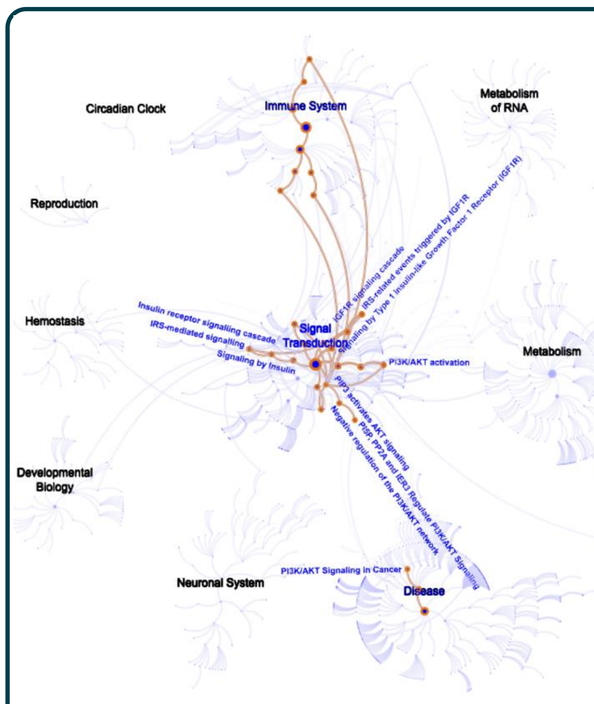


Figure 1: Schematic of the bioinformatics analysis pipeline.

Results

- A Reactome pathway enrichment analysis showed that genes from ageing-similar human traits were enriched for the insulin and insulin-like growth factor (IGF) signaling (IIS) pathway (see Fig 2).



Reactome Pathway Enrichment Analysis	
Pathway name	**FDR**
Signaling by Interleukins	3.75E-12
Diseases of signal transduction	1.72E-10
Signaling by SCF-KIT	2.59E-10
Insulin receptor signalling cascade	3.04E-10
Signaling by VEGF	3.04E-10
Signaling by EGFR	3.04E-10
PIP3 activates AKT signaling	3.04E-10
IRS-mediated signalling	3.04E-10
Negative regulation of the PI3K/AKT network	3.04E-10
Signaling by Insulin receptor	3.05E-10
IRS-related events triggered by IGF1R	3.05E-10
PI3K/AKT activation	3.05E-10
GAB1 signalosome	3.05E-10
IGF1R signaling cascade	3.05E-10
Signaling by Type 1 Insulin-like Growth Factor 1 Receptor (IGF1R)	3.19E-10
Downstream signal transduction	3.90E-10
VEGFA-VEGFR2 Pathway	4.34E-10
Signaling by PDGF	4.34E-10
DAP12 signaling	4.34E-10
Downstream signaling events of B Cell Receptor (BCR)	6.34E-10
PI5P, PP2A and IER3 Regulate PI3K/AKT Signaling	6.34E-10
DAP12 interactions	9.63E-10
MAPK1/MAPK3 signaling	1.22E-09
PI3K/AKT Signaling in Cancer	1.22E-09

Figure 2: Pathway enrichment analysis of human traits related to ageing genes.

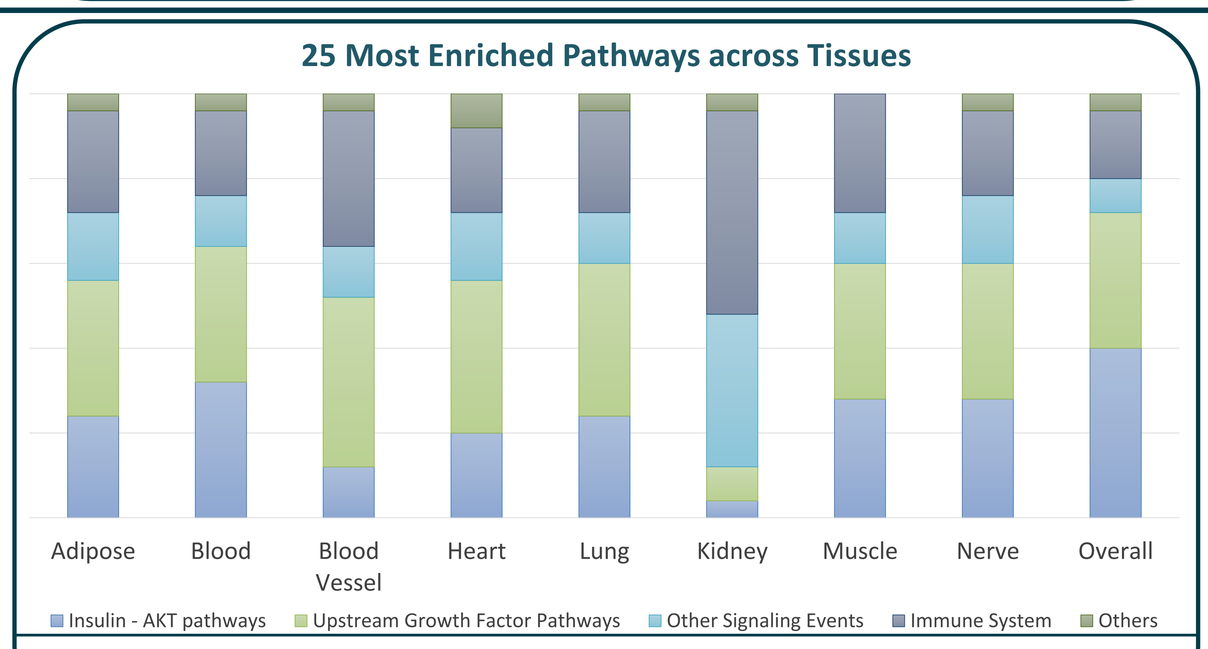


Figure 3: Pathway enrichment analysis across tissues.

- Figure 3 shows the composition of the top 25 enriched pathways from the tissue-specific analysis.
- IGF-IIS pathways again prominently appear among the top 25 enriched pathways across all tissues, along with upstream growth factor signaling pathways that act via P13K signaling cascade and immune system related pathways.

Summary

- Age-related changes in human transcriptomics are closely linked to human phenotypes that are related to alterations in nutrition signaling pathways (insulin, growth factor) and immune system response.
- Direct pathway and GO enrichment analysis of the ageing genes gave starkly different results, indicating a major role of mitochondria, inflammatory response, cell cycle and oxidative stress[4].
- Overall, our analysis pointed to the dysregulation of signaling pathways as a possible effector of human age-related phenotypes.

Acknowledgment

We would like to acknowledge the financial support from the Swiss National Science Foundation (grant number 163390).

References

[1] López-Otin, C., Blasco, M.A., Partridge, L. *et al.* (2013). *Cell*, **153**, 1194-1217.
[2] Simon, C.J., Dong, X., Vijg, J., *et al.* (2015). *Aging Cell*, **14,** 809-817.
[3] Mele, M., Ferreira, P.G., Reverter, F. *et al.* (2015). *Science*, **348,** 660-665.
[4] Yang, J., Huang, T., Petralia, F., *et al.* (2015). *Scientific Reports*, **5,** 15145.