Multiomics longitudinal study of aging in *Nothobranchius furzeri*

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N. furzeri
Multiomics
Aging

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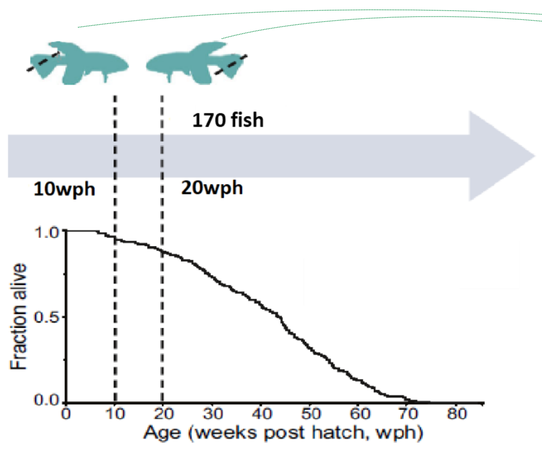
Background

Aging has been found to be associated with changes in DNA methylation, in gene expression, with progressive loss of protein homeostasis, decoupling between mRNA and proteins, and alterations in richness and composition of gut microbiota. Moreover, expression of RNAs and microbiome composition can predict individual lifespan in *Nothobranchius furzeri*. However, a holistic view of these different layers of molecular changes, which are interconnected during aging, is missing.

Study design: longitudinal study

We propose an integrated analysis of multi-omics datasets to provide a global and comprehensive profile of the heterogeneous aging process.

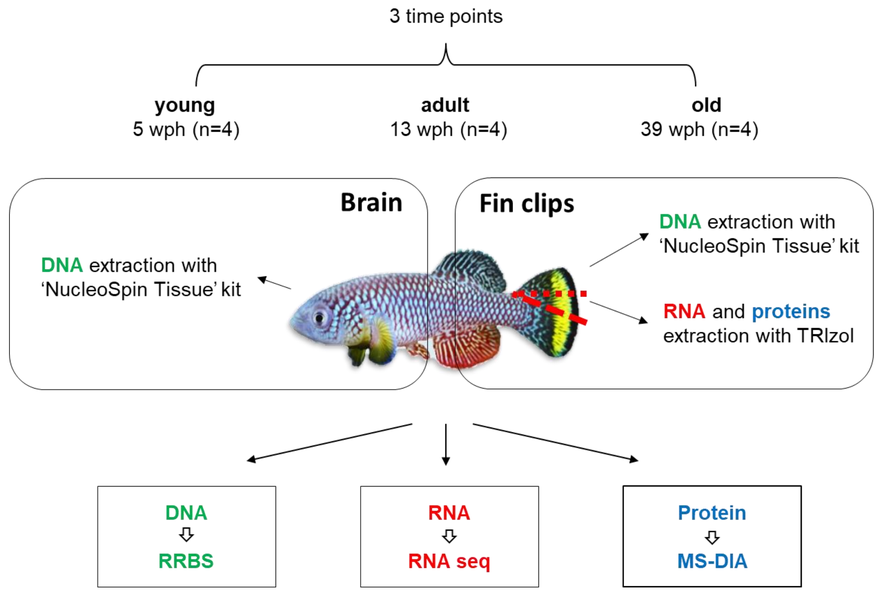


- Transcriptome → RNA-seq
- Proteome → MS-DIA
- Methylome → RRBS
- Microbiome → 16S rRNAseq

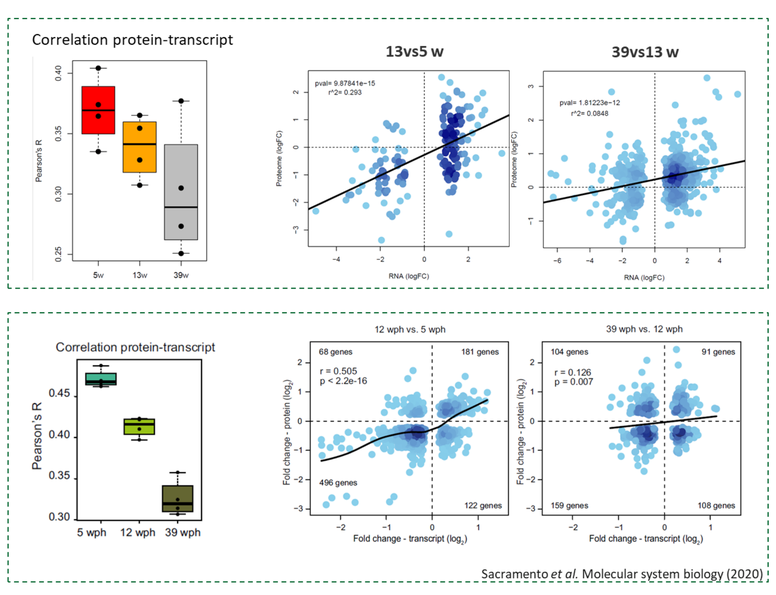
To this end, we initiated a longitudinal study inspired by our previous approach (Baumgart et al., 2016) in which we will analyze at 10 and 20 weeks of age methylome, transcriptome, proteome from fin biopsies and faecal microbiome in 170 fish to correlate all these variables one with another and with individual lifespan.

Preparation phase: cross-sectional study

Methods



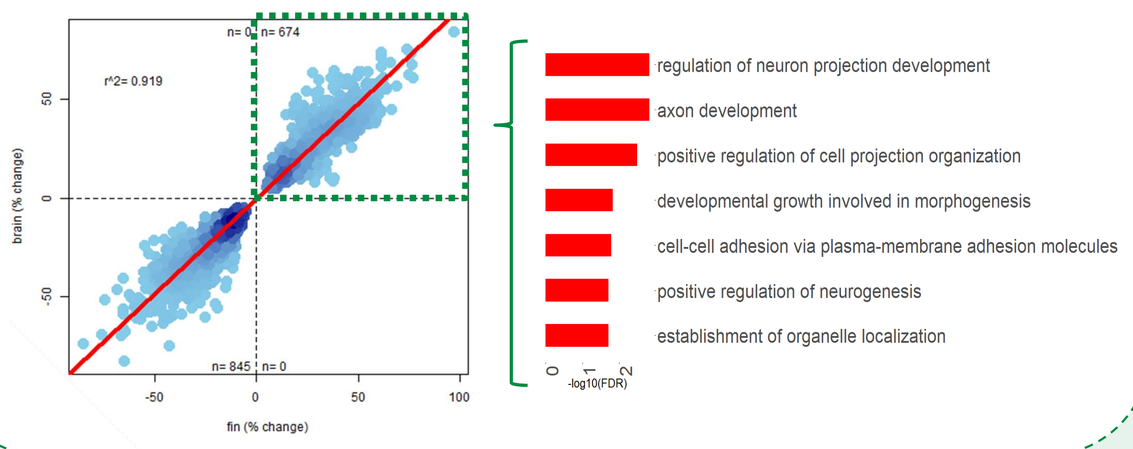
Comparison transcriptome-proteome



We observed that in the fin, a progressive reduction in the global correlation between proteins and mRNA occurs during aging, as we previously found in the brain (Kelmer et al. 2020).

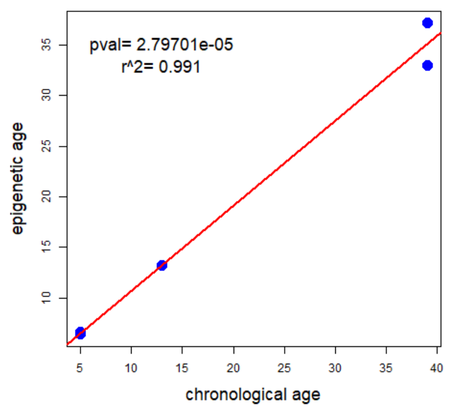
DNA methylation analysis

We have established a protocol for DNA methylation analysis, carried out here for the first time in *N. furzeri* through reduced-representation bisulfite sequencing. All the differentially methylated regions during aging show the same direction in brain and fin.



Epigenetic clock

Since methylation at many CpG sites change in an age-dependent manner, similarly to what had already described in mammals, we have built in *N. furzeri* an "epigenetic clock", able to predict with high precision the chronological age and compared it with mammalian epigenetic clocks.



- Tissues: brain and fin
- Age-related CpG sites: 5172
- Split dataset: 75% for training, 25% for testing
- Run Elastic Net Regression

→ Estimate epigenetic age

Future directions

The ultimate goal of our study will be to:

- identify which among transcripts, proteins, differentially methylated regions and bacterial species is more predictive for individual lifespan,
- construct a multi-layer network,
- identify its main hubs and driver candidates for experimental validation.

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