The impact of biological ageing on RNA processing

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Ageing of humans has been associated with large-scale changes in gene expression, however, influence of biological ageing on RNA processing has not been extensively studied yet. In this work we utilized an unprecedented collection of transcriptomes to uncover changes that encompass alternative splicing over the process of human ageing.

Whole blood was collected from a large cohort of 626 individuals with a broad age distribution (20-80 years) and subjected to RNA-sequencing. Analyzing this RNA-Seq data, we developed a statistical model to evaluate characteristics of alternative splicing, accounting for potential confounder effects of phenotypic traits and age-related switching in the cell composition of blood.

We discovered that the rates of exon skipping and intron retention significantly elevate with age, and that affected genes show no functional selectivity. GC content of the transcriptome was found to increase temporatily, and the changes in alternative splicing were recognized contributing to that.

We discovered that the usage of non-canonical donor splice sites increases with age, furthermore, we show that the number of acceptors paired with one donor significantly increases with age leading to potential functional changes.

Our findings indicate that splicing machinery undergoes significant age-related changes. They lead to the increased incidence of such alternative splicing events as intron retention and exon skipping, and promote implication of novel splice sites with unconventional nucleotide motifs.