ROLE OF ALTERNATIVE SPLICING IN A MOUSE MODEL OF CANCER CACHEXIA: IMPLICATIONS FOR CANCER PROGRESSION AND AGING PROCESS

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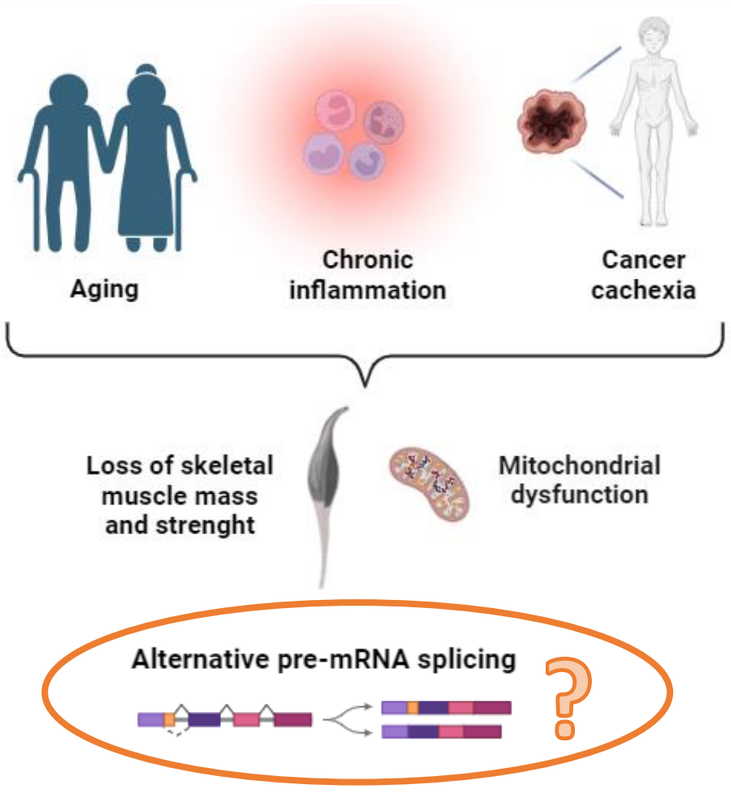
Introduction



- ✓ Both ageing-associated **sarcopenia** and **cachexia** are driven by a **pro-inflammatory status** driven respectively throughout the individual life or by chronic inflammatory diseases, including **cancer**, thus we may consider cancer cachectic muscle as a model for ageing-associated sarcopenia.
- ✓ On the cellular and molecular level both sarcopenic and cachectic muscles are characterized by **energetic stress** driven by **mitochondrial dysfunction**.
- ✓ Emerging evidence indicates in ageing energetic stress triggers an **alternative pre-mRNA splicing program**, which modifies post-transcriptionally the structure and the function of the proteins expressed in the muscle, and also increases nonsense-mediated mRNA decay. However, both the molecular mechanisms driving aberrant splicing and its biological role in sarcopenic and cachectic muscle is poorly understood.

Thus, the present work aims to identify alternatively spliced genes differentially expressed in murine models of cancer cachexia at two different timepoints and investigate possible implications also in aging condition.

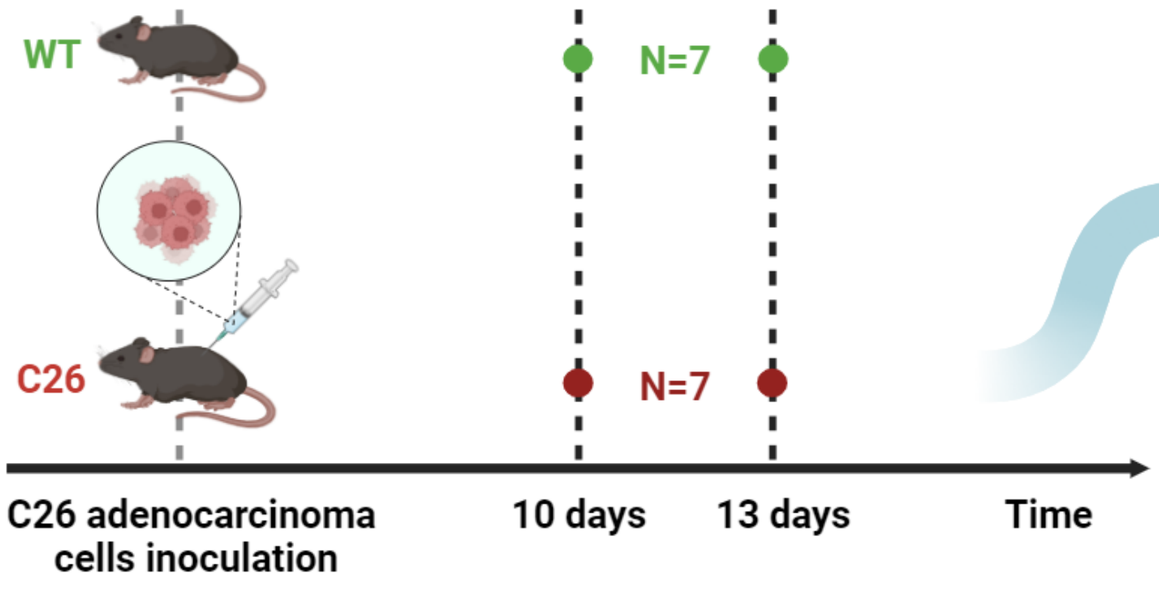
References:

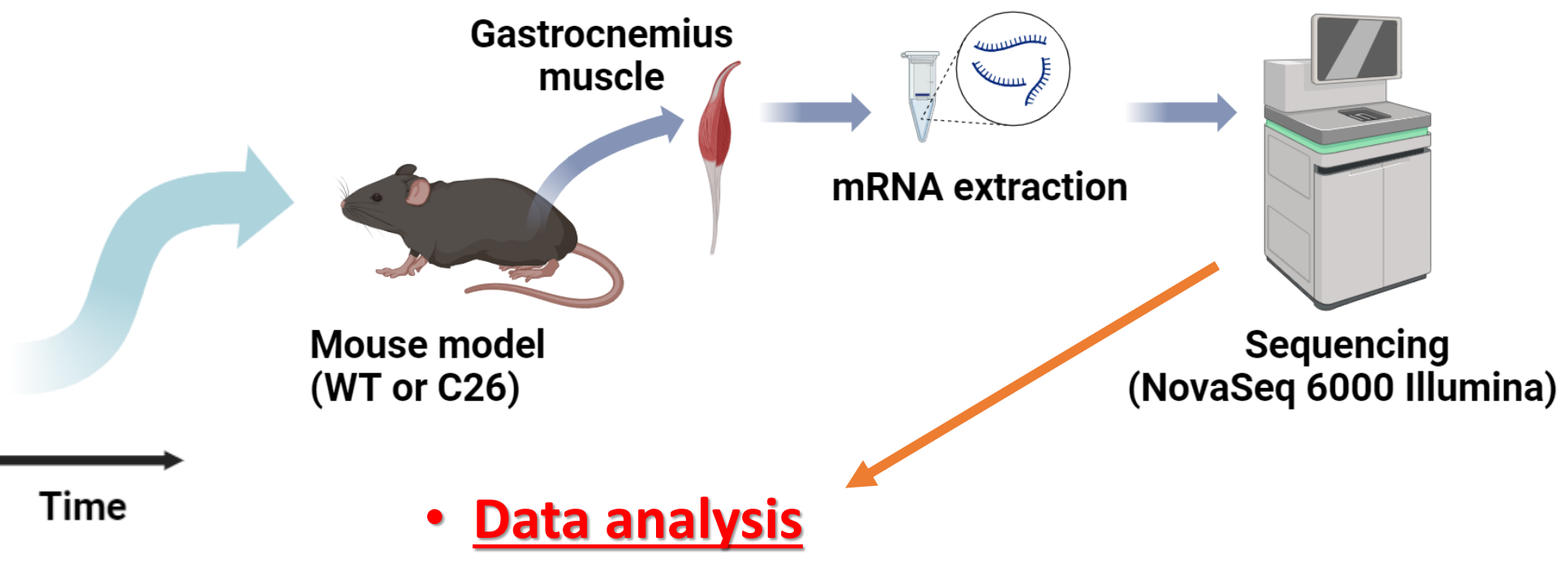
Bhadra et al., 2020, doi: 10.1007/s00439-019-02094-6.

López-Otín et al., 2023 doi: 10.1016/j.cell.2022.11.001.

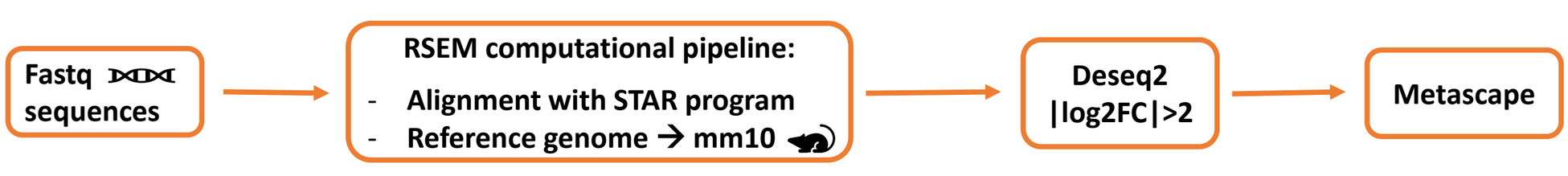
Materials & Methods

- **Experimental design**



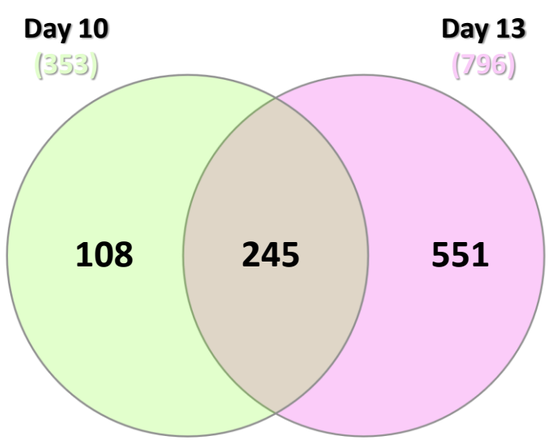


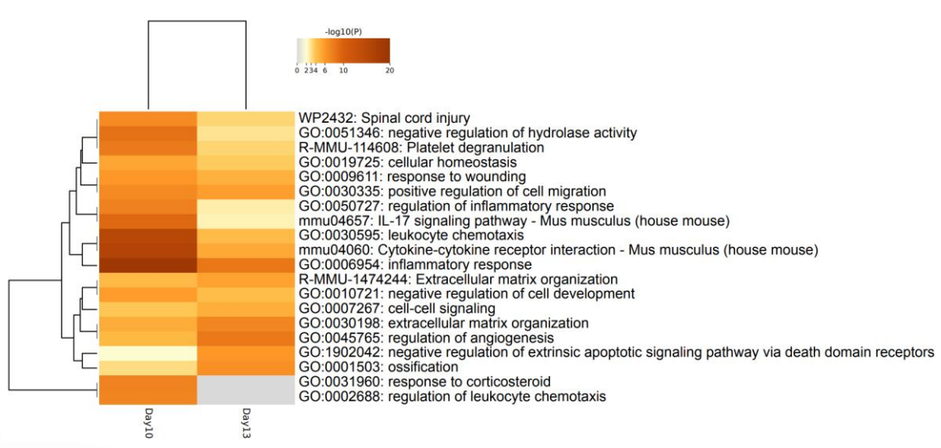
- **Data analysis**

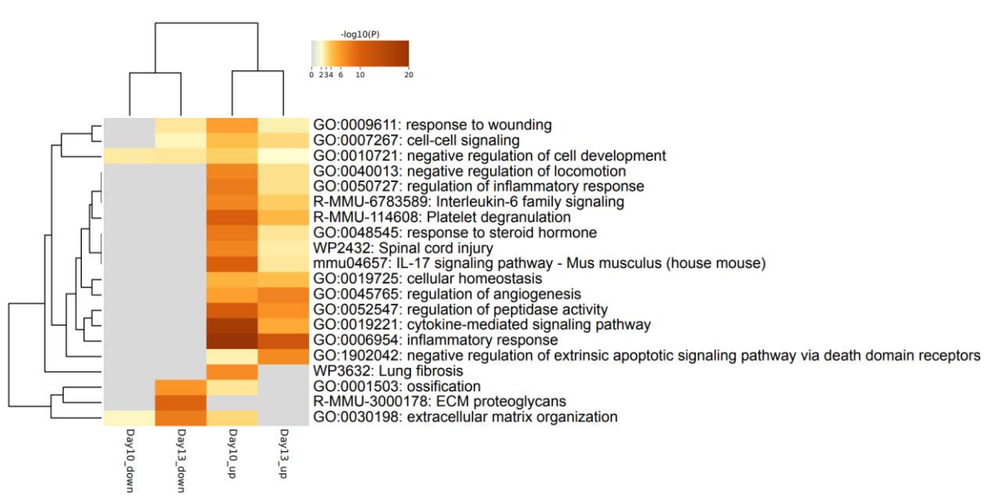


Results

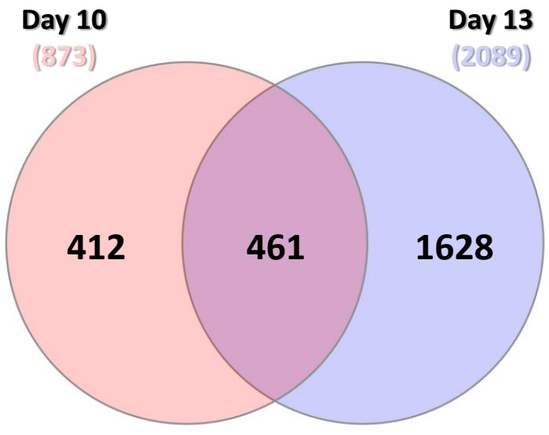
- **Genes** → **pre-cachectic vs cachectic** → **Upregulated and downregulated genes**

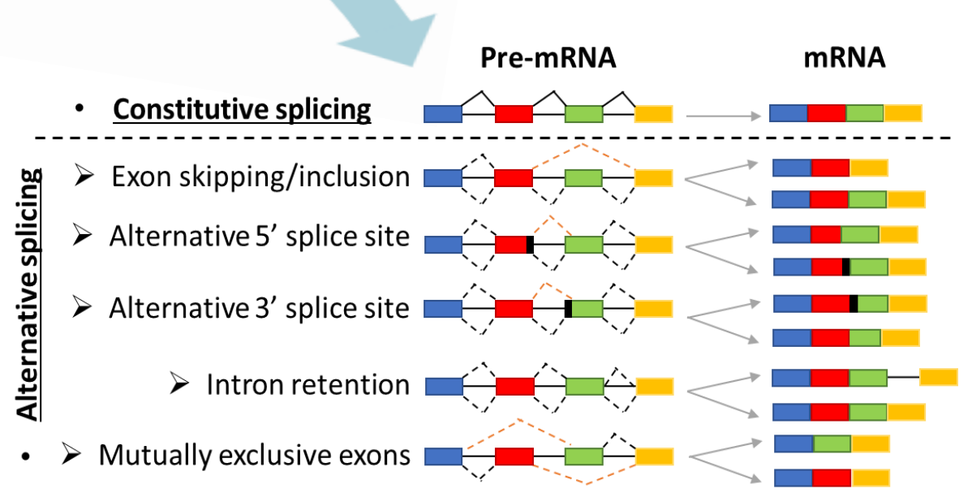




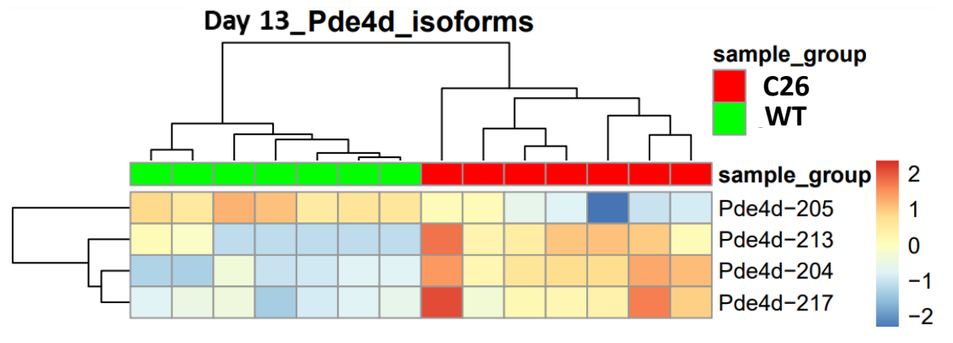


- **Transcript isoforms**





- **Multiple spliced isoforms of Pde4d gene at 13 days**



Conclusions

- ✓ **mRNA splicing** of a group of proteins **is altered in both pre-cachectic and cachectic muscle** and a subset of these proteins is also differentially expressed in both groups.
- ✓ Interestingly, the appearance of these differentially spliced isoforms correlates with mitochondrial dysfunction and energetic stress, suggesting that **cachectic muscle is a suitable model to investigate the molecular mechanisms and the biological role of ageing-associated aberrant mRNA splicing in skeletal muscle**.
- ✓ A better understanding of how **mRNA splicing machinery** and its related downstream targets are involved **in aging process and cancer cachexia** represents a promising research area with key implications for both the identification of potential biomarkers and signatures and for development of novel therapeutic options.

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