Strategies for the selection of miRNA candidates for the treatment of Sarcopenia using network-based analysis and differential expression scoring

Sarcopenia is a progressive muscle wasting and it is a natural consequence of aging. There is not a cure for muscle loss. Target identification and validation is a pressing challenge, with many targets failing in clinical trials or showing poor association with the disease. This project aims to create model(s) of microRNA:target interactions for more efficient in silico selection of potentially therapeutic targets for sarcopenia.

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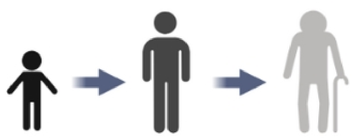
MicroRNA (miRNAs)

MicroRNAs (miRNAs) are small single stranded RNAs (ssRNAs), which are produced from hairpin shaped precursors [Wahid et al., 2010].

They are conserved small non-coding RNAs that play a role in the regulation of gene expression [Wu et al., 2018]. miRNAs have been found to regulate almost all cellular functions [Ranganathan and Sivasankar, 2014]

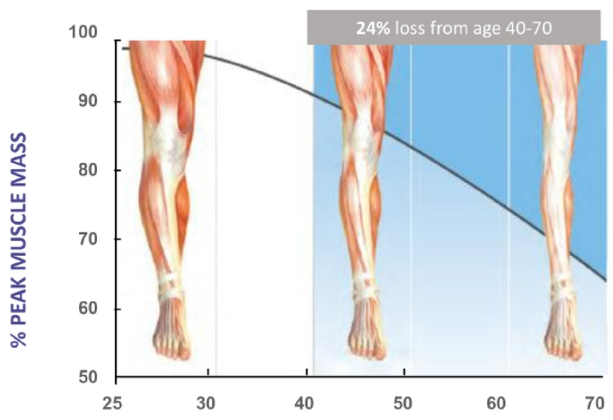
Aging and Sarcopenia



Aging is a time--dependent functional decline of an organism at all levels.

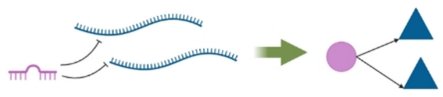
Sarcopenia is an age-related disease characterized by the loss of muscle mass and muscle function.

Muscle mass decreases approximately **3-8% per decade** after the age of 30 and this rate of decline is even higher after the age of 60 [Brocklehurst, 1976].
miRNAs as therapeutics are appealing given the potential to target multiple genes and pathways [Badalian-Very and Hydbring, 2013].



Source: https://waytowellness.co.za/

Network density



The miRNA:target interactions can be represented as a graph where both miRNAs and mRNAs are nodes and the edges are the relationship they have.

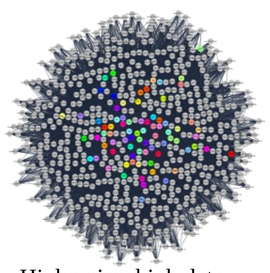
A miRNA can have thousands of targets and an mRNA can be targeted by multiple miRNAs. If we account for every possible target, we can easily pass from graph **A** on the picture below to graph **B**. Selection techniques, such as the one proposed here, can allow the filtering of nodes increasing the information the graph gives and reducing noise as shown in graph **C**.

More data ≠ More information

A) Starting mRNAs and their interactions

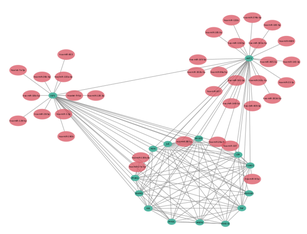
Low noise, low data

B) mRNAs with all miRNAs that targets them



High noise, high data

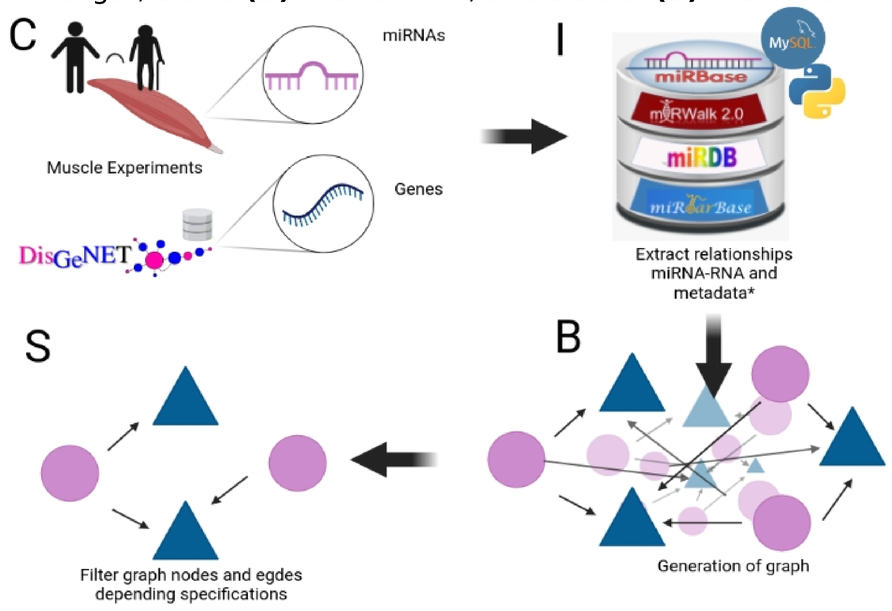
C) mRNAs and miRNAs classified as "relevant"



Low noise, high data

Methodology

We aim create a graph with relevant nodes, for this, we follow a 4 step methodology; **Collect (C)** mRNAs and miRNAs form literature and databases, **Increase (I)** the information adding the relationship miRNA:target, **Build (B)** the network, and **Select (S)** the nodes.



Each node (miRNA or mRNA) has a **normalized abundance** in the muscle in the range 0 to 1. Then, we define a threshold for the abundance to label the node as "muscle node".

Nodes also have a **normalized differentiation** score in the range -1 to 1 based on their old (O) vs young (Y) muscle DE.

Edges are weighted with the binding affinity (mirWalk/mirDB) and a binary label; 1 if it is validated experimentally and 0 if not.

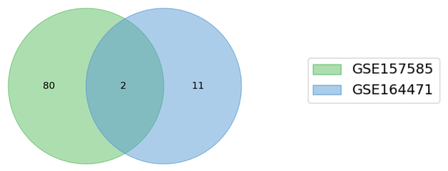
RNA-Seq

In order to create the microRNA:target network we need an initial set of nodes; genes and miRNas.
Differential Expression Analysis (DEA) was done based on 3 RNA-Seq experiments in the literature for skeleton muscle comparing young (**Y**; younger than 35 years old), middle age (**MA**; between 35 and 65) and old (**O**; older than 65) samples.

Experiment	Samples	Age groups
GSE152558	5	MA, O
GSE164471	53	Y, O
GSE157585	136	Y, MA, O

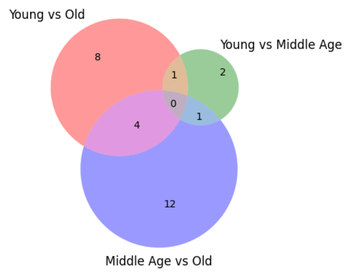
For GSE157585 we looked for the DE genes in Y vs MA, MA vs O, and Y vs O. The result of these comparison where 5 different sets of DE genes; GSE164471 with 82 genes, the rest between 4 and 17.

We found that GSE164471 and GSE157585 shared some genes when comparing Y vs O.



Shared DE genes when comparing O vs Y of two different experiments

Also, some genes in GSE164471 are shared among Y vs O, Y vs MA and MA vs O.
This can be sing of compensatory mechanisms.



Shared DE genes within GSE164471 age groups

Future work

Target identification and validation is a pressing challenge, with many targets failing in preclinical trials for efficacy reasons or showing poor association with the disease. Computational prediction of therapeutic targets could significantly decrease the attrition rates in the drug discovery pipeline by significantly reducing the initial search phase.

We will analyze the pathways that the union of all the experiments DE genes and microRNA alter, focosig in how individualy they up or downregulate those pathways.

The resulting microRNA:target intera-ctions modeled within the network presented in this poster will serve to select the microRNA to be study as Sarcopenia treatment.

References and Acknowlegements

References:

[Badalian-Very and Hydbring, 2013] Badalian-Very, G. and Hydbring, P.(2013). Clinical applications of microRNAs. F1000Research, 2.
[Brocklehurst, 1976] Brocklehurst, G. (1976). The structure of the rhomben-cephalic roof in the frog. Acta neurochirurgica, 35(1-3):205–214.
[Dragomir et al.,] Dragomir, M., Carolina Mafra, A. P., G Dias, S. M.,Vasilescu, C., and Calin, G. A. Molecular Sciences Using microRNA Net-works to Understand Cancer.1

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