Transcriptional Genetic Networks in the Aging Satellite Cell

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Satellite Cells contribute to sceletal muscle throughout life

Satellite Cells (SaC) reside at the basal lamina of muscle fibres throughout life in a quiescent state. Upon activation SaC proliferate and differentiate, replenishing the muscle.

Muscle is lost with age

Skeletal muslce is lost in aging and in disease. The number of SaC in an old individual may be reduced, and their ability to be activated decreases. It has been shown that this reduced potential depends largely on extrinsic factors.

Transcriptional genetic networks in SaC activation

Signals from the exterior milieu drives SaC activation, including stable changes in gene expression. We aim to map the genetic networks involved in this switch, taking a structured data mining aproach.

What are the transcriptional networks relevant for SaC activation?

What are the changes related to age, and can we protect SaC from these changes?

We mine databases for • genetic interactions and • gene expression searching for genetic networks driving satellite cell activation.

Workflow

We have developed a structured literature and database mining strategy to search for genetic networks relevant in SaC activation.

1. Collect known genetic interactions

Transcriptional genetic interactions have been collected from publicly available databases, including curated databases as well as predicted transcriptionfactor binding sites. We also add interactions by manual curation.

2. Collect and process expression data

We designed a tool that can upload and process gene expression data. Raw data from multiple experiments are normalized and analysed for changes in gene expression. Each gene is assigned an activity value: present, absent or uncertain. This value can be caculated using ANOVA or nonparametric methods within an experiment. Often there are not sufficient replications, or there may be a need to compare results from many experiments. For this purpose we calculate limit values for activity for individual genes, based on thousands of pooled experiments on the GEO database.

3. Find signature genes

Signature genes show a unique expression signature, either present or absent, in the cell type or state under study.

4. Search for networks

Among signature genes and extending one degree in the network of listed genetic interactions, we search for the largest transcriptional genetic networks. An activity value is assigned to each network by measuring the number of genes that change expression in the contrasting expression datasets. A Z-test is performed comparing the network activity to randomly resampled groups of genes within the dataset.

Results

The results include software tools we developed to support the structured database mining and statistics workflow. We have used the tools to analyze gene expression datasets on GEO to find genetic networks active in SaC activation. Examples of these results are presented here.

1. A database of 40000 interactions

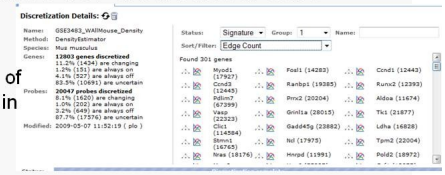
We have now a database of more than 40000 transcriptional genetic interactions in man and mouse. 21000 are from curated public databases 15000 are predicted transcription factor binding sites, 5000 are our own curated interactions, to a large part chromatin immunoprecipitation (ChIP) results.

2. Gene expression in SaC vs other cells

A data set of gene expression in activated SaC from the GEO database (GSE3483) was analysed and contrasted to hundreds of datasets representing a variety of cell types. Gene activity values were assigned both comparing the activities in the chosen data sets, and using a reference set of close to thousand experiments.

3. Signature genes for activated SaC

Signature genes for activated SaC are filtered out and sorted by number of genetic interactions listed in the database.



4. Networks in activated SaC

We are now analyzing the transcriptional networks for relevance and experimental accessibility.

Next step – validation in human SaC

The next step will be to assay genes from the mining approach in an experimental model system, primary cultures of human SaC.

Dynabyte BioLabs

Declaration of competing interests

Andreas Montelius is an owner of Dynabyte Biolabs, a systems biology company that develops software support for the work presented on the poster. http://biolabs.dynabyte.se/

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