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Gymnastik- och Idrottshögskolan

Nr 999

DETERMINANTS OF INTRA-INDIVIDUAL VARIATION IN
ADAPTABILITY TO RESISTANCE TRAINING OF DIFFERENT
VOLUMES WITH SPECIAL REFERENCE TO SKELETAL MUSCLE
PHENOTYPES

Determinants of intra-individual
variation in adaptability to resis-
tance training of different volumes
with special reference to skeletal
muscle phenotypes

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THESIS FOR DOCTORAL DEGREE (Ph.D.)

The title of your thesis

by

Your name

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Opponent

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Profesor . . .

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-Professor . . .

-Professor . . .

Examination board

-Associate professor . . .

-Professor . . .

-Professor . . .

Abstract

The preface pretty much says it all.

Second paragraph of abstract starts here.

List of scientific papers

- I. **Hammarström D**, Øfsteng S, Koll L, Hanestadhaugen M, Hollan I, Apró W, Blomstrand E, Rønnestad B, Ellefsen S Benefits of higher resistance-training volume are related to ribosome biogenesis. *The Journal of physiology*. 2020;598(3):543-65.
- II. Khan Y, **Hammarström D**, Rønnestad B, Ellefsen S, Ahmad R Increased biological relevance of transcriptome analyses in human skeletal muscle using a model-specific pipeline. *Submitted*.
- III. **Hammarström D**, Øfsteng S, Koll L, Jacobsen N, Flobergseter K, Rønnestad B, Ellefsen S Ribosome accumulation during early phase resistance training. *Manuscript*
- IV. **Hammarström D**, Ellefsen S. generefer: A R package for unbiased selection of reference genes for qPCR in repeated measures designs. *Manuscript*

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1. Introduction

Proper skeletal muscle functioning is essential in everyday life by enabling movement and thus complex interaction with our environment. Nutrition and pharmacological agents can have substantial effects on skeletal muscle mass and function. However, resistance exercise of sufficient volume, intensity and frequency is the most potent stimuli to promote morphological and functional changes in the human neuromuscular system. Exercise training can be modulated indefinitely by combining different variations of training variables and in addition, adaptation to exercise training is a phenomenon characterized by great inter-individual variability. The purpose of the present project is therefore to explore potential determinants of variation in adaptability to resistance-exercise modulated by selected exercise-training variables.

Functional independence

(???)

(Pinedo-Villanueva et al., 2019)

(???)

(???)

(???)

(???)

(???)

2. Background

2.1 Exercise training variables affecting training outcomes

2.2 Exercise volume

2.2.1 Meta-analysis of exercise volume

2.3 Molecular determinants of training-induced muscle hypertrophy

2.3.1 Protein synthesis

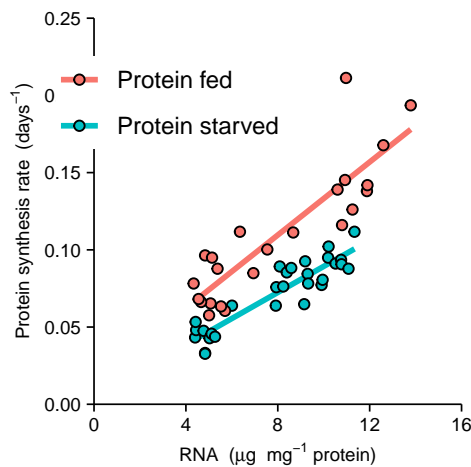


Figure 2.1: Data from Millward et al. 1973. Group A were fed a diet containing protein, group B were starved or fed a diet not containing protein.

2.3.2 The mammalian target of rapamycin (mTOR) and translational efficiency

The mammalian target of rapamycin (mTOR) is a large serine-threonine protein kinase which in complex with other regulatory proteins forms a signaling hub responsible for responses to environmental cues such as nutrients and mechanical stress.

mTOR has several phosphorylation sites

Phosphorylation of Ser2448 is mediated by S6K1 to reduce mTOR activity in a negative feedback loop .

Ser2448 is phosphorylated by S6K1, changes in nutrient availability modifies S6K1 and Ser2448, Ser2448 phosphorylation is abolished when S6K1 is depleted

When the C-terminal is deleted, mTOR gets constitutively active

2.3.3 Ribosome biogenesis

Transcription of ribosomal RNA (rRNA)

2.4 Transcriptional activity related to muscle hypertrophy

2.4.1 Methods for studying transcriptional regulation

3. Aims

The primary aim of this thesis was to relate the adaptive response to resistance training with low- and moderate-volume to skeletal-muscle characteristics in previously untrained individuals. The key question was whether manipulation of exercise-volume will have diverse effects in different individuals related to muscular intrinsic characteristics. A further aim was to characterize exercise-volume dependence and time course profiles of molecular mechanism thought to control resistance training-induced muscle growth. Based on these aims, the objectives of the present thesis were;

- to relate skeletal muscle and systemic characteristics to benefit of moderate-compared to low-volume resistance training;
- To determine volume-dependence in molecular networks related to muscle growth and remodelling in response to mechanical stress
- To determine a time course of markers related to ribosome biogenesis in the early phase of resistance training.

4. Methods

4.1 Participants

TO DO:

- For methods discussion, compare product length, efficiencies and ct values in relation to RQI-values. See Fleige 2006 for reference.

4.2 Gene expression analysis

4.2.1 Normalization

- An external reference gene was added at a constant amount in Trizol preps
- A normalization factor was used to express relative target gene abundance per-weight tissue.
- In qPCR the linearised expression (effectively $2^{-\Delta Cq}$) was used to express the fraction of external reference per total RNA.
- In RNA-seq the external reference gene was sequenced and counts were used to express external RNA as a fraction of total RNA.
- In both cases the normalization factor was calculated as $mw * counts$.

A simulation to see that this is equivalent to tissue used in prep when no measurement errors exists.

```
library(tidyverse)

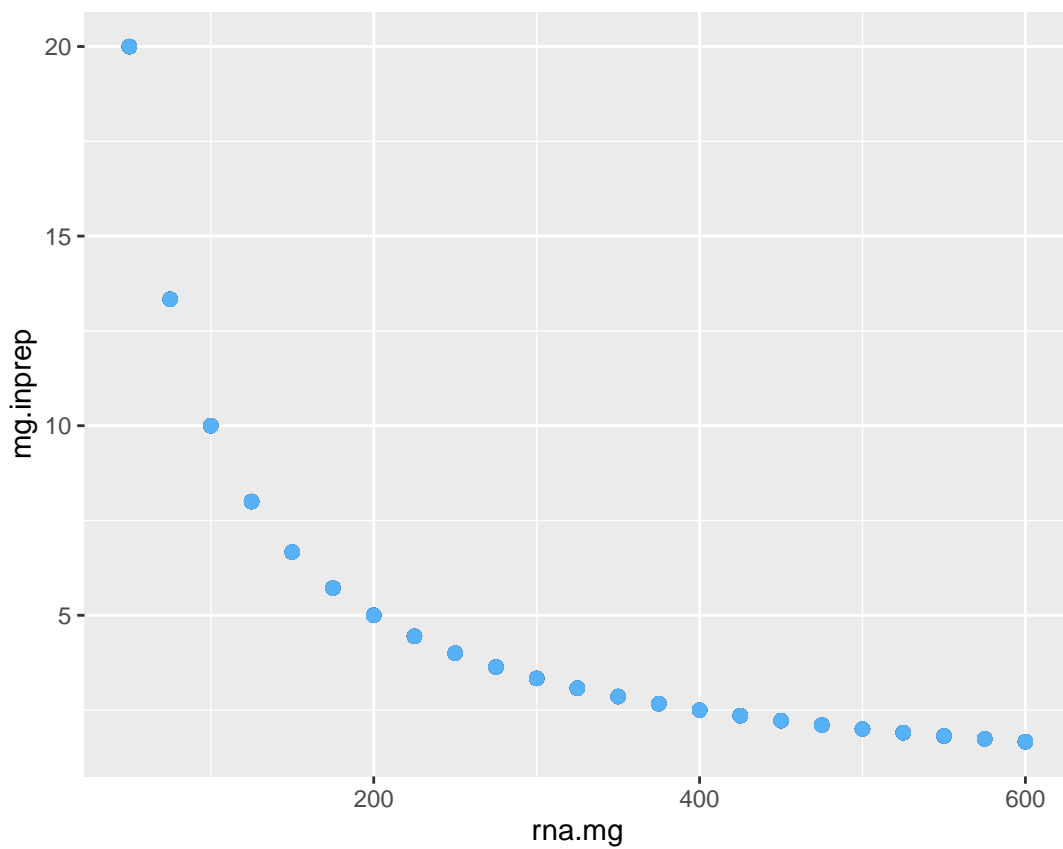
expand_grid(mg = seq(from = 5, to = 100, by = 5),
            rna.mg = seq(from = 250, to = 600, by = 25),
            ext = 0.04) %>%
mutate(tot.rna = mg * rna.mg,
       ext.frac = ext / (ext + tot.rna),
       mg.inprep = 1000 / ((ext + tot.rna) / mg),
       nf = ext.frac * mg)
```

```
# A tibble: 300 x 7
```

	mg	rna.mg	ext	tot.rna	ext.frac	mg.inprep	nf
	<dbl>	<dbl>	<dbl>	<dbl>	<dbl>	<dbl>	<dbl>
1	5	250	0.04	1250	0.0000320	4.00	0.000160
2	5	275	0.04	1375	0.0000291	3.64	0.000145
3	5	300	0.04	1500	0.0000267	3.33	0.000133
4	5	325	0.04	1625	0.0000246	3.08	0.000123
5	5	350	0.04	1750	0.0000229	2.86	0.000114
6	5	375	0.04	1875	0.0000213	2.67	0.000107
7	5	400	0.04	2000	0.0000200	2.50	0.000100
8	5	425	0.04	2125	0.0000188	2.35	0.0000941
9	5	450	0.04	2250	0.0000178	2.22	0.0000889
10	5	475	0.04	2375	0.0000168	2.11	0.0000842

```
# ... with 290 more rows
```

```
expand_grid(mg = seq(from = 5, to = 100, by = 5),
             rna.mg = seq(from = 50, to = 600, by = 25),
             ext = 0.04) %>%
  mutate(tot.rna = mg * rna.mg,
         ext.frac = ext / (ext + tot.rna),
         mg.inprep = 1000 / ((ext + tot.rna) / mg),
         nf = ext.frac * mg) %>%
  ggplot(aes(rna.mg, mg.inprep, color = mg)) + geom_point(size = 2)
```

4.3 Training protocols

A full body protocol was used in study I including

5. Results

6. Discussion

Conclusion

If we don't want Conclusion to have a chapter number next to it, we can add the `{-}` attribute.

More info

And here's some other random info: the first paragraph after a chapter title or section head *shouldn't be* indented, because indents are to tell the reader that you're starting a new paragraph. Since that's obvious after a chapter or section title, proper typesetting doesn't add an indent there.

References

Pinedo-Villanueva, R., Westbury, L. D., Syddall, H. E., Sanchez-Santos, M. T., Dennison, E. M., Robinson, S. M., & Cooper, C. (2019). Health care costs associated with muscle weakness: A uk population-based estimate. *Calcif Tissue Int*, 104(2), 137–144. Journal Article. <http://doi.org/10.1007/s00223-018-0478-1>