MoTrPAC
The Molecular Transducers of Physical Activity Consortium

The multi-omic response to exercise training across rat tissues

Data dissemination through the MoTrPAC data hub

Christopher Jin

RGD 2024

October 3rd, 2024

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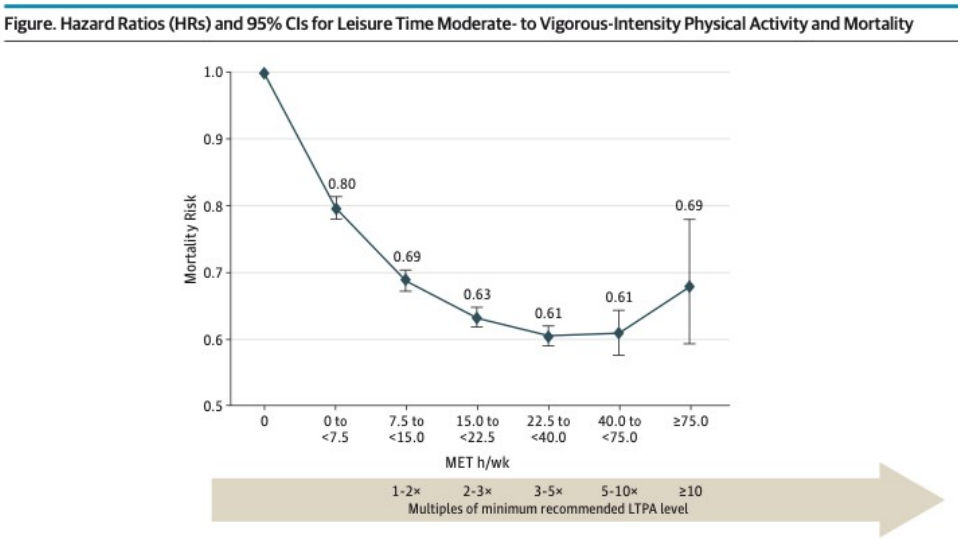
Physical inactivity is a major cause of chronic disease

- Regular exercise improves metabolic health and reduces risk of chronic disease[1]
- Exercise has positive effect on treatment of at least 26 different diseases[2]
- Physically active individuals tend to live longer[3]



[3]*Arem H, et al., JAMA Intern Med. 2015*

[1] *Booth FW, et al., Compr Physiol. 2012*
[2] *Pedersen BK and Saltin B, Scand J Med Sci Sports 2015*

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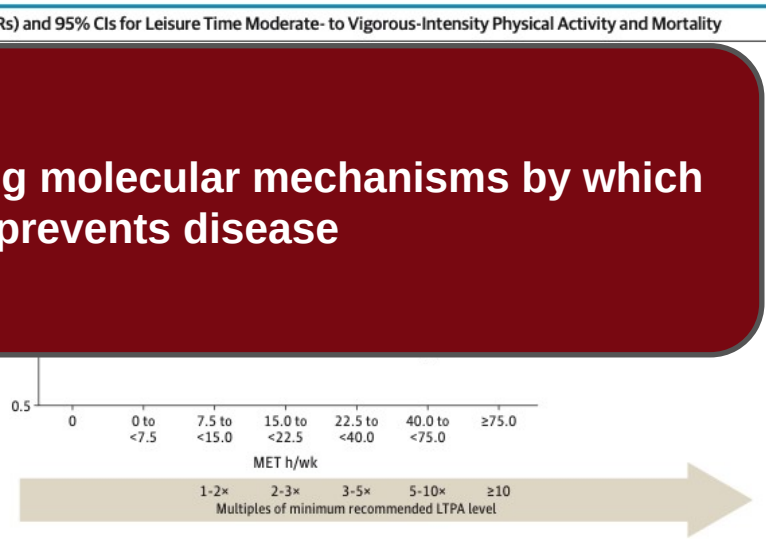
Physical inactivity is a major cause of chronic disease

- Regular exercise improves metabolic health and reduces risk of chronic disease[1]

There is a limited understanding of the underlying molecular mechanisms by which exercise promotes health and prevents disease

to live longer[3]



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Existing exercise omics studies are limited

Study	Species	Exercise type	Sample size	Number of tissues	Genomics	Epigen-omics	Transcript-omics	Proteomics	Metabolomics/ Lipidomics
HERITAGE Family Study (1992-2013)	Human	Endurance training (20 w)	~650	1-2	X		Muscle (N=78)		Targeted
Robbins, 2021 Nature Metab.	Human	Endurance training (20 w)	650 (HERITAGE)	1 (plasma)				X	
Contrepois, 2020 Cell	Human	Acute endurance	36	1 (blood/ plasma)			X	X	X
Robinson, 2017 Cell Metab.	Human	HIIT, resistance, combined (12 w)	72	1 (muscle)		X	X	X	Targeted
Sato, 2022 Cell Metab.	Mouse	Acute endurance	5-6 per group	8					X

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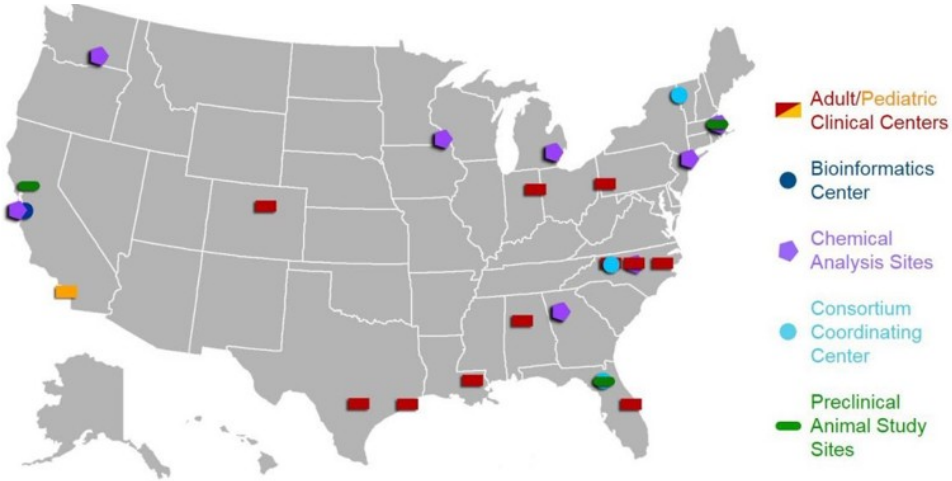

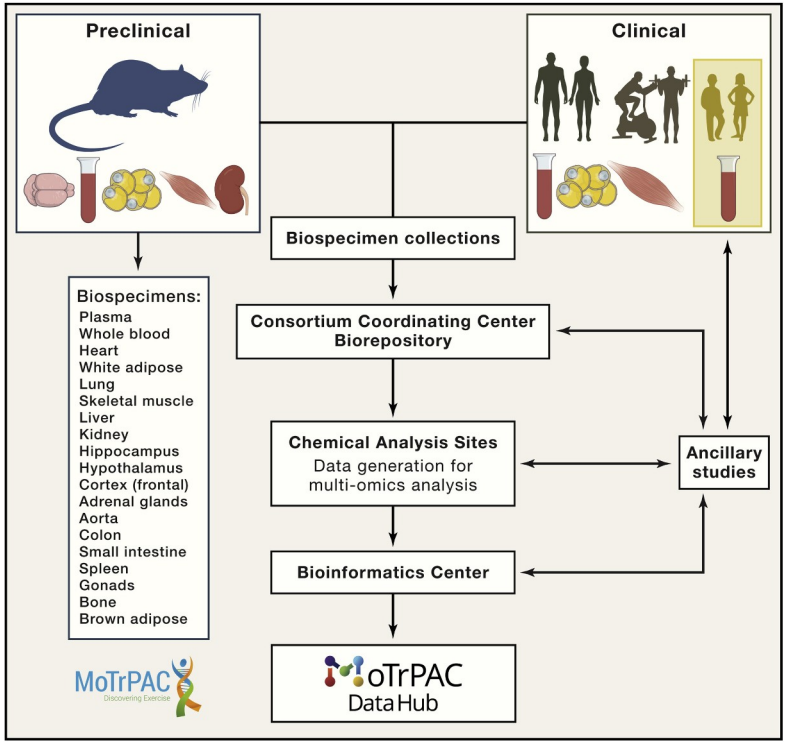

Sanford, Nogiec, Lindholm et al., Cell 2020

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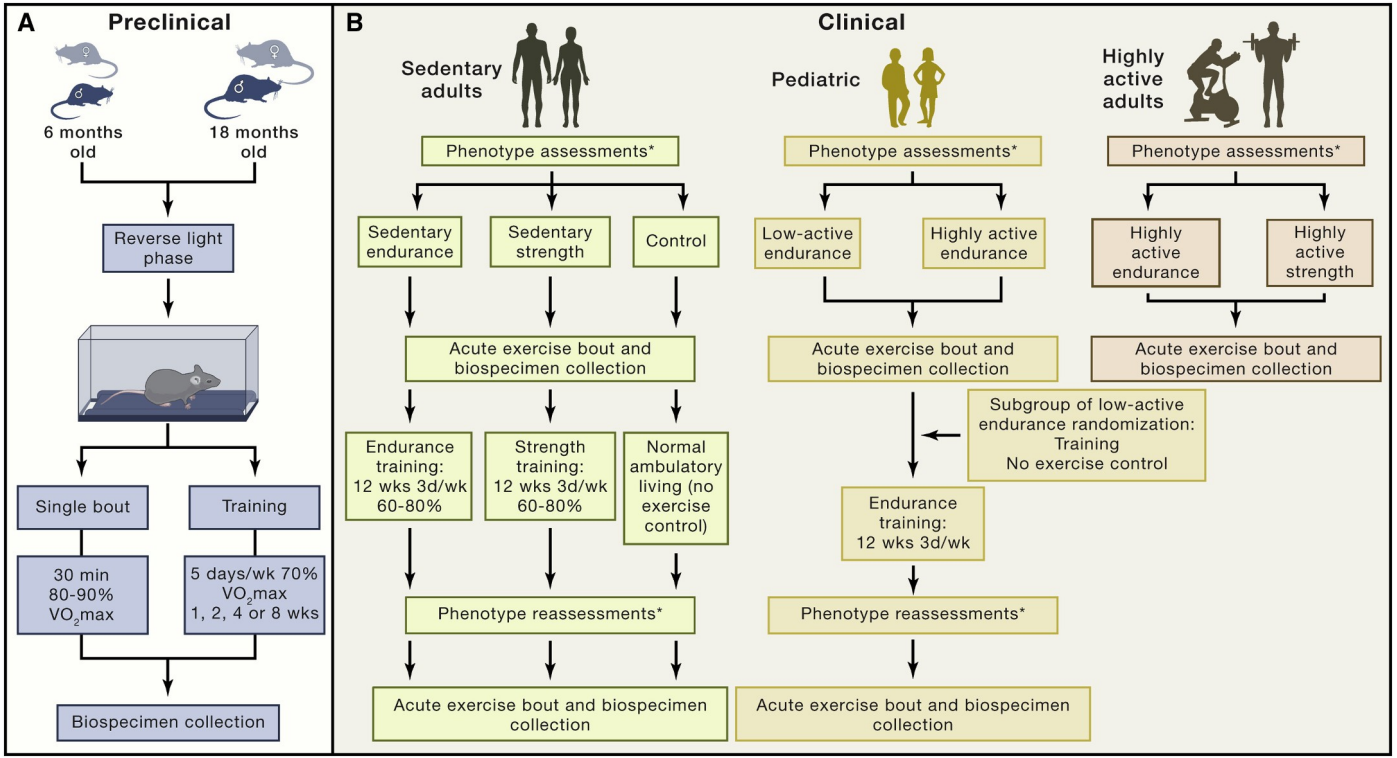

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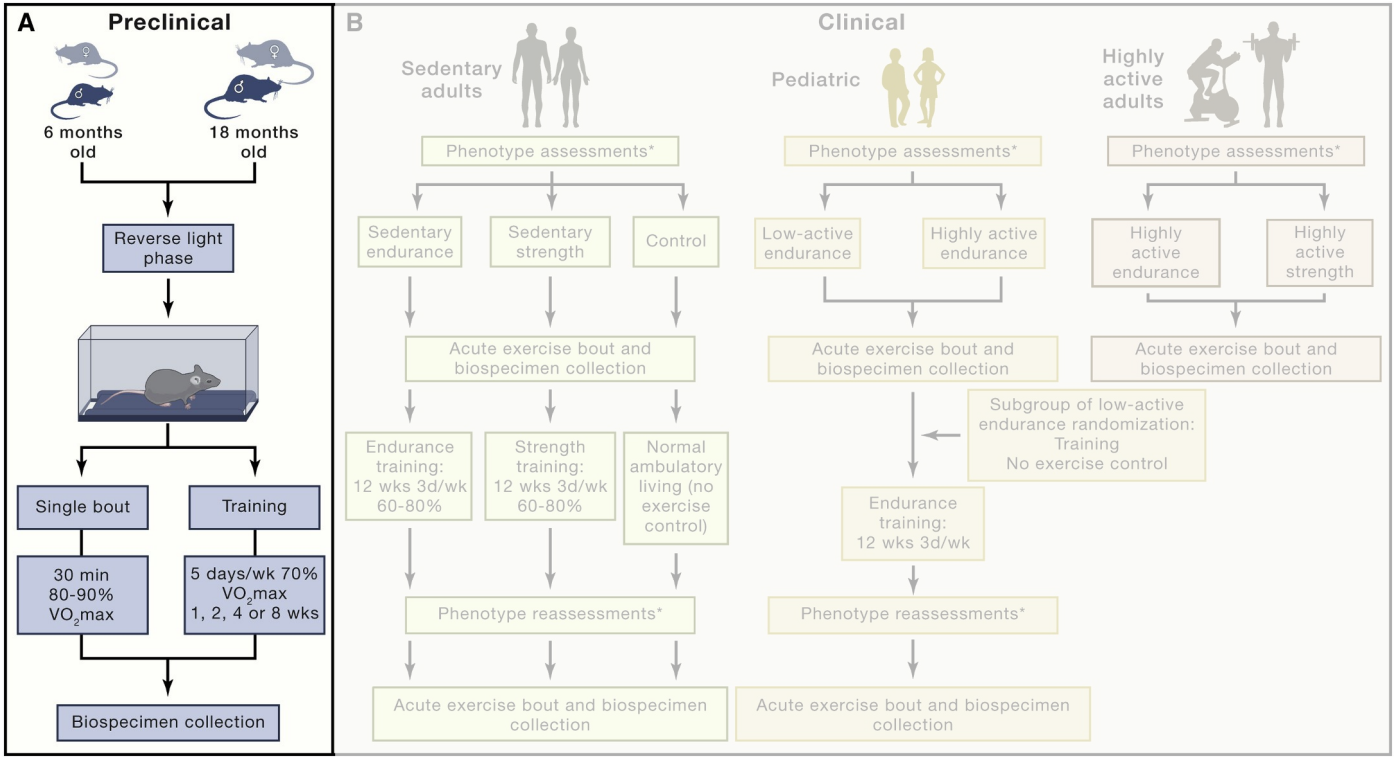

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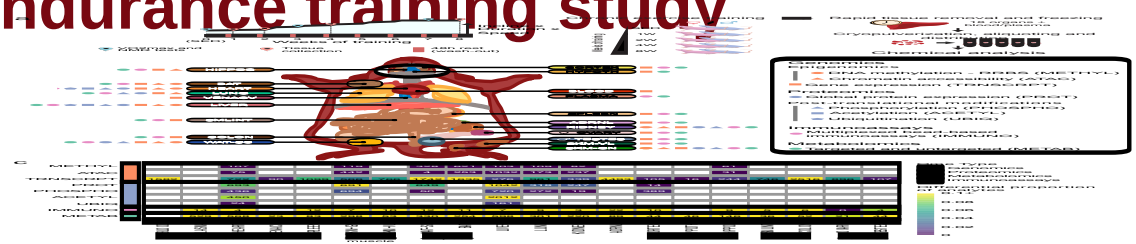
Sato, 2022 Cell Metab.	Mouse	Acute endurance	5-6 per group	8					X
MoTrPAC animal studies	Rat	**Endurance**, acute and **training (8 w)**	3-6 per group	19		X	X	X	X
MoTrPAC human studies	Human	Endurance or resistance, acute and training (12 w)	~2000	3	X	X	X	X	X

MoTrPAC preclinical endurance training study



- Progressive protocol
- Male and female 6mo animals
- Time-series
- Multiple tissues
- Multiple -omes

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MoTrPAC preclinical endurance training study

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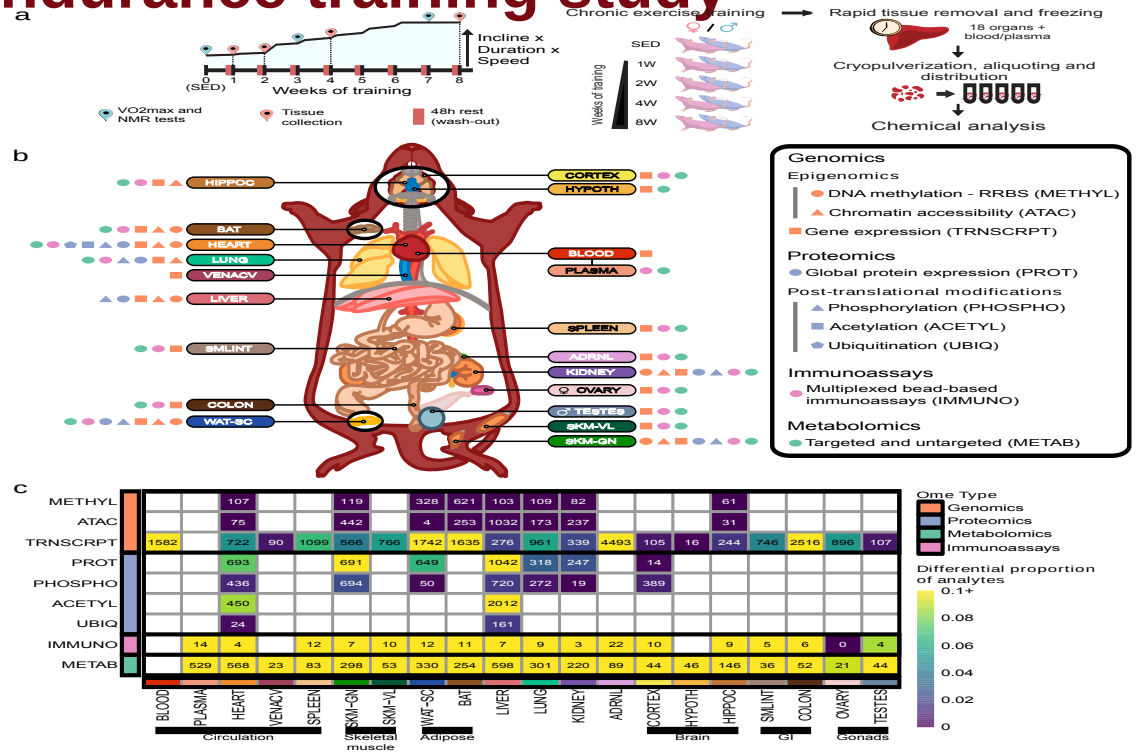

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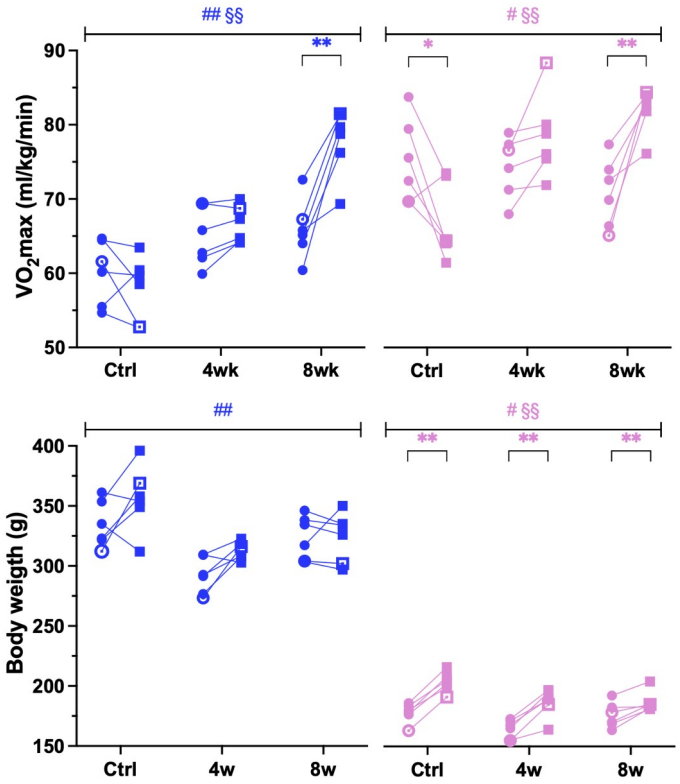
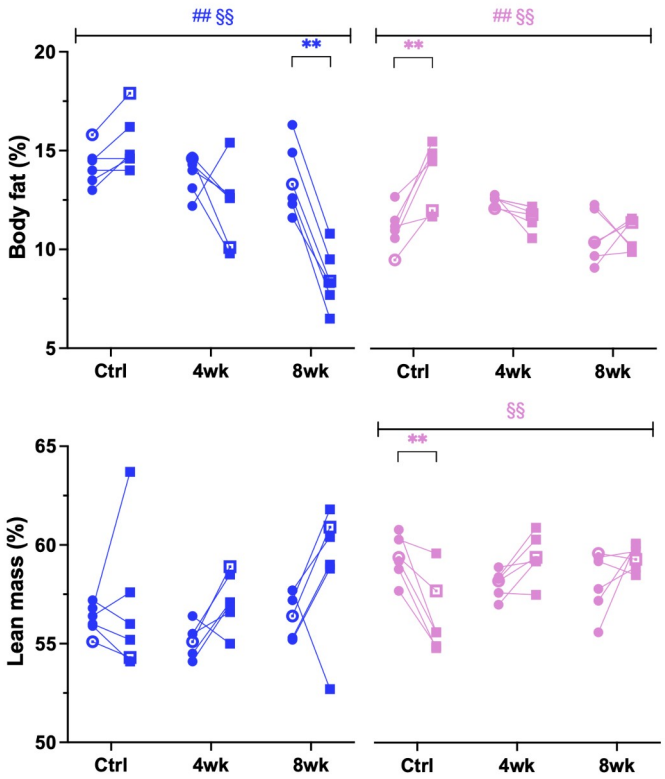
Phenotypic changes





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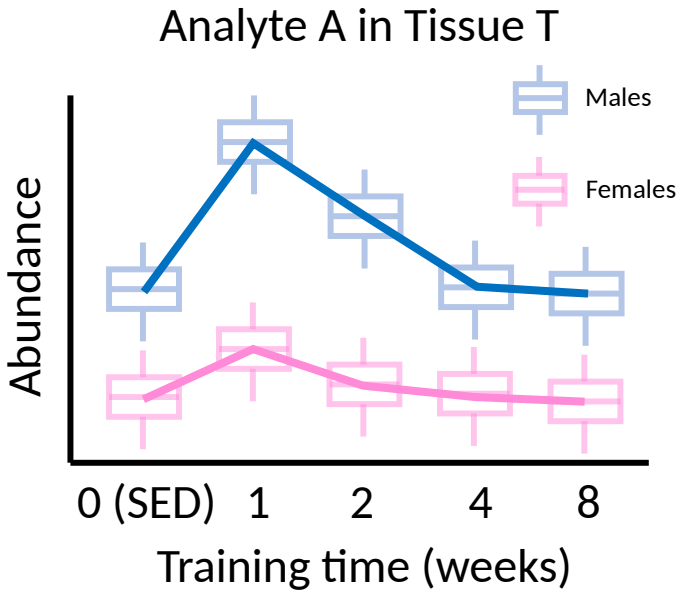
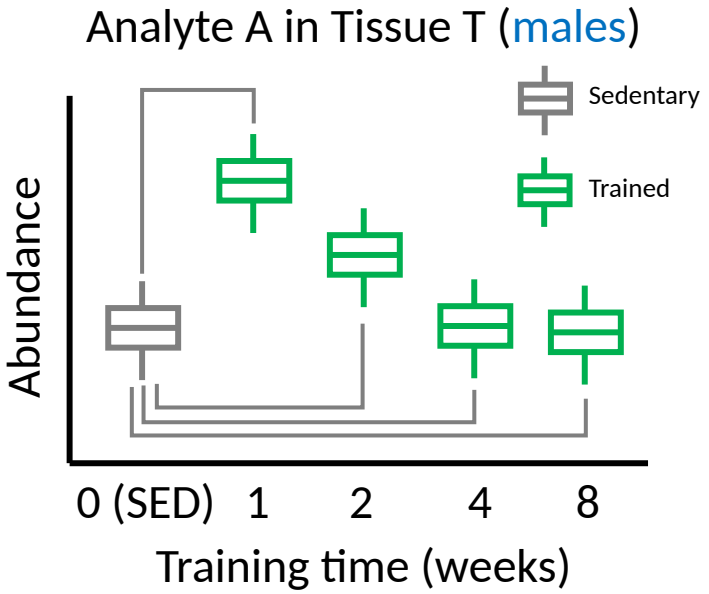
Differentially regulated analytes

1. Is the analyte level changing at any time in either sex?



2. What are the per-time and per-sex effects relative to the control?



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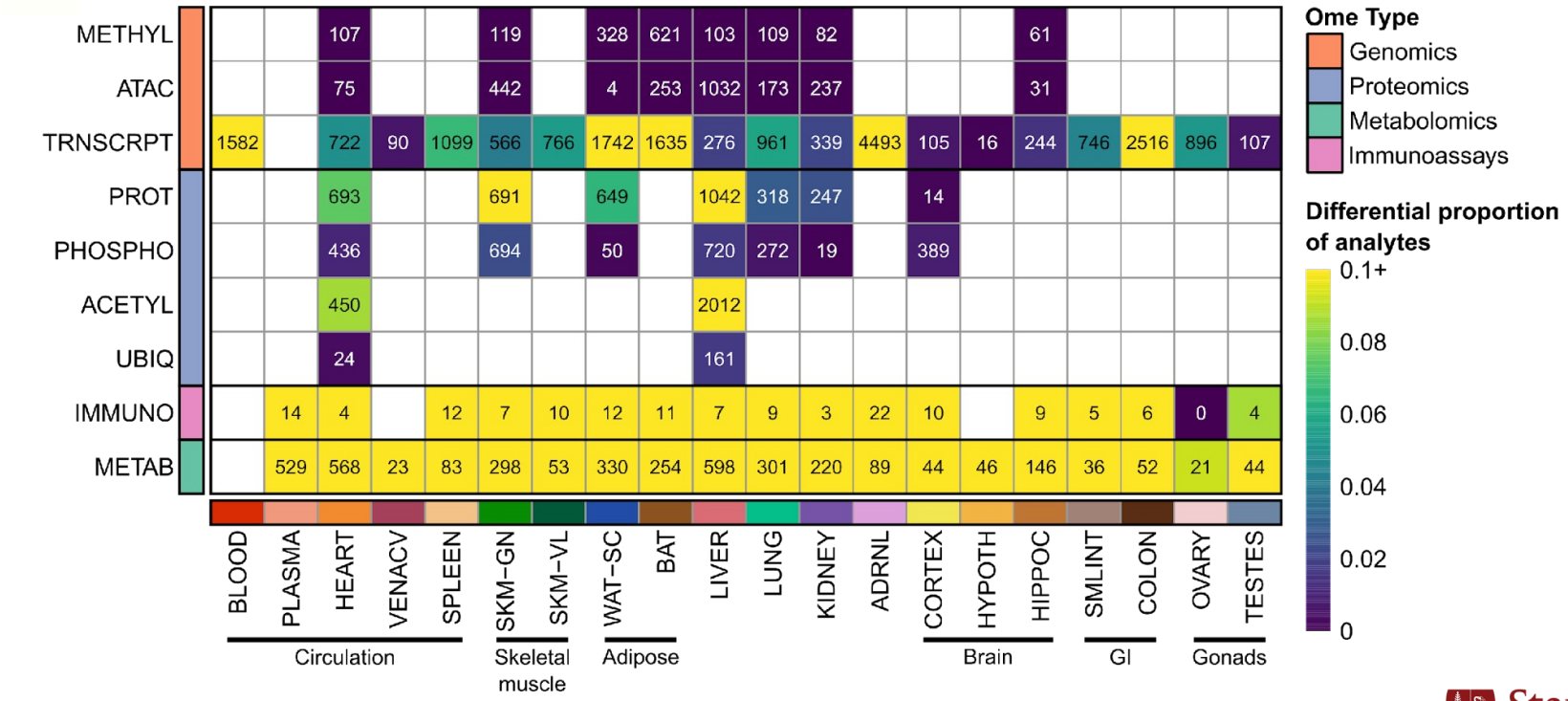
Training-regulated analytes across -omes



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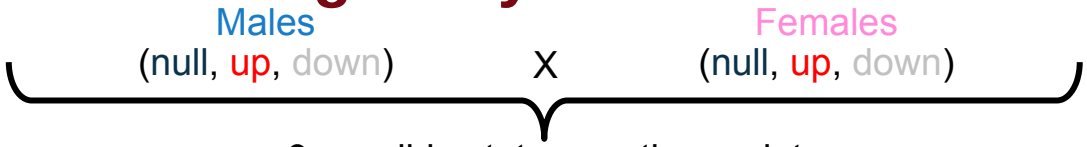
Clustering analysis to visualize timewise changes



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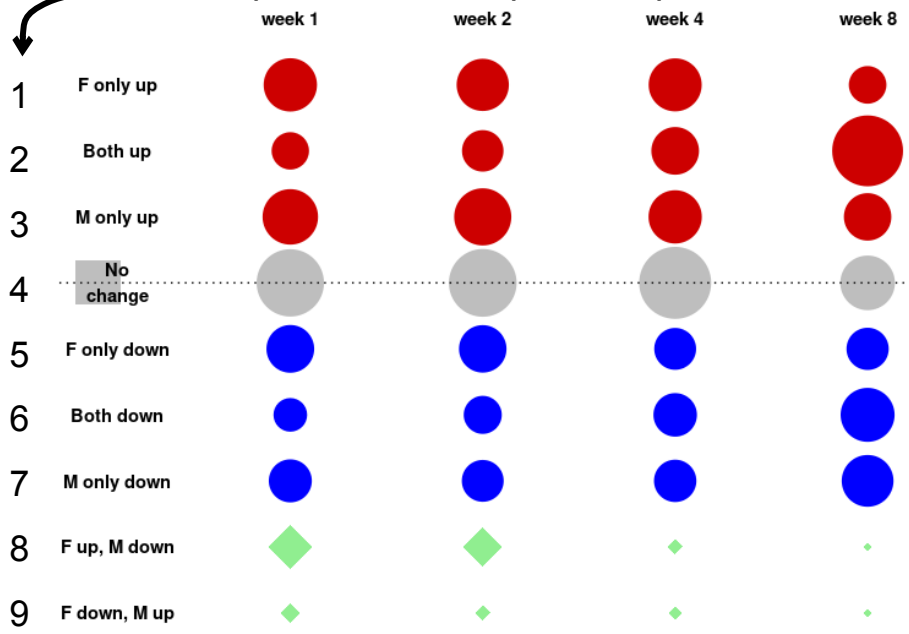
Clustering analysis to visualize timewise changes

Males (null, up, down) X Females (null, up, down)

9 possible states per time point



Up-regulated (at least one sex)

Null in both sexes

Down-regulated (at least one sex)

Opposite directions

*node size = N features

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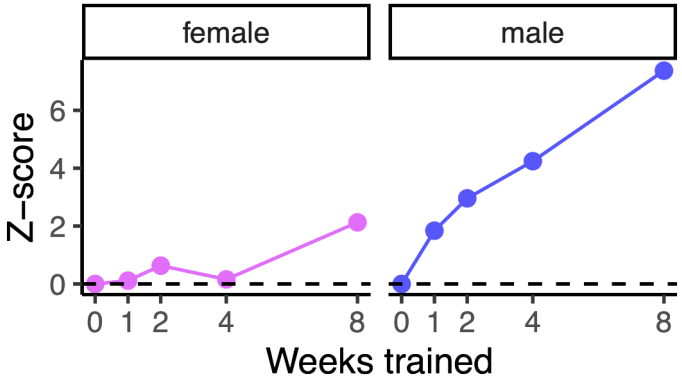
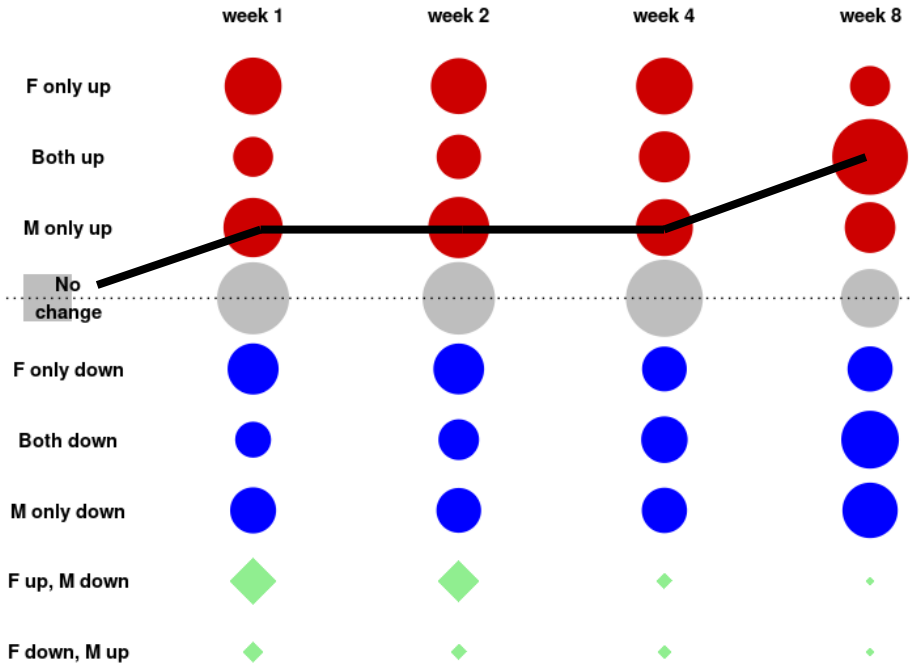
Clustering analysis to visualize timewise changes





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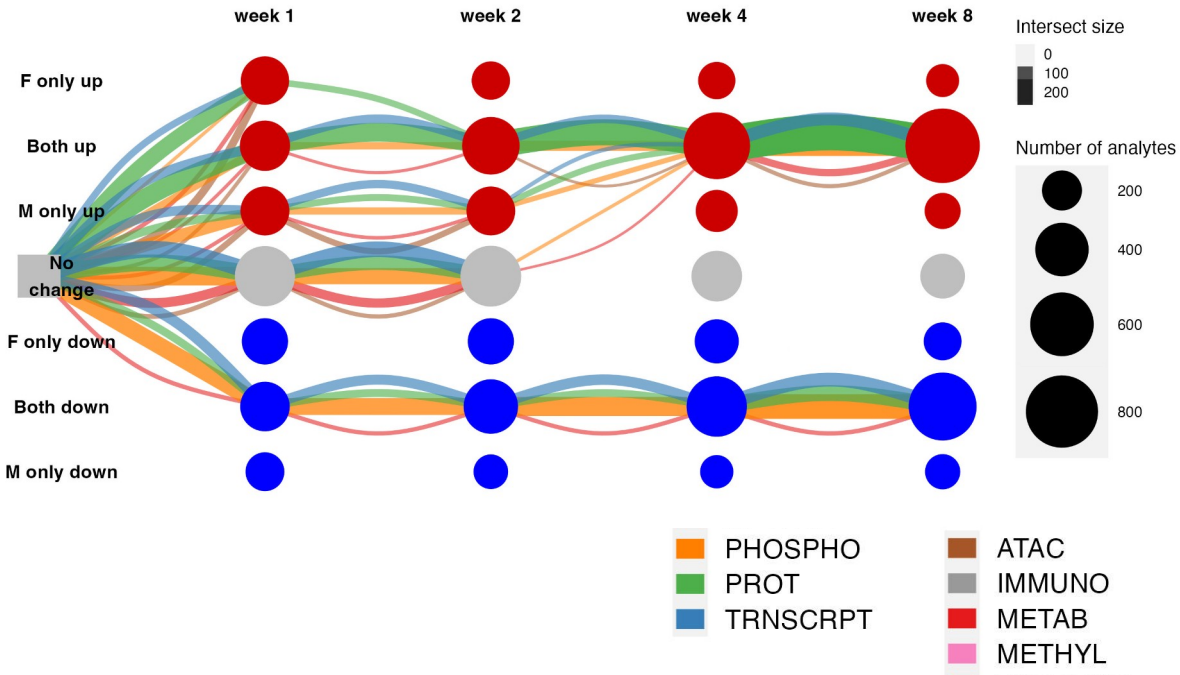
Temporal dynamics of the multi-omic response to exercise

Common analytical questions

- What analytes increase in abundance across both sexes at 8 weeks?
- What proteins decrease in abundance at all timepoints in females only?
- What is the top trajectory for a certain –ome in a certain tissue?



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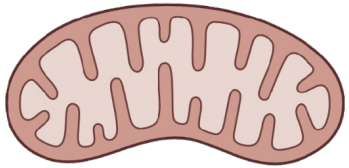
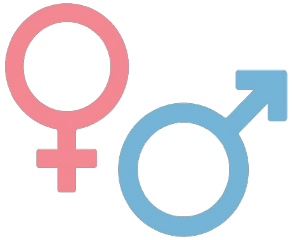
Exploring the multi-omic response to exercise training

Whole-body responses to training



Metabolic adaptations



Sex differences in the training response

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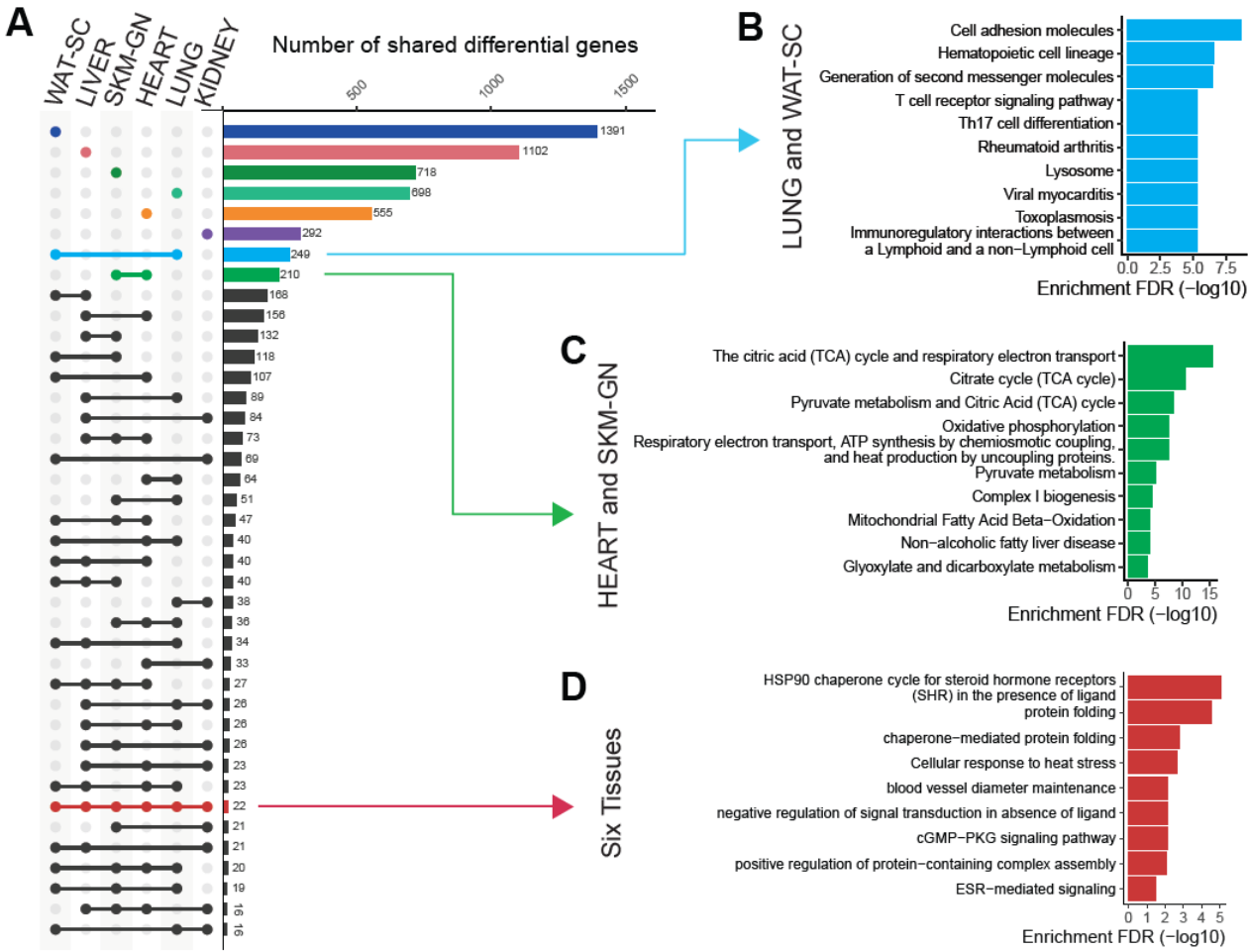
Multi-tissue molecular responses to training



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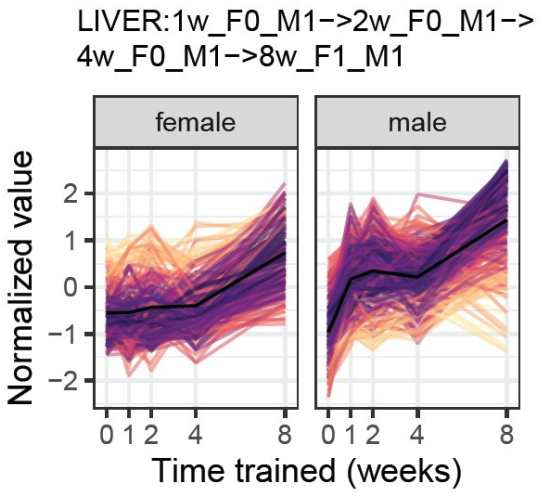
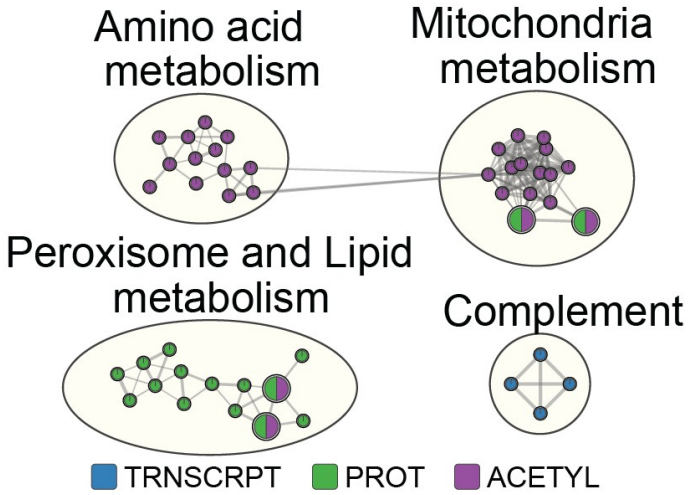
Increases in metabolic protein abundance and acetylation in the liver





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Data dissemination through the

oTrPAC Data Hub

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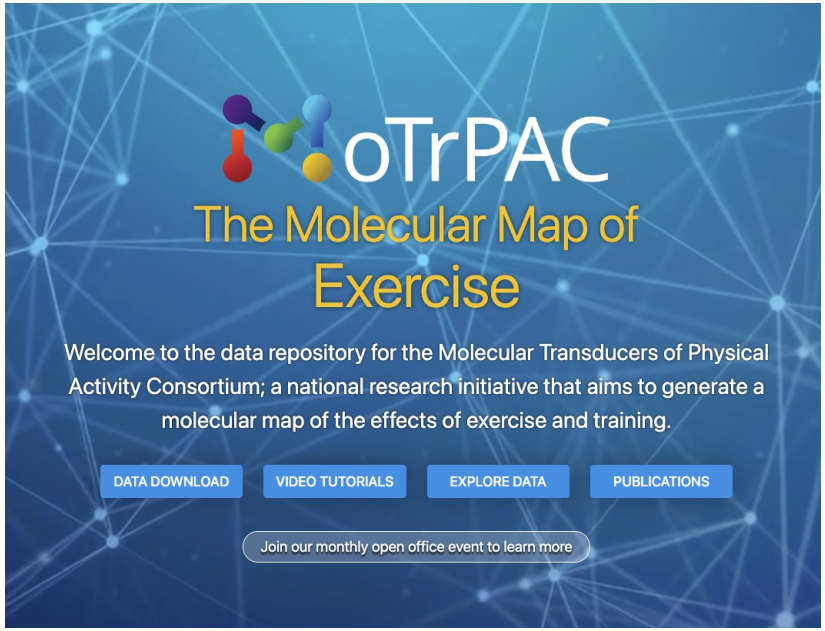

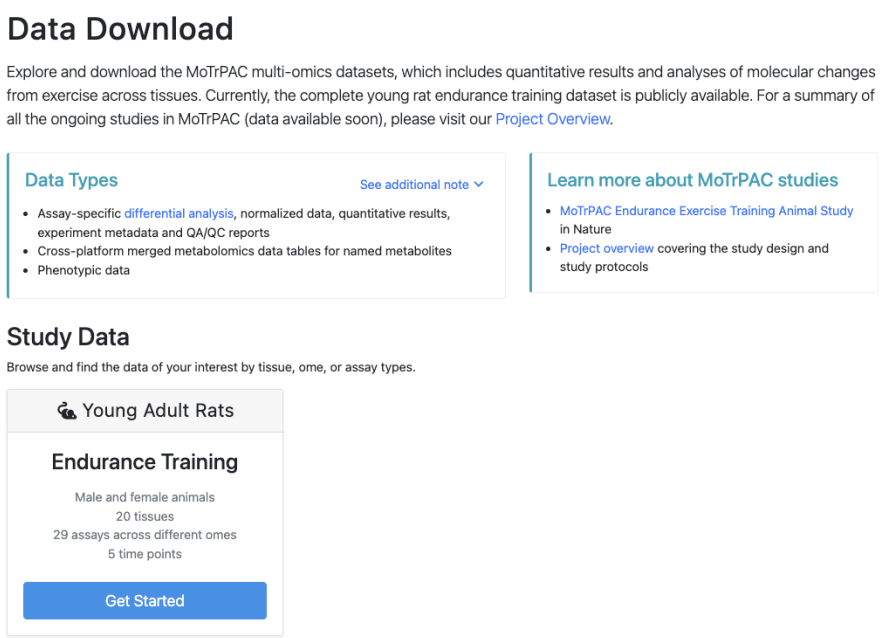

motrpac-data.org

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Search differential abundance data

Search by gene ID, protein ID or metabolite name to examine the timewise endurance training response over 8 weeks of training in adult rats. **Multiple search terms MUST be separated by comma and space. Examples: "NP_001000006.1, NP_001001508.2, NP_001005898.3" or "8,9-EpETrE, C18:1 LPC plasmalogen B".**

Gene Protein ID Metabolite PPARGC1A × All omics Search Reset

Filter results: Update results Reset filters

Tissue

Adrenal Blood RNA Brown Adipose Colon
Cortex Gastrocnemius Heart Hippocampus
Hypothalamus Kidney Liver Lung Ovaries
Plasma Small Intestine Spleen Testes
Vastus Lateralis Vena Cava White Adipose

Timewise Training

Show: 50 entries Download results

Gene	Feature ID	Tissue	Assay	Sex	Timepoint	logFC	P-value	Adj p-value	Selection FDR
PPARGC1A	chr14:62894569-62894843	Lung	ATAC-seq	Female	1 week	-1.3556	0.0687	1	0.9755
PPARGC1A	chr14:62894569-62894843	Lung	ATAC-seq	Female	2 week	-0.4039	0.573	1	0.9755
PPARGC1A	chr14:62894569-62894843	Lung	ATAC-seq	Female	4 week	0.4438	0.5291	1	0.9755
PPARGC1A	chr14:62894569-62894843	Lung	ATAC-seq	Female	8 week	0.626	0.3781	1	0.9755

Tissue: Gastrocnemius

Graph characteristics
- All paths
- Top clusters

Top 5 trajectories
- All omes
- Split by ome group

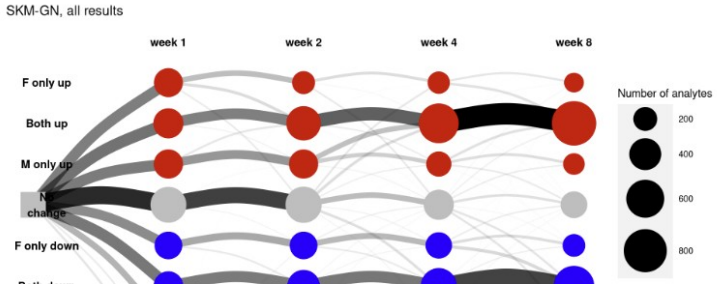
Detailed view of selected clusters
- Selected paths
  - SKM-GN:1w_F1_M1->2w_F1_M1->4w_F1_M1->8w_F1_M1
  - SKM-GN:1w_F-1_M-1->2w_F-1_M-1->4w_F-1_M-1->8w_F-1_M-1
  - SKM-GN:1w_F0_M1->2w_F0_M1->4w_F1_M1->8w_F1_M1
  - SKM-GN:1w_F0_M0->2w_F0_M0->4w_F1_M1->8w_F1_M1
  - SKM-GN:1w_F1_M0-

Graph characteristics

Graphical analysis has replaced clustering as the primary method of exploring main patterns in the PASS1B data. This approach is more flexible and gives us better resolution.

All paths

Tree of ALL differential analytes (all paths)



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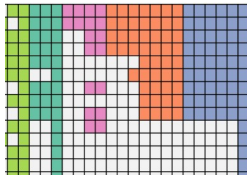
Summary

Unparalleled exercise biology molecular resource

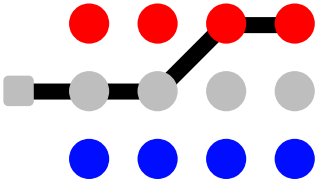


- 19 tissues, 9 omes, 90 datasets
  34,000 analytes regulated over the training time course
- Substantial regulation of transcripts, proteins, PTMs, metabolites

Mechanisms explaining health benefits of exercise

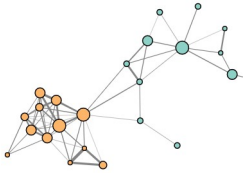
- Whole body responses
- Molecular hubs through interaction networks
- Sex differences in exercise adaptation
- Metabolic adaptations

Molecular dynamics in response to training



- Pipelines for robust statistical analysis and data integration
- Analytical methods for graphical representation of temporal dynamics

Tools for exploration and interpretation



- Pathway analysis aid in biological interpretation
- Computational and visualization tools facilitate data access
  (R package and MoTrPAC Data Hub)

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Acknowledgements

Coordinating Centers

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MoTrPAC is supported by the National Institutes of Health (NIH) Common Fund through cooperative agreements managed by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of Arthritis and Musculoskeletal Diseases (NIAMS), and National Institute on Aging (NIA).