Metabolic adaptations to cardiac rehabilitation through physical exercise: Insights from untargeted metabolomics using dried blood spots in post-myocardial infarction patients

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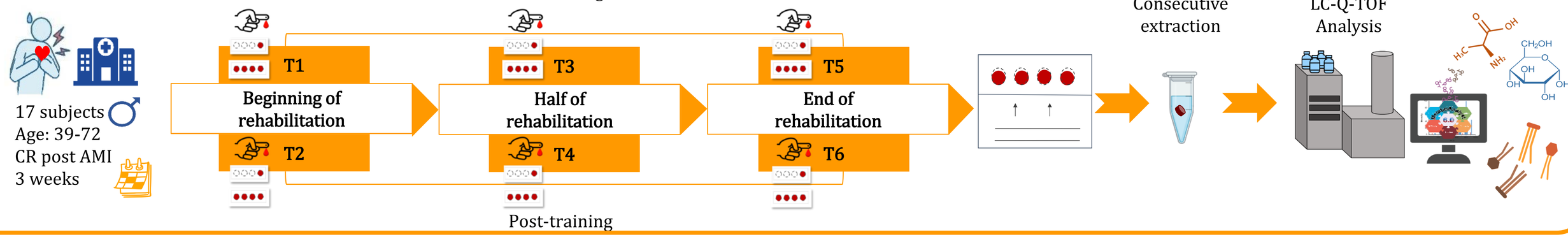
Background

Ischemic heart disease remains the leading cause of death from cardiovascular diseases worldwide. The beneficial effects of cardiac rehabilitation (CR) through physical exercise on disease progression in patients after acute myocardial infarction (AMI) are well known, while knowledge of the effects on metabolic processes is still limited.

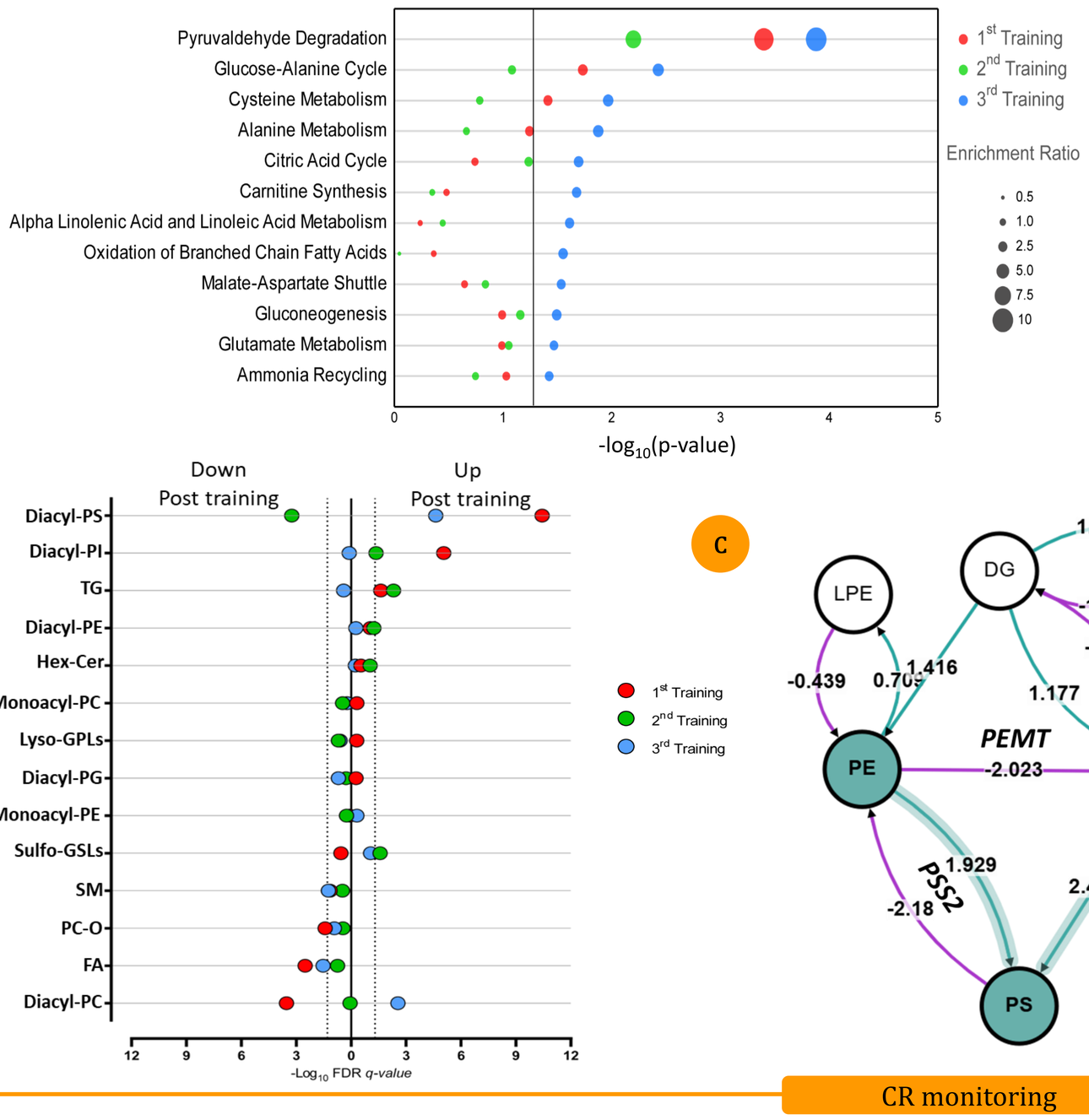
- Investigate CR efficacy through physical exercise with a metabolomic approach
- Training session monitoring - Evaluate metabolic effects of the single training session
- CR monitoring - Evaluate metabolic effects of the CR over time

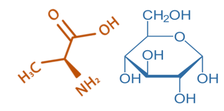
Workflow



Results

Training session monitoring





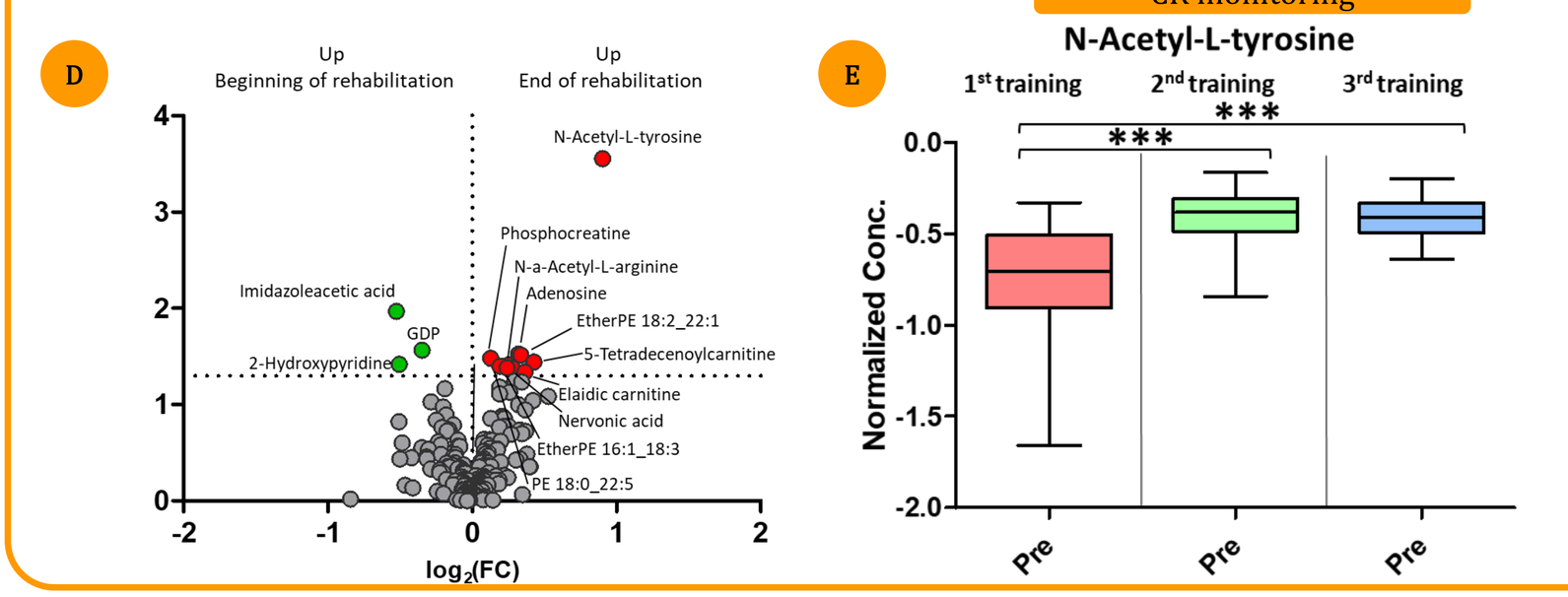
Polar metabolite analysis

Panel A: Overlaid quantitative enrichment analysis. Each training implies the pre- vs post- training comparison. Each dot shows how much a single pathway is enriched in the considered comparison. The more enriched the pathway, the bigger the dot, according to the enrichment ratio, which is proportional to the number of metabolites seen in that pathway. The highest number of metabolic pathways resulted significantly enriched only after the 3rd training, and overall, they were mostly associated with energy metabolism.

Lipid analysis

Panel B: Lipid ontology enrichment analysis using LION/web. Each training implies the pre- vs post-training comparison. The impact of CR training on the lipidome was mainly detected on the 1st training. Overall, PS and PI were upregulated post 1st training, while FA and PC were downregulated post 1st training. **Panel C**: Functional analysis performed using BioPAN Lipidmaps on post vs pre 1st training (T2 vs T1), with T2 chosen as condition of interest. PSS1 and PSS2 (phosphatidylserine synthase 1 and 2) were predicted as the most active enzymes. Increased activity of these enzymes results in more active reactions, converting PE and PC into PS. Our data suggests that physical exercise during CR induces a protective mechanism leading to upregulation of PSS1 that may be a promising therapeutic approach to mitigate MI.

CR monitoring



CR monitoring

Panel D: Volcano plot pre-1st training (beginning of rehabilitation) vs pre-3rd training (end of rehabilitation) (*p-value* threshold 0.05, FC 1). **Panel E:** Boxplots - significant changes of N-acetyl-L-tyrosine (NAT) (pre-1st training vs pre-2nd training vs pre-3rd training), *p-value* threshold 0.05. NAT was upregulated at the end of the CR protocol and significantly increased pre-2nd training. NAT has been identified as an endogenous factor in the stress response that appears to trigger a cytoprotective state called mitohormesis. Mild mitochondrial stresses induce a protective mitochondrial effect mediated by ROS, and this mechanism has been linked to physical activity in humans.

Conclusions

- Training has a long-term positive effect on metabolism, likely because performance improved during the third week, which boosted energy metabolism.
- In the short term, we observed an increase in PS levels. This upregulation suggests that both PSS1 and PS may offer cardioprotective benefits.
- PS and NAT show promise as potential biomarkers to monitor CR.
- Mitohormesis could be a central molecular mechanism in regulating exercise-mediated adaptations.
- Although our findings align with existing scientific literature, further studies are needed to validate our hypothesis.

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