Relationship Between Physical Exercise and Chronic Pain Intensity

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INTRODUCTION

Pain serves an **adaptive survival function**, an inner warning system pointing to harm or a treatment. Pain management and loss of productivity during chronic pain result in substantial societal costs. In 2018 it was reported that the **prevalence** of chronic pain is more than **30**% in America alone, with chronic low back pain being the **most reported condition** (1).

Drugs have shown **minimal effectiveness**, moreover, some of them have substantial side effects, and **exercise** is the current **first-line treatment** prescribed to patients with chronic pain. Many studies suggest that physical exercise might contribute to chronic pain improvement (2). Therefore, we decided to **investigate** the **molecular pathophysiological mechanisms** underlying the **improvement of chronic low back pain** (LBP) following **exercise** through a **transcriptome-wide analysis** of the peripheral immune cells.

METHODS

Study design and Grouping: The blood samples were collected from 32 low back pain patients who underwent 14 weeks of physical exercise. The statuses of improved and persistent pain group were assigned based on the pain score difference between the first and second time points .

Statistical analysis: FASTQ files of the sequencing data are mapped on the human genome GRCh38 using STAR (3). Five specific contrasts both on gene and pathways levels were performed. Differential expression of genes was detected with the help of the "DESeq2" R package (4). The differential expression gene analysis results were given for input to "fgsea" R package for pathways analysis.

CONCLUSIONS

The results of our transcriptomics analyses of the cohort of LPB patients undergoing physical exercise provided few insights. First, it indicated that the relative abundance and magnitude of changes of an active biological processes is a major contributor to pain improvement over time of physical exercise. Second, we found d that there is a downregulation of inflammatory pathways over time driven by long-term exercise associated with pain improvement, which is consistent with previous research done by Parisien et al., on the transition from acute to chronic pain state. (5)

RESULTS

Differential Gene Expression:

We assessed genome-wide transcriptomics differences in a cohort of 32 low back pain patients at the first blood collection time point, 2 weeks after the start of exercise (T1), at the second blood collection time point, after the last exercise session on week 14th(T2), and differences within both groups over time.

We observed a substantial difference in gene expression over the time of cohort observation (Fig. 1A).

We identified 101 significantly differentially expressed genes in the improved pain group with an about equal amount of up- and down-regulated genes (Fig. 1B), while there were 0 in the persistent pain group over time (Fig. 1C).

At the T1 snapshot we didn't detect any significantly differentially expressed genes, suggesting similar activity on the gene level between groups (Fig. 1D), while at the second dime point the changes started to appear causing an increase in number of significantly differentially expressed genes (Fig. 1E). The Kolmogorov-Smirnov test analysis indicated that distributions of changes in gene expression betas were significantly different between the groups ($D = 0.16$, P-value < 2.2x10-16), suggesting that there are more regulations of the gene expression in the improved pain group than in the persistent pain group.

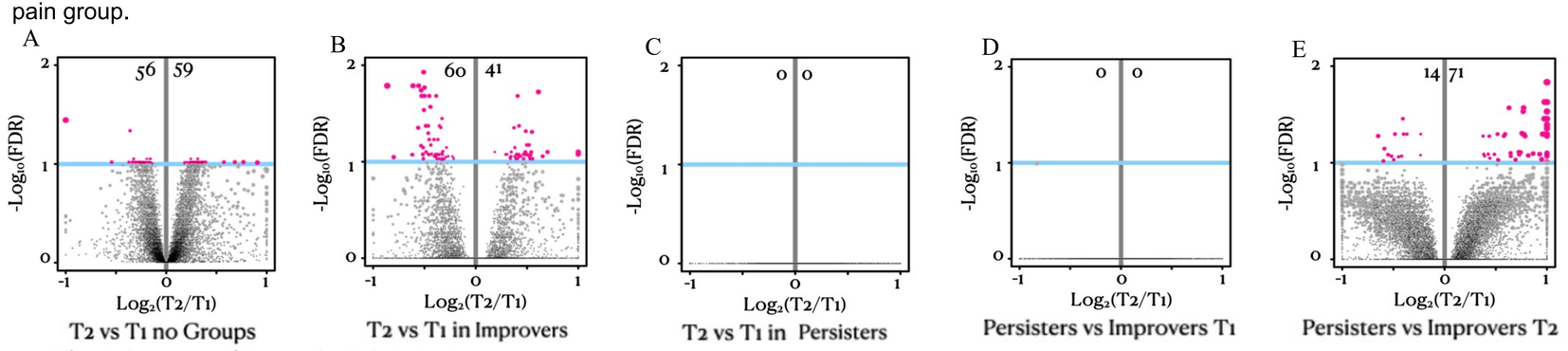

Fig 1. **Differential Expression of Genes in the Study Contrasts.**
The volcano plot shows statistical significance (*y-axis*) as a function of fold change in gene expression (*x-axis*); each dot is a gene. Genes that would end up outside of the plot are squeezed inside. The vertical gray line indicates null fold change. Genes reaching statistical significance at the FDR 10% level (blue horizontal line) are highlighted in pink. Numbers in bold indicate counts of significantly differentially expressed genes that are down-regulated or up-regulated. (A) – Differences in gene expression in patients over the time of exercise. (B,C) - Difference in gene expression over time in the improved pain group (B) or the persistent pain group (C), (D,E) – Difference in gene expression between groups at the first time point T1 (D) and at the second time point T2 (E).

General Pathway Analysis:

We next calculated the correlation of changes in transcriptionally-based biological pathways over the time of exercise between persistent and improved pain groups. We found that the majority of transcriptional changes over time have a positive correlation.

The improved pain group's response intensity was about 63% smaller than that of the persistent pain group calculated using rate of change based on the slope.

Most of the pathways, located at the top right and bottom left corners, have similar directionality reflecting the similar biological responses of both groups to the exercise. Pathways located at the top left and bottom right quadrants of the plot, indicating that there are some pathways with opposite directions (Fig. 2)

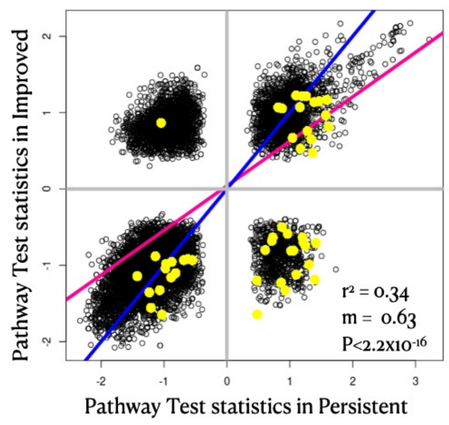

Fig. 2 **Pathway Trajectories in Time Between the Two Pain Groups**
Each dot is a pathway. Pathways coordinates are in test statistics space, obtained from pathway analyses by fgsea. The pink line was obtained from linear regression of the data, whereas the blue line is from theoretical expectation of equal trajectories. Yellow dots represent inflammatory pathways. Percent variance explained (Pearson's r^2), slope (m), and P-value of regression are reported.

Inflammatory and Cell Activation Pathway Analysis:

We next focused on the differences in the improved and persistent pain groups for the Inflammatory and Cell Activation biological pathways. We found that patients from the improved pain group had inflammatory response pathway downregulated over the time of exercises, when the persistent pain group did not show any significant differences (Fig. 3A,B). Also, our analysis comparing both groups at a specific time point showed that there are two inflammatory pathways upregulated in the persistent pain group at T1 and 6 – at T2 (Fig. 3C and D), consistent with more efficient down-regulation of inflammatory pathways in the in the improved pain group over the time of exercise.

When analyzed blood cells activation pathways, we found that all of the detected significantly expressed cell type activation pathways were downregulated overtime in both pain groups (Fig. 4A,B). However, more pathways were downregulated in the improved pain group. Furthermore, the macrophage activation was already higher in the persistent pain group at T1, and at T2, this difference between persistent and improved pain groups further increased. At T2, neutrophils activation pathways was also significantly higher in persistent pain group in comparison with improved pain group (Fig. 4C,D).

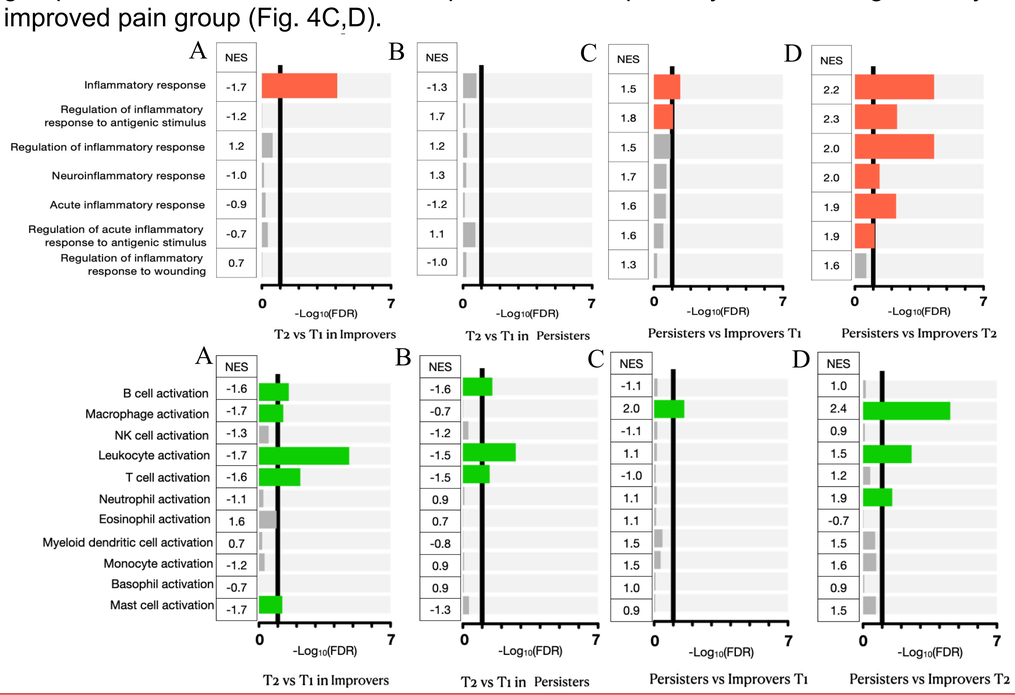

Fig. 3 **Functional Difference in the Inflammatory Pathways Between the Improved and Persistent Pain Groups.**
Functional differences assessed for selected pathways in Gene Ontology's (GO) biological processes, overarching under "inflammatory response" (GO: 0006954). Statistically significant pathways at the FDR 10% level are highlighted in orange. NES column shows normalized enrichment scores for every pathway. (A,B) - Differentially expressed pathways over the time of exercise for improved pain group (A) or persistent pain group (B). (C, D) - Differentially expressed pathways between the persistent and improved pain group at the first time point T1 (C) and the second time point T2(D).

Fig. 4 **Functional Difference in the Cell Activation Pathways Between the Improved and Persistent Pain Groups.**
Functional differences assessed for selected pathways in Gene Ontology's (GO) biological processes overarching pathway of "leukocyte activation" (GO:0045321). Statistically significant pathways at the FDR 10% level are highlighted in green. NES column shows normalized enrichment scores for every pathway. (A,B) - Differentially expressed pathways over the time of exercise for improved pain group (A) or persistent pain group (B). (C, D) - Differentially expressed pathways between the persistent and improved pain group at the first time point T1 (C) and the second time point T2(D).

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