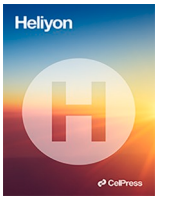
Heliyon 10 (2024) e38152

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Unraveling the role of lactate-related genes in myocardial infarction

Rui Xu [a], YanYan Li [b], Hong Xu [a,*], HongMei Lai [c,**]

[a] Gerontology Center, People's Hospital of Xinjiang Uygur Autonomous Region, Urumqi, 830001, China
[b] Department of Cardiac Surgery, People's Hospital of Xinjiang Uygur Autonomous Region, Urumqi, 830001, China
[c] Department of Cardiology, People's Hospital of Xinjiang Uygur Autonomous Region, Urumqi, 830001, China

ARTICLE INFO

Keywords:
Lactate
Myocardial infarction
Gene
Immune infiltration
Enrichment analysis

ABSTRACT

Background: Lactate is a crucial intermediary, facilitating communication between myocardial energy metabolism and microenvironmental regulation. The present study aimed to investigate the relationship between lactate-related genes (LRGs) and myocardial infarction (MI).
Methods: A total of 23 LRGs exhibited differential expression between individuals with MI and healthy controls. Lasso regression analysis and validation with the GSE61144 dataset identified three hub genes: COX20, AGK, and PDHX. Single-gene GSEA of these genes revealed strong enrichment in pathways related to amino acid metabolism, cell cycle, and immune functions. Quantitative reverse transcription-polymerase chain reaction (qRT-PCR) was utilized to validate the expression levels of the hub genes.
Results: Immune infiltration analysis revealed differences in $CD4^+$ T and $CD8^+$ T cells between the MI and control groups. Additionally, 67 candidate drugs targeting the three hub LRGs were identified, and a ceRNA network was constructed to explore the intricate interactions among these genes.
Conclusions: These findings enhance the understanding of MI and have potential therapeutic implications.

1. Introduction

Myocardial infarction (MI) is a well-known outcome of persistent inadequate blood flow to the heart or coronary arteries, and it is linked to high mortality rates [1]. Advanced myocardial protection techniques have provided significant benefits for many high-risk individuals [2]. Despite these advancements, current methods do not always prevent myocardial stunning or complete tissue necrosis [3]. It is well recognized that restricted blood flow and subsequent reperfusion lead to global or regional metabolic changes in the cardiac muscle, significantly affecting its functional recovery [4]. The occurrence of acidosis and lactate production within cardiac tissue serves as a reliable indicator of insufficient preservation of the myocardium [5]. Previous research has demonstrated a correlation between lactate concentration and patient outcomes in consecutive cohorts with MI [6].

Lactate, a common intermediate in glycolysis, was traditionally viewed as a metabolic by-product [7]. However, due to the Warburg effect, cancer cells exhibit excessive lactate accumulation, which is a hallmark of cancer and contributes to an acidic tumor

* Corresponding author. N°. 91 Tianchi Road, Tianshan Disztrict, Urumqi, Xinjiang, China.
** Corresponding author. N°. 91 Tianchi Road, Tianshan Disztrict, Urumqi, Xinjiang, China.
E-mail addresses: dengta2022@126.com (H. Xu), laihongmei430@163.com (H. Lai).

https://doi.org/10.1016/j.heliyon.2024.e38152
Received 22 May 2024; Received in revised form 30 August 2024; Accepted 18 September 2024
Available online 19 September 2024

microenvironment [8]. Recent studies have shown that lactate can serve as a precursor for gluconeogenesis or enter the mitochondrial matrix, either directly or indirectly, to supply energy [9]. It also acts as a signaling molecule, playing a role in maintaining subcellular organelle homeostasis and facilitating communication between neurons to modulate immunity through various signaling pathways [10]. Interestingly, lactate directly regulates protein function to control cell proliferation [11]. Additionally, lactate serves as a substrate for epigenetic modifications, such as lactylation of histone or non-histone lysine residues, which influences gene transcription and protein function [12]. Emerging evidence suggests that lactate may be involved in various diseases, including MI, beyond its role in tumors [13,14]. Serum lactate levels reflect the state of blood circulation, with elevated levels indicating reduced oxygen delivery or inadequate blood flow to tissues [15,16]. Thus, serum lactate serves as a prognostic marker for critically ill patients with MI. Given lactate's crucial role as a signaling molecule in regulating hemodynamics and energy metabolism, conducting a comprehensive analysis of lactate-related genes is essential to understand their potential contribution to MI.

This study utilized transcriptome sequencing and bioinformatics analysis to investigate lactate-related genes (LRGs) in individuals with myocardial infarction (MI). Whole blood samples from MI patients were collected, and the LRGs were validated by qRT-PCR. The primary goal was to propose new strategies for diagnosing and treating MI.

2. Materials and methods

2.1. Obtain data

The data analysis was conducted utilizing two datasets obtained from the Gene Expression Omnibus (GEO) database. The first dataset, GSE141512, served as the microarray training dataset and included peripheral blood samples from 6 MI patients and 6 healthy controls. Whole transcriptome sequencing was performed utilizing the GPL17586 platform [17]. The second dataset, GSE61144, was used as the microarray validation dataset and comprised full blood samples from 14 individuals with MI and 10 healthy controls. Whole transcriptome sequencing was performed utilizing the GPL6106 platform [18].

2.2. Identification of DE-LRGs

In this study, data analysis was conducted utilizing the 'limma' package in R software. The expression matrix for LRGs was obtained from the GSEA website (https://www.gsea-msigdb.org/gsea/downloads.jsp). From the gene sets available on the site, a collection of 219 LRGs was curated. To identify differentially expressed LRGs (DE-LRGs), a differential expression analysis was performed by comparing the MI and control groups. The analysis focused on genes that showed significant differences, applying a cutoff of p-value <0.05 and fold change (FC) > 1.2 for adjustment. A Venn plot was utilized to illustrate the overlap between differentially expressed genes (DEGs) and LRGs.

2.3. Functional enrichment analyses

Enrichment analyses on Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) were performed utilizing the R package 'clusterProfiler'. Statistical evaluation was conducted with a significance threshold of FDR <0.05 and adjusted p-value <0.05. GO terms were categorized into three classifications: biological process (BP), molecular function (MF), and cellular component (CC).

2.4. Optimal hub gene selection

DE-LRGs were identified by comparing control and MI samples, with the resulting DEGs serving as features for subsequent selection using the LASSO algorithm implemented in the 'glmnet' package. This approach effectively reduced data complexity and enabled the identification of potential biomarkers associated with MI. An independent validation was performed utilizing the GSE61144 dataset to confirm these key DE-LRGs and identify relevant hub genes. The diagnostic performance of each hub DE-LRG was assessed by calculating the area under the receiver operating characteristic curve (AUC).

2.5. Single-gene GSEA analyses of identified DE-LRGs

The Single-gene GSEA method was utilized to investigate the associations between pathways and functions of the hub DE-LRGs. To determine statistical significance, thresholds were set at $p < 0.05$, normalized enrichment scores (NES) > 1, and false discovery rate (FDR) q-values <0.25.

2.6. Immune cell analyses

The GSE141512 dataset was analyzed utilizing the CIBERSORT algorithm to investigate immune cell populations, identifying 24 distinct types of immune cells. CIBERSORT was run in relative and absolute modes, using the LM24 signature gene file, with 100 permutations and quantile normalization disabled. Although 100 permutations were used as the recommended minimum, increasing to 1000 permutations did not alter the absolute proportion of each cell type. The data were visually represented through boxplots. To further examine the relationship between hub DE-LRGs and immune cell populations, Spearman correlation analyses were performed

and visualized utilizing the 'corrplot' package.

2.7. Patient recruitment and sample collection

qRT−PCR experiments were applied to validate the biomarkers in the peripheral blood of MI patients. The study was granted by the Ethics Committee of the People's Hospital of Xinjiang Uygur Autonomous Region (Ethics approval number: KY20240312074). The inclusion criteria for MI patients were as follows: 1) age ≥18 years; 2) diagnosis of MI based on ESC guidelines; 3) symptom onset within 12 h before percutaneous coronary intervention (PCI); and 4) informed consent obtained. Exclusion criteria included: 1) cardiogenic shock; 2) prior myocardial infarction or coronary artery bypass grafting; 3) severe hepatic conditions. All participants provided written consent before enrollment.

2.8. qRT−PCR experiment to verify the expression of diagnostic biomarkers

Total RNA was extracted from blood sample based on standard protocols of RNA Extraction Reagent (Invitrogen, USA). The 5X All-In-One RT MasterMix (abm, China) was used to synthesize cDNA. PCR amplification was performed by a CFX96 real-time PCR instrument (BIO-RAD, USA) with EvaGreen Express 2 × qPCR MasterMix-Low Rox (abm, China). PCR data was normalized by actin expression. The method of quantification for PCR data was calculated with the $2^{-\Delta\Delta Ct}$ computation method. The primers we used are listed in Table S1.

2.9. Drug prediction analysis

The Coremine Medical website was utilized to calculate the correlation between drugs and gene targets. The results of this analysis were utilized to identify potential therapeutic agents targeting the hub DE-LRGs.

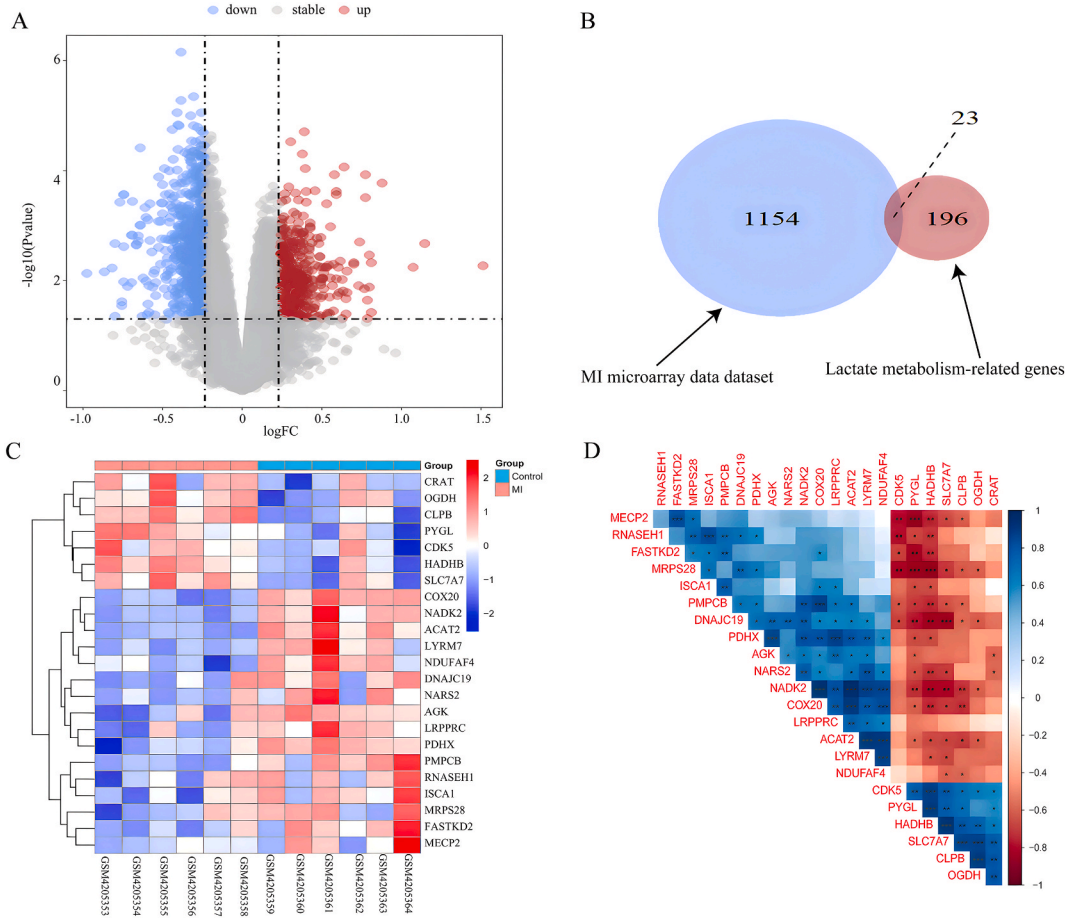


Fig. 1. (A) Volcano map of GSE151412 (MI = 6, Control = 6), Upregulated genes are marked in light red; downregulated genes are marked in light blue. (B) The two datasets showed an overlap of 23 DEGs. (C) Heat maps of DE-LRGs in MI and Control. (D) Interrelationships among DE-LRGs. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

2.10. ceRNA network development

To identify relevant miRNAs interacting with hub DE-LRGs, the starBase database was utilized. mRNA sequences corresponding to these DE-LRGs were acquired from NCBI, while human miRNA sequences were downloaded from miRbase. Prediction of miRNA target genes was conducted using the TargetScan, miRNet, and miRanda databases. Additionally, starBase was utilized to screen for mRNA-lncRNA interactions, facilitating the construction of an mRNA-miRNA-lncRNA network. A competing endogenous RNA (ceRNA) network was then mapped using Cytoscape.

2.11. Statistical analyses

All statistical analyses were performed utilizing R software (version 4.1.2; https://www.r-project.org/). The R packages used for generating plots are detailed in Table S2. The Wilcoxon rank-sum test and *t*-test were employed for difference analysis, while Spearman correlation analysis was utilized to evaluate correlations. A value of $p < 0.05$ was considered significant.

3. Results

3.1. Identification of LRGs in the GSE141512 cohort

A total of 1177 DEGs were identified between the MI patients and the control group. Among these, 719 genes exhibited up-regulation, while 458 genes showed down-regulation. These DEGs are visually represented in a volcano plot (Fig. 1A). From the GSEA website, a set of 219 LRGs was obtained, and 23 overlapping genes were identified between the DEGs and LRGs (Fig. 1B). To examine the expression patterns of these differentially expressed and literature-reported genes across the samples, a clustering heatmap was generated, illustrating the expression profiles of these genes across various samples (Fig. 1C). Moreover, the interrelationships among these genes were computed and illustrated. For example, MECP2 showed a positive correlation with FASTKD2 and MRPS28 but a negative correlation with CDK5 and PYGL. Similarly, RNASEH1 had a negative correlation with CDK5, PYGL, and HADHB, while displaying a positive correlation with ISCA1, MRPS28, and PMPCB (Fig. 1D).

3.2. Functional DE-LRGs analyses

The LRGs were subjected to GO/KEGG enrichment analysis. KEGG analysis indicated significant enrichment in pathways like fatty acid degradation, fatty acid metabolism, and the degradation of valine, leucine, and isoleucine (Fig. 2A). GO analysis showed notable enrichment in BP, particularly those related to fatty acid oxidation and lipid modification signaling pathways. Regarding CC, the mitochondrial matrix and inner membrane were significantly enriched (Fig. 2B).

3.3. Identification of hub DE-LRGs

Using the GSE151412 training dataset, Lasso regression was applied to the expression matrix of 23 DE-LRGs. This analysis identified COX20, AGK, PDHX, and CLPB as potential candidates (Fig. 3A and B). To validate these findings, the GSE61144 validation dataset was analyzed. Notably, the expression levels of COX20, AGK, and PDHX were significantly lower in the MI group versus the control group (Fig. 4A). The AUC values for these three DE-LRGs were determined to be 0.979, 0.943, and 0.786, respectively, indicating their high accuracy and specificity in distinguishing MI samples from control samples (Fig. 4B–D). These results highlight

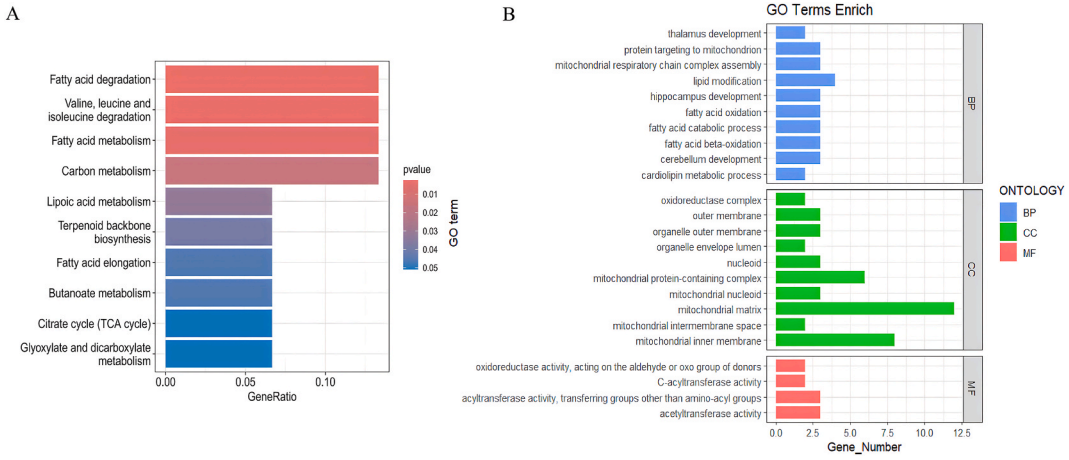


Fig. 2. (A, B) The KEGG and GO terms pathways which is enriched by the DE-LRGs (MI = 6, Control = 6).

the potential of COX20, AGK, and PDHX as promising biomarkers for MI detection.

3.4. Single-gene GSEA gene set enrichment analysis

Single-gene GSEA analysis was performed on these 3 DE-LRGs to obtain the related pathways of each gene (Fig. 5A–C). The analysis revealed that these genes were predominantly enriched in amino acid and derivative metabolism pathways, the major pathway of rRNA processing in the nucleolus and cytosol, cell cycle regulation, and immune pathways.

3.5. Analysis of immune cell infiltration

The examination of immune cell infiltration revealed significant variations in the levels of CD4+T, CD8+T, DC, TCM and TEM cells between the MI and control groups (Fig. 6A). Furthermore, a correlation analysis was performed to investigate the correlation between the 3 DE-LRGs and immune cells (Fig. 6B). COX20 was found to have a strong positive correlation with CD4+T, CD8+T, Naive CD4+T, Tfh, central memory and effector memory cells. AGK showed a positive correlation with CD8+T, Tfh and effector memory cells. Additionally, PDHX demonstrated a significant link between CD8+T, central memory, and effector memory cells.

3.6. Expression level of COX20, AGK and PDHX in peripheral blood samples

Seven MI patients and Thirteen age- and gender-matched controls were enrolled in the study. Demographic characteristics are detailed in Table S3. The mRNA expression levels of COX20, AGK, and PDHX were found to be downregulated in the MI group compared to the control group (Fig. 7). Table S4 listed the hub DE-LRGs.

3.7. Screening of potential therapeutic drugs

The Coremine Medical website was employed to predict potential therapeutic drugs that could effectively target hub DE-LRGs associated with MI (Fig. 8A). A total of 17 potential therapeutic agents were identified for COX20, 25 for AGK, and 26 for PDHX.

3.8. ceRNA regulatory network

A ceRNA network was constructed using the DE-LRGs. This network included 179 nodes, comprising 3 DEGs, 7 miRNAs, and 169 lncRNAs, with a total of 368 edges, highlighting the complex interactions among these genes (Fig. 8B). For instance, several lncRNAs (23, 41, 0, 72, 72, and 40, respectively) were predicted to competitively bind to hsa-mir-21-5p, hsa-mir-25-3p, hsa-mir-33a-3p, hsa-mir-17-5p, hsa-mir-93-5p, and hsa-mir-146a-5p, influencing the expression of COX20. Additionally, 36 lncRNAs were found to potentially regulate the expression of AGK and PDHX by competitively binding to hsa-mir-582-5p. The lncRNA NEAT1 was predicted to modulate the expression of COX20, AGK, and PDHX by interacting with hsa-mir-146a-5p, hsa-mir-17-5p, hsa-mir-93-5p, and hsa-mir-582-5p.

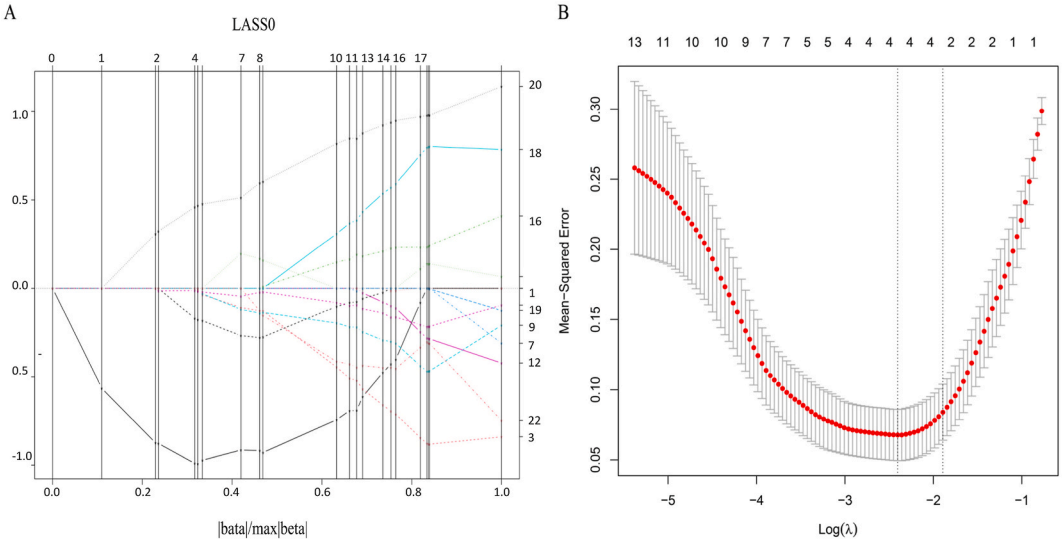


Fig. 3. (A, B) Screening DE-LRGs: 4 genes are screened by Lasso regression method (MI = 6, Control = 6).

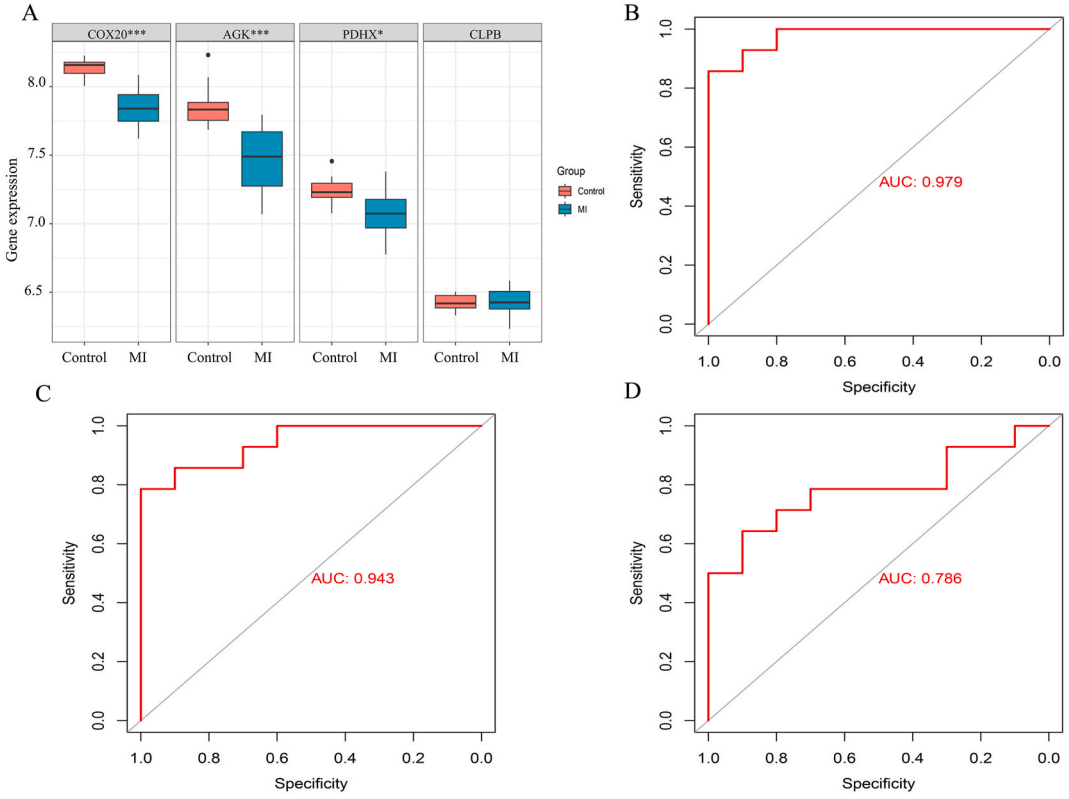


Fig. 4. (A) Expression of the hub DE-LRGs in the validation dataset (GSE61144, MI = 14, Control = 10). ROC curves were generated for three individual marker genes, (B) COX20, (C) AGK, and (D)PDHX, using the GSE61144 dataset.

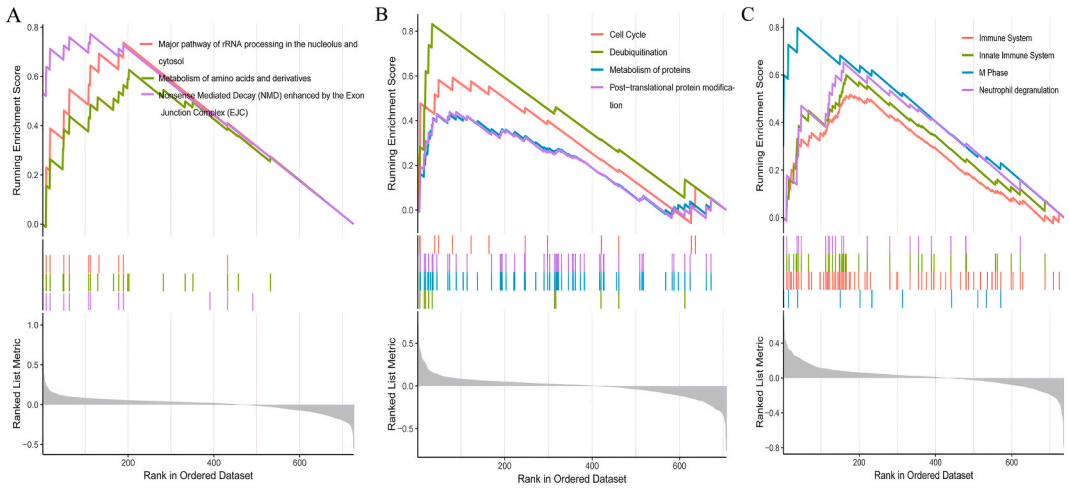


Fig. 5. (A) Single gene GSEA. 3 hub DE-LRGs are analyzed by single gene GSEA, and the related pathways of each gene are obtained (MI = 6, Control = 6).

4. Discussion

MI is a severe form of coronary artery disease caused by the narrowing and blockage of coronary arteries, which reduces oxygen supply to myocardial cells [19]. This condition results in a decline in mitochondrial oxidative phosphorylation and an increase in glycolytic activity within these cells [20,21]. Consequently, cardiac myocytes produce elevated levels of lactate, a finding that is consistent with numerous clinical studies reporting increased circulating lactate levels in MI patients [22]. Extensive clinical research

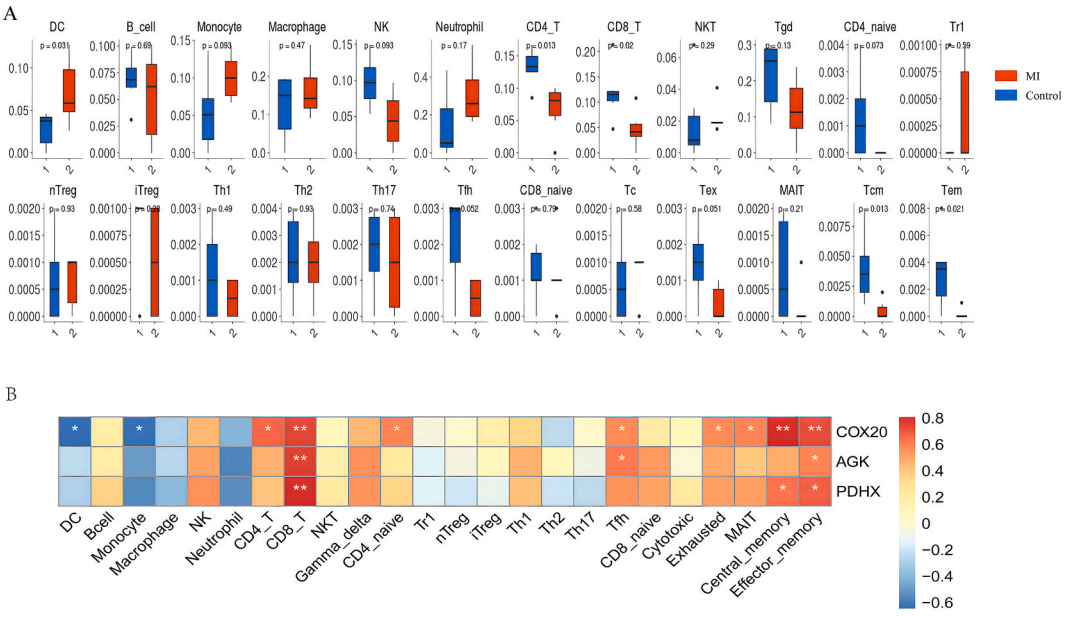


Fig. 6. (A) The analysis of immune cell infiltration (MI = 6, Control = 6). (B) Correlation between immune cells and 3 hub DE-LRGs, $*p < 0.05$; $**p < 0.01$; $***p < 0.001$.

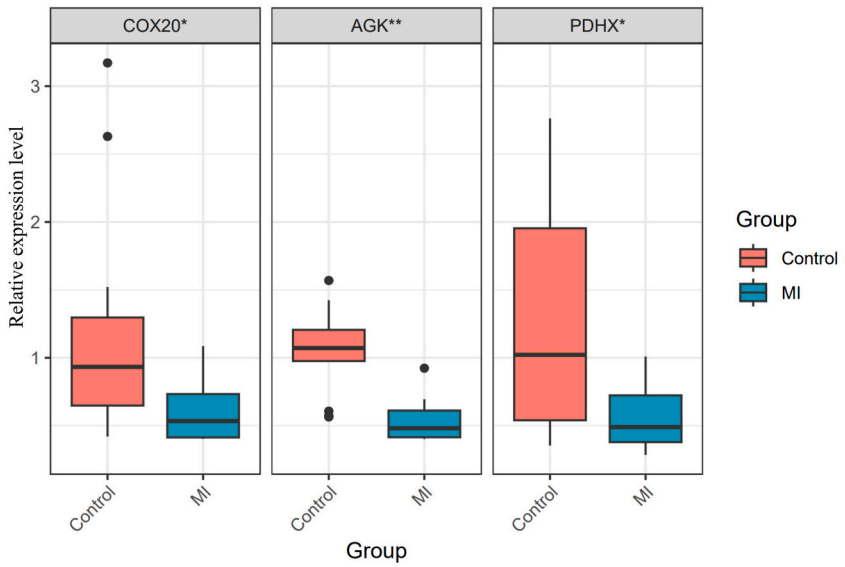


Fig. 7. Quantitative reverse transcription polymerase chain reaction (qRT−PCR) analyses of the expression levels of COX20, AGK and PDHX in peripheral blood samples isolated from controls (n = 7) and MI patients (n = 13), $*p < 0.05$; $**p < 0.01$; $***p < 0.001$.

has consistently shown that measuring circulating lactate levels has significant prognostic value for predicting adverse clinical outcomes in individuals with MI [6,23].

Several factors contribute to elevated blood lactate levels in individuals experiencing acute myocardial infarction (AMI), including increased glycolytic activity, inadequate tissue perfusion, insulin resistance, and impaired hemodynamics due to myocardial infarction [24–27]. Currently, there are limited basic research studies investigating the correlation between lactate and MI. Lactate influences gene transcription through lactylation of histones and non-histone proteins, a novel post-translational modification [28]. In the early phase of MI, lactylation of H3K18la in monocytes has been reported to stimulate the expression of genes involved in cardiac repairs, including *Lrg1*, *Vegf-a*, and *IL-10*, thereby promoting the healing of damaged hearts [29]. After MI, the lactylation of the transcription factor Snail1 in endothelial cells stimulates *TGF-β* gene expression, resulting in endothelial-to-mesenchymal transition and negatively impacting cardiac repair [13]. These findings highlight the crucial role of lactate in MI. Nevertheless, further research is required to

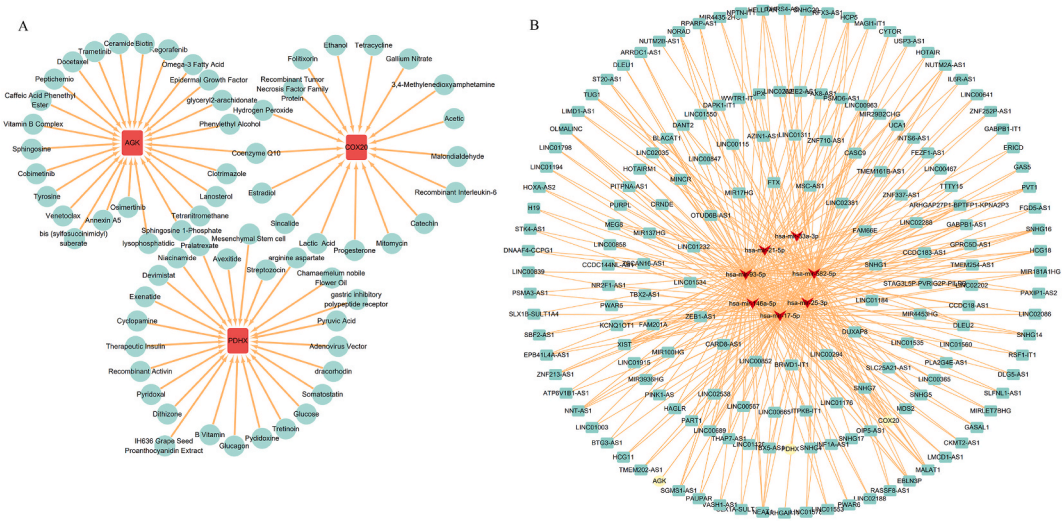


Fig. 8. (A) To predict the potential effective therapeutic drugs for 3 hub DE-LRGs. (B) ceRNA regulatory network. LncRNA, miRNA and mRNA interactions regulating of 3 hub DE-LRGs.

comprehensively understand the mechanism and predictive value of LRGs in MI patients.

In this study, bioinformatics methods were employed to analyze the DE-LRGs between MI patients and healthy individuals. A total of 23 LRGs were identified as differentially expressed, including MECP2, FASTKD2, MRPS28, CDK5, PYG, COX20, AGK, and PDHX. Enrichment analysis of DE-LRGs showed significant enrichment in BP related to fatty acid oxidation and lipid modification signaling pathways. KEGG enrichment analysis of these 23 genes further revealed their concentration in pathways such as fatty acid degradation and fatty acid metabolism. Recent studies have demonstrated that fatty acid oxidation can reduce ischemia-reperfusion injury in myocardial infarction and support cardiac regeneration. Lipids, which serve as a concentrated energy source, are crucial for the biological activities of mammals [30]. Lipid modification regulates the location and activity of signaling proteins under both physiological and pathophysiological conditions, including MI [31]. Previous research has established a correlation between lactate, fatty acids, and lipids [32]. These findings provide additional insights into the relationship between MI and fatty acid metabolism from the perspective of LRGs.

LASSO regression is commonly used for screening disease risk factors and developing prediction models. While it effectively identifies important variables, it does not provide causal interpretations. Thus, careful consideration of study design and data quality is essential [33]. In this study, LASSO regression was employed to identify hub genes associated with MI, which were then validated using the GSE61144 database and a small retrospective analysis. This approach led to the identification of COX20, AGK, and PDHX as potential biomarkers. The ROC curve analysis showed that these three hub genes (AUC >0.8) had strong discriminatory power between MI and control samples in the GSE61144 database. The reliability of these hub genes, identified through bioinformatics analysis, was further supported by qRT-PCR validation.

The COX20 gene encodes a protein involved in the cytochrome C oxidase assembly, a key component of the respiratory pathway [34]. Recent research has shown that the long non-coding RNA differentiation antagonizing non-protein coding RNA (DANCR) promotes arteriosclerosis progression by targeting the miR-214-5p/COX20 axis, suggesting that COX20 may play a role in the initiation of arteriosclerosis [35]. AGK, a kinase in the mitochondrial membrane, is involved in lipid and glycerolipid metabolism [36]. A study reported two cases where AGK mutations manifested as severe heart failure in infants, highlighting its critical role in cardiac function [37]. PDHX, located in the mitochondrial matrix, catalyzes the conversion of pyruvate to acetyl coenzyme A, a crucial step in energy metabolism [38]. There is a correlation between PDHX and myocardial energy metabolism disorders [39]. These findings suggest that lactate-related genes may be implicated in the development of myocardial infarction. The identification of specific lactate-related genes in this study lays a solid foundation for future research aimed at understanding the pathogenesis of MI.

Single-gene GSEA analysis revealed the upregulation of various pathways in MI, including those related to the metabolism of amino acids and derivatives, cell cycle regulation, and immune pathways. Numerous preclinical studies have suggested that the regulation of immunity-related cytokines, such as interleukin-4, -13, and −33, can influence cardiac function following MI [40]. A proteomics study has shown that the metabolism of amino acids and derivatives plays a role in endothelial dysfunction, a key factor in the onset and progression of atherothrombosis, which leads to MI [40]. Recent studies have highlighted a strong association between amino acid metabolism, cell cycle regulation, immune response, and lactate levels [7,41,42]. Notably, our study demonstrates that LRGs associated with MI are enriched in the same pathways linked to the metabolism of amino acids, cell Cycle, and immune response from an LRG perspective, further emphasizing the shared mechanisms underlying MI and this signaling pathway.

The analysis of immune cell infiltration predictions revealed significant differences in $CD4^+$T, $CD8^+$T, DC, TCM and TEM cells between patients with MI and healthy individuals. Animal studies have shown that $CD8^+$T T-cells act as regulators in the MI wound-healing process [43]. The expansion and activation of $CD4^+$T T cells in the heart have been identified to facilitate pathological cardiac

remodeling and dysfunction [44]. Subsequent investigation revealed a close association between the COX20 and $CD8^+$T, monocyte, central memory and effector memory cells, while the gene *AGK* and *PDHX* exhibited strong correlations with $CD8^+$T cells. Lactate accumulation can create an inhibitory immune microenvironment through various pathways characterized by T-cell infiltration [45]. These findings suggest that certain DE-LRGs may contribute to MI by impacting the immune system.

This study successfully identified candidate drugs that could target hub genes and established a ceRNA network. Epigenetic mechanisms, particularly those involving non-coding RNAs, play a crucial role in the development and progression of MI, exerting significant regulatory control over these processes [46]. Recent research has shown that hsa-mir-21-5p, hsa-mir-17-5p, and hsa-mir-146a-5p can serve as early biomarkers for MI, while hsa-mir-25-3p and hsa-mir-93-5p have notable clinical utility in managing the condition [47–51]. Among the potential therapeutic drugs identified were various supplements and vitamins, such as Omega-3 Fatty Acid, Coenzyme Q10, and Vitamin B Complex; antineoplastic agents, including Osimertinib, Regorafenib, and Trametinib; and steroid hormones like Estradiol and Progesterone. As a predictive targeted drug for DE-LRGs, Omega-3 Fatty Acid, Coenzyme Q10, Vitamin B, and Estradiol have been suggested to offer cardioprotective effects in MI, though their specific therapeutic benefits remain debated [52–55]. The efficacy of the predicted gene-targeted drugs and non-coding RNAs is still uncertain, and further research is needed to elucidate the specific pathways involved. Therefore, these selected drugs and non-coding RNAs warrant prospective investigation.

The findings presented in this study are based on a comprehensive secondary analysis of existing data, supplemented by validation in a small retrospective analysis. However, the sample size was relatively small, indicating a need for a prospective study with a larger cohort to better determine its clinical applicability. While our study focused on a subset of hub genes associated with DE-LRGs, there is a possibility that other important genes implicated in MI may have been overlooked. The methodologies used primarily involved correlation analysis, necessitating a cautious interpretation of the results: while we observed a significant correlation between alterations in LRGs and the pathogenesis of MI, the causal relationship remains uncertain. Therefore, further *in vitro* and *in vivo* studies will be essential to fully elucidate the role of these LRGs in the progression of MI.

5. Conclusion

In conclusion, our bioinformatics analysis identified 23 potential LRGs associated with MI. Notably, COX20, AGK, and PDHX have been identified as key regulators of lactate metabolism, highlighting their important role in the pathogenesis of MI. However, the specific mechanisms linking LRGs to MI remain unclear, and further research is needed to deepen our understanding of MI.

Fundings

This study was supported by the Natural Science Foundation of Xinjiang Province of China (2023D01C775).

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the People's Hospital of Xinjiang Uygur Autonomous Region (approval no. KY20240312074). It was carried out according to the standards of the Declaration of Helsinki. Written informed consent was obtained from all the participants prior to the enrollment of this study.

Availability of data and materials

The datasets used and analyzed during the current study are available from NCBI GEO: GSE141512 and GSE61144.

CRediT authorship contribution statement

Rui Xu: Methodology, Investigation. **YanYan Li:** Methodology, Investigation. **Hong Xu:** Data curation, Conceptualization. **HongMei Lai:** Investigation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Hong Xu and HongMei Lai contributed equally to this work as the Corresponding author.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e38152.

References

[1] S.S. Dani, A.N. Lone, Z. Javed, M.S. Khan, M. Zia Khan, E. Kaluski, et al., Trends in premature mortality from acute myocardial infarction in the United States, 1999 to 2019, J. Am. Heart Assoc. 11 (1) (2022) e021682, https://doi.org/10.1161/JAHA.121.021682. PubMed PMID: 34935456; PubMed Central PMCID: PMCPMC9075205.

[2] L. Hallqvist, F. Granath, M. Bell, Myocardial infarction after noncardiac surgery in Sweden: a national, retrospective observational cohort study, Br. J. Anaesth. 125 (1) (2020) 47–54, https://doi.org/10.1016/j.bja.2020.03.015. PubMed PMID: 32345437.

[3] R.P. Lustosa, F. Fortuni, P. van der Bijl, M.E. Mahdiui, J.M. Montero-Cabezas, M.V. Kostyukevich, et al., Changes in global left ventricular myocardial work indices and stunning detection 3 Months after ST-segment elevation myocardial infarction, Am. J. Cardiol. 157 (2021) 15–21, https://doi.org/10.1016/j.amjcard.2021.07.012. PubMed PMID: 34366114.

[4] M.V. Basalay, D.M. Yellon, S.M. Davidson, Targeting myocardial ischaemic injury in the absence of reperfusion, Basic Res. Cardiol. 115 (6) (2020) 63, https://doi.org/10.1007/s00395-020-00825-9. PubMed PMID: 33057804; PubMed Central PMCID: PMCPMC7560937.

[5] S. Dong, L. Qian, Z. Cheng, C. Chen, K. Wang, S. Hu, et al., Lactate and myocardiac energy metabolism, Front. Physiol. 12 (2021) 715081, https://doi.org/10.3389/fphys.2021.715081. PubMed PMID: 34483967; PubMed Central PMCID: PMCPMC8415870.

[6] Y. Wu, N. Huang, T. Sun, B. Zhang, S. Zhang, P. Zhang, et al., Association between normalized lactate load and in-hospital mortality in patients with acute myocardial infarction, Int. J. Cardiol. 399 (2024) 131658, https://doi.org/10.1016/j.ijcard.2023.131658. PubMed PMID: 38145657.

[7] S. Hui, J.M. Ghergurovich, R.J. Morscher, C. Jang, X. Teng, W. Lu, et al., Glucose feeds the TCA cycle via circulating lactate, Nature 551 (7678) (2017) 115–118, https://doi.org/10.1038/nature24057. PubMed PMID: 29045397; PubMed Central PMCID: PMCPMC5898814.

[8] E. Kocianova, V. Piatrikova, T. Golias, Revisiting the Warburg effect with focus on lactate, Cancers 14 (24) (2022), https://doi.org/10.3390/cancers14246028. PubMed PMID: 36551514; PubMed Central PMCID: PMCPMC9776395.

[9] B. Glancy, D.A. Kane, A.N. Kavazis, M.L. Goodwin, W.T. Willis, L.B. Gladden, Mitochondrial lactate metabolism: history and implications for exercise and disease, J. Physiol. 599 (3) (2021) 863–888, https://doi.org/10.1113/JP278930. PubMed PMID: 32358865; PubMed Central PMCID: PMCPMC8439166.

[10] D. Wu, K. Zhang, F.A. Khan, Q. Wu, N.S. Pandupuspitasari, Y. Tang, et al., The emerging era of lactate: a rising star in cellular signaling and its regulatory mechanisms, J. Cell. Biochem. 124 (8) (2023) 1067–1081, https://doi.org/10.1002/jcb.30458. PubMed PMID: 37566665.

[11] S. Bandopadhyay, I.M. Kamal, E. Padmanaban, D.D. Ghosh, S. Chakrabarti, S.S. Roy, Oncogene-mediated nuclear accumulation of lactate promotes epigenetic alterations to induce cancer cell proliferation, J. Cell. Biochem. 124 (4) (2023) 495–519, https://doi.org/10.1002/jcb.30381. PubMed PMID: 36999756.

[12] L. Chen, L. Huang, Y. Gu, W. Cang, P. Sun, Y. Xiang, Lactate-lactylation hands between metabolic reprogramming and immunosuppression, Int. J. Mol. Sci. 23 (19) (2022), https://doi.org/10.3390/ijms231911943. PubMed PMID: 36233246; PubMed Central PMCID: PMCPMC9569569.

[13] M. Fan, K. Yang, X. Wang, L. Chen, P.S. Gill, T. Ha, et al., Lactate promotes endothelial-to-mesenchymal transition via Snail1 lactylation after myocardial infarction, Sci. Adv. 9 (5) (2023) eadc9465, https://doi.org/10.1126/sciadv.adc9465. PubMed PMID: 36735787; PubMed Central PMCID: PMCPMC9897666.

[14] Y. Chen, W. Lai, K. Yang, B. Wu, D. Xie, C. Peng, Association between lactate/albumin ratio and prognosis in patients with acute myocardial infarction, Eur. J. Clin. Invest. 54 (1) (2024) e14094, https://doi.org/10.1111/eci.14094. PubMed PMID: 37725487.

[15] I. San-Millan, G.C. Sparagna, H.L. Chapman, V.L. Warkins, K.C. Chatfield, S.R. Shuff, et al., Chronic lactate exposure decreases mitochondrial function by inhibition of fatty acid uptake and cardiolipin alterations in neonatal rat cardiomyocytes, Front. Nutr. 9 (2022) 809485, https://doi.org/10.3389/fnut.2022.809485. PubMed PMID: 35308271; PubMed Central PMCID: PMCPMC8931465.

[16] M.B. Vestergaard, H. Ghanizada, U. Lindberg, N. Arngrim, O.B. Paulson, A. Gjedde, et al., Human cerebral perfusion, oxygen consumption, and lactate production in response to hypoxic exposure, Cerebr. Cortex 32 (6) (2022) 1295–1306, https://doi.org/10.1093/cercor/bhab294. PubMed PMID: 34448827; PubMed Central PMCID: PMCPMC8924433.

[17] G. Osmak, N. Baulina, P. Koshkin, O. Favorova, Collapsing the list of myocardial infarction-related differentially expressed genes into a diagnostic signature, J. Transl. Med. 18 (1) (2020) 231, https://doi.org/10.1186/s12967-020-02400-1. PubMed PMID: 32517814; PubMed Central PMCID: PMCPMC7285786.

[18] H.J. Park, J.H. Noh, J.W. Eun, Y.S. Koh, S.M. Seo, W.S. Park, et al., Assessment and diagnostic relevance of novel serum biomarkers for early decision of ST-elevation myocardial infarction, Oncotarget 6 (15) (2015) 12970–12983, https://doi.org/10.18632/oncotarget.4001. PubMed PMID: 26025919; PubMed Central PMCID: PMCPMC4536992.

[19] A. Schafer, T. Konig, J. Bauersachs, M. Akin, Novel therapeutic strategies to reduce reperfusion injury after acute myocardial infarction, Curr. Probl. Cardiol. 47 (12) (2022) 101398, https://doi.org/10.1016/j.cpcardiol.2022.101398. PubMed PMID: 36108813.

[20] C.J. Zuurbier, L. Bertrand, C.R. Beauloye, I. Andreadou, M. Ruiz-Meana, N.R. Jespersen, et al., Cardiac metabolism as a driver and therapeutic target of myocardial infarction, J. Cell Mol. Med. 24 (11) (2020) 5937–5954, https://doi.org/10.1111/jcmm.15180. PubMed PMID: 32384583; PubMed Central PMCID: PMCPMC7294140.

[21] H. Zhu, S. Toan, D. Mui, H. Zhou, Mitochondrial quality surveillance as a therapeutic target in myocardial infarction, Acta Physiol. 231 (3) (2021) e13590, https://doi.org/10.1111/apha.13590. PubMed PMID: 33270362.

[22] I.H. Park, H.K. Cho, J.H. Oh, W.J. Chun, Y.H. Park, M. Lee, et al., Clinical significance of serum lactate in acute myocardial infarction: a cardiac magnetic resonance imaging study, J. Clin. Med. 10 (22) (2021), https://doi.org/10.3390/jcm10225278. PubMed PMID: 34830561; PubMed Central PMCID: PMCPMC8618836.

[23] H. Zhang, K. Kang, S. Chen, Q. Su, W. Zhang, L. Zeng, et al., High serum lactate dehydrogenase as a predictor of cardiac insufficiency at follow-up in elderly patients with acute myocardial infarction, Arch. Gerontol. Geriatr. 117 (2024) 105253, https://doi.org/10.1016/j.archger.2023.105253. PubMed PMID: 37956585.

[24] G. Hernandez, G.A. Ospina-Tascon, L.P. Damiani, E. Estenssoro, A. Dubin, J. Hurtado, et al., Effect of a resuscitation strategy targeting peripheral perfusion status vs serum lactate levels on 28-day mortality among patients with septic shock: the ANDROMEDA-SHOCK randomized clinical trial, JAMA 321 (7) (2019) 654–664, https://doi.org/10.1001/jama.2019.0071. PubMed PMID: 30772908; PubMed Central PMCID: PMCPMC6439620 Pulsion medical systems outside the submitted work. Dr Cecconi reported receiving personal fees from Edwards Lifesciences, LiDCO, Directed Systems, and Cheeath Medical outside the submitted work. No other authors reported disclosures.

[25] H. Bazaraa, S. Roby, E. Salah, H. Algebaly, Assessment of tissue perfusion using the peripheral perfusion index and lactate clearance in shock in pediatric patients, Shock 56 (6) (2021) 933–938, https://doi.org/10.1097/SHK.0000000000001811. PubMed PMID: 34014888.

[26] Y. Lin, M. Bai, S. Wang, L. Chen, Z. Li, C. Li, et al., Lactate is a key mediator that links obesity to insulin resistance via modulating cytokine production from adipose tissue, Diabetes 71 (4) (2022) 637–652, https://doi.org/10.2337/db21-0535. PubMed PMID: 35044451.

[27] S. Chen, Y. Zou, C. Song, K. Cao, K. Cai, Y. Wu, et al., The role of glycolytic metabolic pathways in cardiovascular disease and potential therapeutic approaches, Basic Res. Cardiol. 118 (1) (2023) 48, https://doi.org/10.1007/s00395-023-01018-w. PubMed PMID: 37938421; PubMed Central PMCID: PMCPMC10632287.

[28] E. Dai, W. Wang, Y. Li, D. Ye, Y. Li, Lactate and lactylation: Behind the development of tumors (2024) [updated Jun 1; cited 591]. 2024/04/20:[216896]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/38641309.

[29] N. Wang, W. Wang, X. Wang, G. Mang, J. Chen, X. Yan, et al., Histone lactylation boosts reparative gene activation post-myocardial infarction, Circ. Res. 131 (11) (2022) 893–908, https://doi.org/10.1161/CIRCRESAHA.122.320488. PubMed PMID: 36268709.

[30] E. Li, H. Liu, Y. Li, L. Liu, F. Wang, D. Li, et al., Determination of net energy content of dietary lipids fed to growing pigs using indirect calorimetry, J. Anim. Sci. 96 (6) (2018) 2184–2194, https://doi.org/10.1093/jas/sky132. PubMed PMID: 29668940; PubMed Central PMCID: PMCPMC6095357.

[31] C. Maldonado, M.D. Nguyen, P. Bauer, S. Nakamura, S.J. Khundmiri, G. Perez-Abadia, et al., Rapid lipid modification of endothelial cell membranes in cardiac ischemia/reperfusion injury: a novel therapeutic strategy to reduce infarct size, Cardiovasc. Drugs Ther. 35 (1) (2021) 113–123, https://doi.org/10.1007/s10557-020-07101-x. PubMed PMID: 33079319; PubMed Central PMCID: PMCPMC8376233.

[32] G.J. van der Vusse, M.J. de Groot, Interrelationship between lactate and cardiac fatty acid metabolism, Mol. Cell. Biochem. 116 (1–2) (1992) 11–17, https://doi.org/10.1007/BF01270563. PubMed PMID: 1480138.

[33] Y. Li, F. Lu, Y. Yin, Applying logistic LASSO regression for the diagnosis of atypical Crohn's disease, Sci. Rep. 12 (1) (2022) 11340, https://doi.org/10.1038/s41598-022-15609-5. PubMed PMID: 35790774; PubMed Central PMCID: PMCPMC9256608.
[34] M. Bourens, A. Boulet, S.C. Leary, A. Barrientos, Human COX20 cooperates with SCO1 and SCO2 to mature COX2 and promote the assembly of cytochrome c oxidase, Hum. Mol. Genet. 23 (11) (2014) 2901–2913, https://doi.org/10.1093/hmg/ddu003. PubMed PMID: 24403053; PubMed Central PMCID: PMCPMC4014192.
[35] R. Zhang, Y. Hao, J. Zhang, The lncRNA DANCR promotes development of atherosclerosis by regulating the miR-214-5p/COX20 signaling pathway, Cell. Mol. Biol. Lett. 27 (1) (2022) 15, https://doi.org/10.1186/s11658-022-00310-2. PubMed PMID: 35177003; PubMed Central PMCID: PMCPMC8903577.
[36] C.W. Wu, M. Caha, L. Smoot, D.J. Harris, A.E. Roberts, S. Sacharow, et al., Sengers syndrome and AGK-related disorders - minireview of phenotypic variability and clinical outcomes in molecularly confirmed cases, Mol. Genet. Metabol. 139 (3) (2023) 107626, https://doi.org/10.1016/j.ymgme.2023.107626. PubMed PMID: 37354892.
[37] B. Wang, Z. Du, G. Shan, C. Yan, V.W. Zhang, Z. Li, Case report: two Chinese infants of sengers syndrome caused by mutations in AGK gene, Front Pediatr 9 (2021) 639687, https://doi.org/10.3389/fped.2021.639687. PubMed PMID: 34164355; PubMed Central PMCID: PMCPMC8215120.
[38] J. Inoue, M. Kishikawa, H. Tsuda, Y. Nakajima, T. Asakage, J. Inazawa, Identification of PDHX as a metabolic target for esophageal squamous cell carcinoma, Cancer Sci. 112 (7) (2021) 2792–2802, https://doi.org/10.1111/cas.14938. PubMed PMID: 33964039; PubMed Central PMCID: PMCPMC8253269.
[39] Y. Zhang, K. Yin, D. Wang, Y. Wang, H. Lu, H. Zhao, et al., Polystyrene microplastics-induced cardiotoxicity in chickens via the ROS-driven NF-kappaB-NLRP3-GSDMD and AMPK-PGC-1alpha axes, Sci. Total Environ. 840 (2022) 156727, https://doi.org/10.1016/j.scitotenv.2022.156727. PubMed PMID: 35714743.
[40] J.Y. Xu, Y.Y. Xiong, X.T. Lu, Y.J. Yang, Regulation of type 2 immunity in myocardial infarction, Front. Immunol. 10 (2019) 62, https://doi.org/10.3389/fimmu.2019.00062. PubMed PMID: 30761134; PubMed Central PMCID: PMCPMC6362944.
[41] M. Hortova-Kohoutkova, J.G. Filep, J. Fric, Editorial: lactate metabolism and regulation of the immune response, Front. Immunol. 13 (2022) 1103379, https://doi.org/10.3389/fimmu.2022.1103379. PubMed PMID: 36569911; PubMed Central PMCID: PMCPMC9788132.
[42] W. Liu, Y. Wang, L.H.M. Bozi, P.D. Fischer, M.P. Jedrychowski, H. Xiao, et al., Lactate regulates cell cycle by remodelling the anaphase promoting complex, Nature 616 (7958) (2023) 790–797, https://doi.org/10.1038/s41586-023-05939-3. PubMed PMID: 36921622.
[43] Y. Zaidi, A. Corker, V.Y. Vasileva, K. Oviedo, C. Graham, K. Wilson, et al., Chronic Porphyromonas gingivalis lipopolysaccharide induces adverse myocardial infarction wound healing through activation of CD8(+) T cells, Am. J. Physiol. Heart Circ. Physiol. 321 (5) (2021) H948–H962, https://doi.org/10.1152/ajpheart.00082.2021. PubMed PMID: 34597184; PubMed Central PMCID: PMCPMC8616607.
[44] H. Inui, M. Nishida, M. Ichii, H. Nakaoka, M. Asaji, S. Ide, et al., XCR1(+) conventional dendritic cell-induced CD4(+) T helper 1 cell activation exacerbates cardiac remodeling after ischemic myocardial injury, J. Mol. Cell. Cardiol. 176 (2023) 68–83, https://doi.org/10.1016/j.yjmcc.2023.01.011. PubMed PMID: 36739942.
[45] Y.T. Zhang, M.L. Xing, H.H. Fang, W.D. Li, L. Wu, Z.P. Chen, Effects of lactate on metabolism and differentiation of CD4(+)T cells, Mol. Immunol. 154 (2023) 96–107, https://doi.org/10.1016/j.molimm.2022.12.015. PubMed PMID: 36621062.
[46] G. Zhang, H. Sun, Y. Zhang, H. Zhao, W. Fan, J. Li, et al., Characterization of dysregulated lncRNA-mRNA network based on ceRNA hypothesis to reveal the occurrence and recurrence of myocardial infarction, Cell Death Dis. 4 (2018) 35, https://doi.org/10.1038/s41420-018-0036-7. PubMed PMID: 29531832; PubMed Central PMCID: PMCPMC5841419.
[47] L. Xu, L. Tian, Z. Yan, J. Wang, T. Xue, Q. Sun, Diagnostic and prognostic value of miR-486-5p, miR-451a, miR-21-5p and monocyte to high-density lipoprotein cholesterol ratio in patients with acute myocardial infarction, Heart Ves. 38 (3) (2023) 318–331, https://doi.org/10.1007/s00380-022-02172-2. PubMed PMID: 36214846; PubMed Central PMCID: PMCPMC9898386.
[48] S. Xue, D. Liu, W. Zhu, Z. Su, L. Zhang, C. Zhou, et al., Circulating MiR-17-5p, MiR-126-5p and MiR-145-3p are novel biomarkers for diagnosis of acute myocardial infarction, Front. Physiol. 10 (2019) 123, https://doi.org/10.3389/fphys.2019.00123. PubMed PMID: 30833907; PubMed Central PMCID: PMCPMC6387945.
[49] A.I. Scarlatescu, T. Barbalata, A.V. Sima, C. Stancu, L.S. Niculescu, M.M. Micheu, miR-146a-5p, miR-223-3p and miR-142-3p as potential predictors of major adverse cardiac events in young patients with acute ST elevation myocardial infarction-added value over left ventricular myocardial work indices, Diagnostics 12 (8) (2022), https://doi.org/10.3390/diagnostics12081946. PubMed PMID: 36010296; PubMed Central PMCID: PMCPMC9406722.
[50] Y. Peng, J.L. Zhao, Z.Y. Peng, W.F. Xu, G.L. Yu, Exosomal miR-25-3p from mesenchymal stem cells alleviates myocardial infarction by targeting pro-apoptotic proteins and EZH2, Cell Death Dis. 11 (5) (2020) 317, https://doi.org/10.1038/s41419-020-2545-6. PubMed PMID: 32371945; PubMed Central PMCID: PMCPMC7200668.
[51] J. Liu, M. Jiang, S. Deng, J. Lu, H. Huang, Y. Zhang, et al., miR-93-5p-Containing exosomes treatment attenuates acute myocardial infarction-induced myocardial damage, Mol. Ther. Nucleic Acids 11 (2018) 103–115, https://doi.org/10.1016/j.omtn.2018.01.010. PubMed PMID: 29858047; PubMed Central PMCID: PMCPMC5852413.
[52] A. Macchia, S. Monte, F. Pellegrini, M. Romero, D. Ferrante, H. Doval, et al., Omega-3 fatty acid supplementation reduces one-year risk of atrial fibrillation in patients hospitalized with myocardial infarction, Eur. J. Clin. Pharmacol. 64 (6) (2008) 627–634, https://doi.org/10.1007/s00228-008-0464-z. PubMed PMID: 18309477.
[53] W. Pan, G. Zhou, M. Hu, G. Li, M. Zhang, H. Yang, et al., Coenzyme Q10 mitigates macrophage mediated inflammation in heart following myocardial infarction via the NLRP3/IL1beta pathway, BMC Cardiovasc. Disord. 24 (1) (2024) 76, https://doi.org/10.1186/s12872-024-03729-x. PubMed PMID: 38281937; PubMed Central PMCID: PMCPMC10822151.
[54] A. Tavani, C. Pelucchi, M. Parpinel, E. Negri, C. La Vecchia, Folate and vitamin B(6) intake and risk of acute myocardial infarction in Italy, Eur. J. Clin. Nutr. 58 (9) (2004) 1266–1272, https://doi.org/10.1038/sj.ejcn.1601960. PubMed PMID: 15054443.
[55] S. Beer, M. Reincke, M. Kral, F. Callies, H. Stromer, C. Dienesch, et al., High-dose 17beta-estradiol treatment prevents development of heart failure post-myocardial infarction in the rat, Basic Res. Cardiol. 102 (1) (2007) 9–18, https://doi.org/10.1007/s00395-006-0608-1. PubMed PMID: 16817027.