Cardiomyopathy Mechanisms: Meta-analysis of Expression Profiles for Z-disc-associated Genes Across Multiple Microarray Datasets

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***Abstract*–Cardiomyopathies (CM) encompass ischemic and non-ischemic subtypes, with evidence increasingly supporting the involvement of Z-disc-associated genes in their pathogenesis. This study conducted a meta-analysis of ten such genes across six microarray datasets, including 142 samples, to explore their expression patterns in CM. Statistical analyses revealed significantly higher expression levels in CM groups compared to controls, with ischemic CM showing greater variability and heterogeneity than non-ischemic CM. Differential expression analysis highlighted substantial downregulation of Filamin C in non-ischemic CM and significant upregulation of PDZ and LIM domain proteins in ischemic CM. These findings enhance our understanding of the molecular mechanisms underlying CM and suggest potential therapeutic targets.**

Keywords-Cardiomyopathies; Z-disc; Gene expression

I. INTRODUCTION

Cardiomyopathies (CM) are a diverse group of cardiac disorders, broadly categorized into non-ischemic forms, primarily caused by genetic factors or non-coronary conditions, and ischemic subtypes, resulting from reduced myocardial blood flow due to coronary artery disease [1]. The Z-disc, a crucial sarcomeric structure, maintains cardiac muscle integrity and function, serving as an anchor point for thin filaments and a mechanotransduction signaling hub [2]. Several Z-disc-associated genes have been implicated in various cardiomyopathy subtypes [2][3]. To date, no systematic analysis has been conducted on the expression levels of these genes across different cardiomyopathy subtypes.

II. RESULTS

This study focused on ten genes selected based on two criteria: structural or functional association with the Z-disc and published involvement in cardiomyopathy in human and/or animal models. Their expression patterns were compared across control, non-ischemic CM, and ischemic CM to elucidate their role in different CM subtypes. We employed a meta-analysis approach, integrating data from six microarray datasets (Table I). Expression data from 3,882 genes shared across 142 samples were retrieved from GEO, normalized, and merged using the ComBat function (sva package). Differential expression analysis was conducted using the limma package in R.

TABLE I. SUMMARY OF GEO SERIES AND SAMPLES IN THE STUDY

GEO Series	Control	Non-Ischemic CM	Ischemic CM	Total Samples
GDS651 / GSE1145	11	15	11	37
GDS1362 / GSE1869	6	21	10	37
GDS2205 / GSE3585	5	7	-	12
GDS2206 / GSE3586	15	13	-	28
GDS3115 / GSE9128	3	4	4	11
GDS4772 / GSE42955	5	12	-	17

Both CM subtypes showed distinct expression patterns compared to the control group, with some variations between subtypes. Statistical analyses revealed significantly higher median expression values in CM groups, highest in ischemic CM, intermediate in non-ischemic CM, and lowest in controls ($p < 2.2e\text{-}16$).

The ten target genes mirrored these overall trends. Analyzing these genes separately showed narrow interquartile ranges (IQRs) in non-ischemic CM samples, while ischemic CM exhibited wider IQRs, validating the selection of these genes as representative markers. Fold change analysis ($p < 0.05$, $|\log2Fc| > 0.5$) revealed substantial downregulation of Filamin C and slight upregulation of PDZ and LIM domain protein 3 in non-ischemic CM. In ischemic CM, Alpha-actinin-2 and PDZ and LIM domain protein 5 were moderately upregulated, while FH1/FH2 domain-containing protein 3, LIM domain-binding protein 3, and PDZ and LIM domain protein 3 showed the most profound upregulation.

Multiple mutations in the target genes of this study have been previously associated with cardiomyopathies in the literature. A notable example is the Filamin C gene, where mutations have been linked to non-ischemic cardiomyopathy [4]. Our meta-analysis revealed substantial downregulation of Filamin C in non-ischemic

CM samples, aligning with clinical observations. This concordance validates our meta-analysis approach and underscores the potential clinical relevance of our findings.

III. CONCLUSION

This study represents the first comprehensive meta-analysis of Z-disc-associated gene expression across multiple CM subtypes, providing a unique perspective on the role of these genes in CM pathogenesis. Overall, gene expression levels differed significantly among the three groups, with several Z-disc-associated genes exhibiting notable up- or down-regulation in either non-ischemic or ischemic CM compared to the control group. Our comprehensive description of gene expression distributions, coupled with the differential expression analysis of ten target Z-disc-associated genes across multiple microarray datasets, provides valuable insights into the pathogenesis of cardiomyopathies. These findings may contribute to the identification of novel therapeutic targets and enhance our understanding of the molecular mechanisms underlying different forms of cardiomyopathy.

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