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Meta-analysis of mitochondrial ubiquitin ligase-1 (MUL1) and its relationship with cardiac ischemia/reperfusion injury

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Abstract:. Myocardial infarction develops when major coronary arteries supplying the heart with blood become damaged or blocked due to atheroma limiting blood flow. These ischemic and reperfusion events cause functional and structural alterations of mitochondria. The mitochondrial protein E3 ubiquitin ligase 1 (MUL1) has been involved in heart disease in preclinical models, regulating apoptosis, mitophagy, and mitochondrial dynamics. However, there is little information on how MUL1 exerts its biological role in response to ischemia/reperfusion in patients. Through bioinformatics, we performed a meta-analysis of transcriptomic studies in 5 clinical studies in patients with myocardial infarction to elucidate the expression profile of MUL1 under this condition. We observed that the expression of MUL1 was not altered in patients with coronary artery disease and myocardial infarction. However, we identified MUL1 expression networks where the expression of TLR4, DYSF, and CTSD genes was inhibited in the study condition. These molecules have been associated with cardiac ischemia/reperfusion injury. Under this observation, MUL1 putatively has a regulatory effect on the expression of these genes. Thus, ischemia/reperfusion-induced cardiac damage could be mediated by MUL1 by unknown intracellular pathways in the context of myocardial infarction. However, their roles will be addressed in future studies **Funding: FONDECYT 1200490. & FONDAP 15130011** .

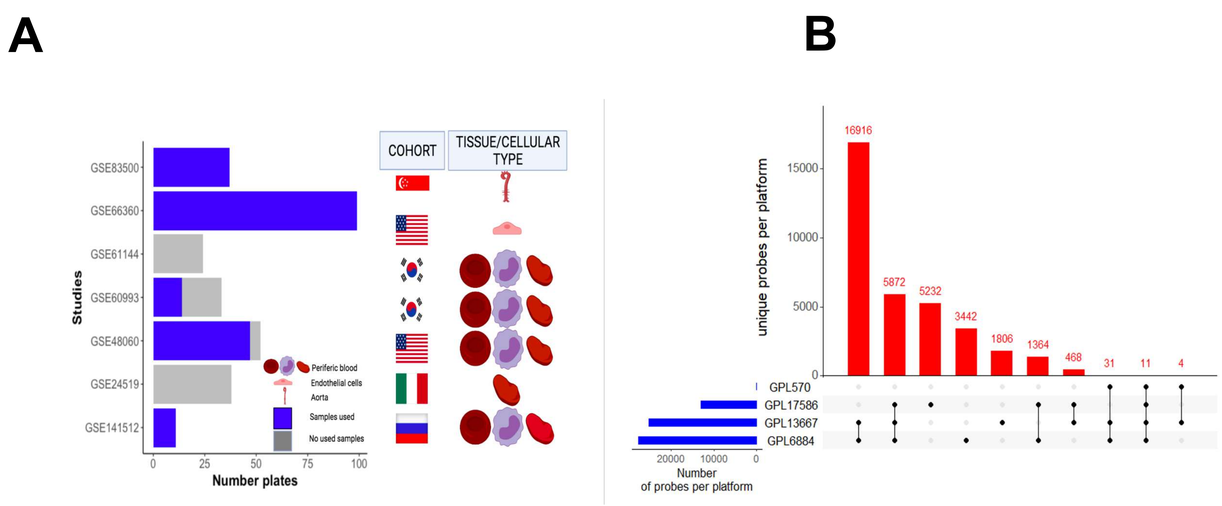

Figure 1.Selection of clinical studies of trancriptomic analysis of patients with coronary artery disease and myoardial infarction. A. Graph shows the GEO accession number of each study, together with the country of origin and the type of cell or tissue used. Also is shown the samples used, not used and the studies that were not considered for further analysis.**B.** Shared genes between microarray platforms of RNAs.The size of the bar represents the number of mRNAs shared between the platforms.

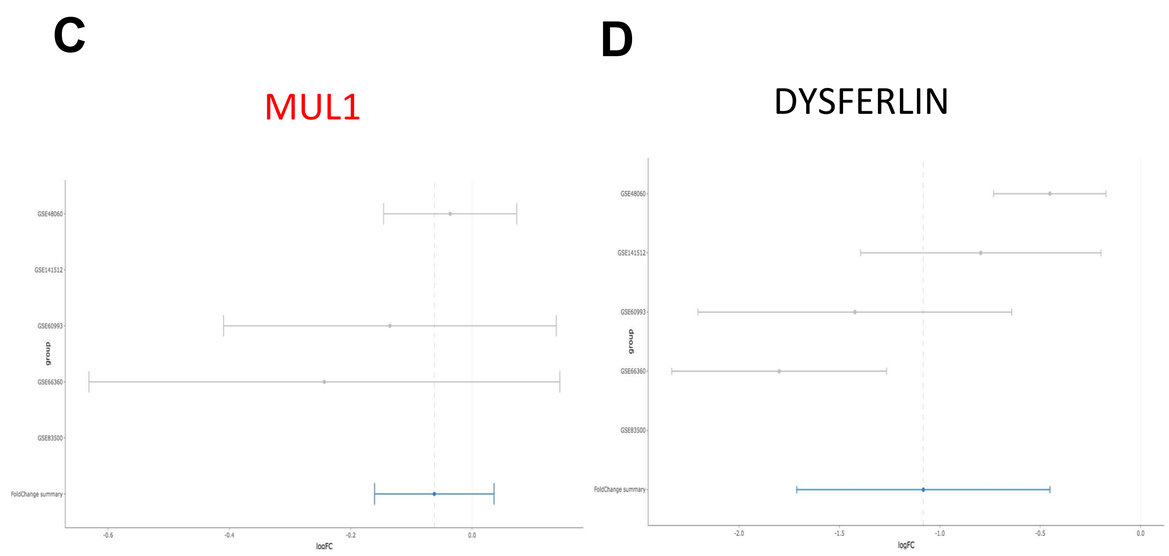

Figure 3. Gene fold change of independent studies on myocardial infarction in humans. MUL1 (**C**) and Dysferlin (**D**) gene fold change in selected studies. Fold change summary of MUL1 (red) and DYSF (black) is shown.

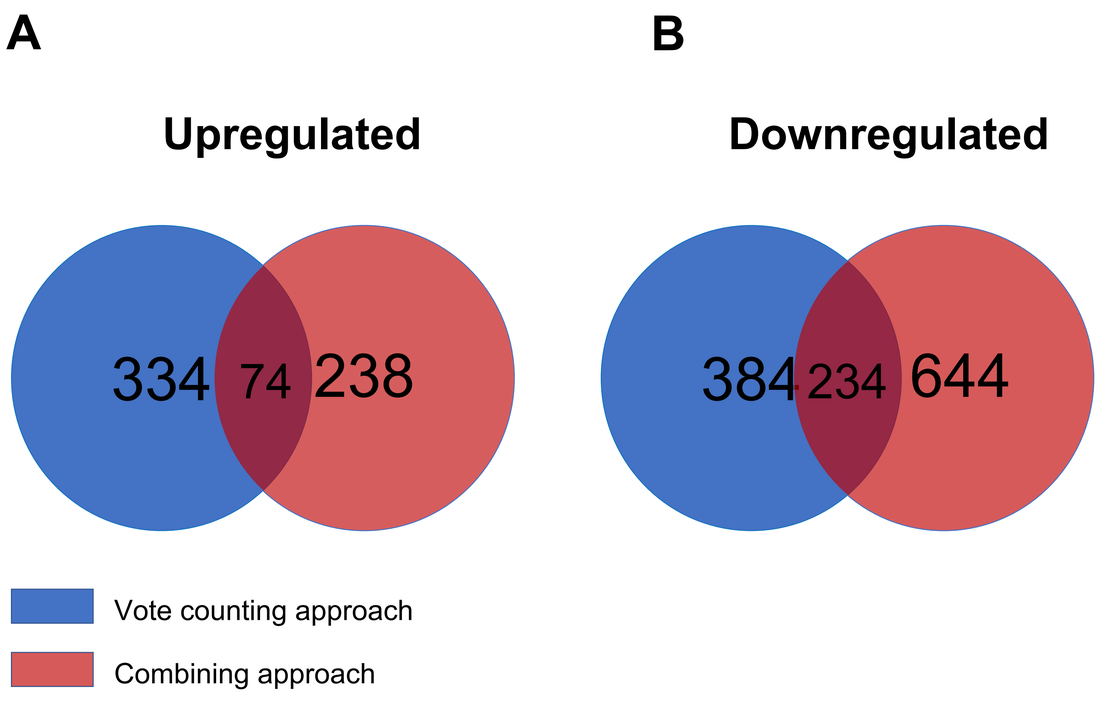

Figure 2. Gene fold change of independent studies on myocardial infarction in humans. A & B. Venn diagrams of differential expressed genes per study obtained using the Vote counting approach (blue) and Combining-approach (red). The intersection represent the number of genes shared between both approaches

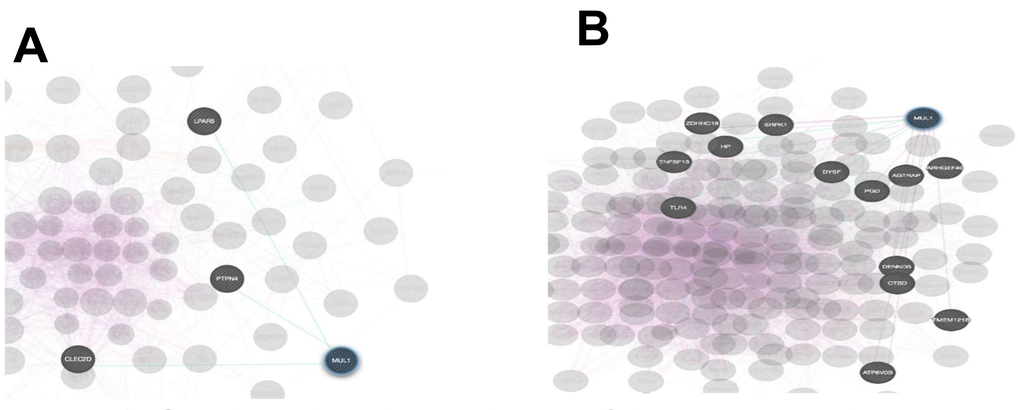

Figure 4. Genetic interaction network of the gene and transcribed MUL1. A. Genetic interaction network of MUL1 with studies-upregulated genes. **B.** Genetic interactions of MUL1 with studies-downregulated genes. **A & B.** Genes with no seen interaction with MUL1 are shown as brighter spheres and those which have interaction are shown as grey spheres**.** Genes that have biological relevance regarding myocardial ischemia/reperfusion injury and are shown to interact with MUL1 are DYSF, TLR4 and CTSD genes.

Conclusion: Myocardial infarction process in human does not alter the expression of MUL1 gene. In this sense, ischemia/reperfusion-induced cardiac damage could be mediated by MUL1 through unknown intracellular pathways in the context of myocardial infarction . However, the role of MUL1 in myocardial infarction will be clarified in future studies**.**