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Transcriptional Reprogramming of Senescent Human Cardiomyocytes by Cardiometabolic and Geroprotective Compounds

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Abstract

Introduction: Cellular senescence is a fundamental hallmark of aging and a critical driver of cardiometabolic disease progression. In cardiomyocytes, senescence is characterized by stable cell-cycle arrest, chromatin remodeling, mitochondrial dysfunction, and acquisition of a pro-inflammatory senescence-associated secretory phenotype (SASP). Although multiple cardiometabolic and geroprotective compounds are clinically used or experimentally proposed, their capacity to transcriptionally modulate senescent cardiomyocytes remains insufficiently defined. This study aimed to systematically evaluate how diverse pharmacological interventions remodel the transcriptome of senescent human pluripotent stem cell–derived cardiomyocytes and to quantify their potential to reverse a defined senescence gene expression signature.

Methodology: Senescent cardiomyocytes (K-cardiom-sen) were treated with IGF-1, insulin, glucagon, metformin, rapamycin, bisoprolol, dasatinib, and quercetin at three concentrations each. RNA sequencing was performed, and differential gene expression was calculated relative to untreated senescent controls using DESeq2. A senescence transcriptional signature was derived from senescent versus non-senescent cardiomyocytes. Treatment-induced log2 fold changes were integrated with this signature to calculate a senescence-reversal score based on Spearman correlation with the inverse senescence profile. Differential expression thresholds were defined as adjusted p-value <0.05 and $|\log2FC| \geq 1$. Gene-level and compound-level summaries were generated, including DEG counts, directionality, and dose–response relationships.

Results & Discussion: Substantial heterogeneity in transcriptomic remodeling was observed across compounds. Glucagon and insulin induced extensive global gene expression changes, indicating strong metabolic reprogramming. In contrast, metformin and quercetin showed comparatively modest but consistent effects. Importantly, the magnitude of differentially

expressed genes did not directly predict senescence modulation. Dasatinib demonstrated the strongest senescence-reversal score, particularly at low-to-intermediate doses, characterized by downregulation of cell-cycle arrest markers (e.g., CDKN1A-associated pathways), inflammatory mediators, and chromatin stress signatures. Metformin and IGF-1 displayed weaker yet directionally consistent reversal patterns, whereas glucagon primarily induced broad metabolic shifts without coherent reversal of senescence-associated pathways. These findings highlight the distinction between large-scale transcriptomic remodeling and targeted senescence modulation. **Conclusion:** Pharmacological interventions differ markedly in both magnitude and biological direction of transcriptomic effects in senescent cardiomyocytes. Integrative reversal scoring enables discrimination between global metabolic remodeling and genuine senescence-modulating activity. Dasatinib emerged as the most coherent senescence-reversal candidate in this model. This framework provides a systematic strategy for prioritizing interventions targeting cardiac aging and cardiometabolic resilience.

Keywords: Cardiomyocyte senescence, Transcriptomics, Geroprotection, Pharmacological reprogramming, Dose-response

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