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NOVEL APPROACHES FOR ENDOGENOUS HEART REPAIR

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Background: Heart failure is often caused by loss of cardiac cells that are unable to re-enter the cell cycle for regeneration. Numerous attempts to identify such cell cycle regulators that could induce cell division of cardiomyocytes, or other cell types, have resulted in nuclear division (karyokinesis), but inefficient cleavage into two distinct daughter cells (cytokinesis) and subsequent survival. Such strategies stimulate cell cycle markers in no more than 1% of cardiomyocytes, limiting their utility.

Methods and results: Here, we took a combinatorial approach to screen for cell cycle factors and conditions that could recapitulate the fetal state of cardiomyocyte division. We found that ectopic introduction of the Cdk1/CyclinB1 and the Cdk4/CyclinD1 complexes promoted cell division in at least 15% of mouse and human cardiomyocytes *in vitro*. Rigorous assessment of cell division *in vivo* with the cardiac specific (-MHC) Cre-recombinase dependent Mosaic Analysis with Double Markers (MADM) lineage tracing system revealed similar efficiency in adult mouse hearts, leading to cardiac regeneration upon delivery of cell cycle regulators immediately after myocardial infarction and even one week after injury. This ability of cardiac regeneration resulted in significant improvement in cardiac function following acute or subacute myocardial infarction. Intra-myocardial injection of adenoviruses encoding the 4 cell cycle gene either injected at the time of the infarction or one week following myocardial infarction resulted in significant improvement in cardiac function as assessed by echocardiography and MRI compared to animals received control virus. Furthermore, chemical inhibition of Tgf and Wee1 made CDK1 and cyclin B dispensable, simplifying the minimal genetic requirement.

Conclusion: These findings reveal a discrete combination of genes that can unlock the proliferative potential in cells that had permanently exited the cell cycle.

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