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A meta-analysis and systematic review of myocardial infarction-induced cardiomyocyte proliferation in adult mouse heart

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 2 December 2024 and was last updated on 2 December 2024.

INTRODUCTION

Review question / Objective The proliferation capacity of adult cardiomyocytes is very limited in the normal adult mammalian heart. Previous studies implied that cardiomyocyte proliferation increases after injury stimulation, but the result is controversial partly due to different methodologies. We aim to evaluate whether myocardial infarction (MI) stimulates cardiomyocyte proliferation in adult mice.

Condition being studied Myocardial infarction (MI) is a life-threatening heart disease characterized by the occlusion in the coronary arteries, leading to a great loss of functional cardiomyocytes. The current therapies such as reperfusion therapy and medications can only partially delay the pathological remodeling process, but they do not replenish cardiomyocyte numbers to replace the lost myocardium.

Fetal and neonatal cardiomyocytes have a remarkable ability to proliferate. When MI or apex resection injury was induced in a postnatal day 1 (P1) mice/pigs, the remaining cardiomyocytes can proliferate to repair the injury and fully restore the cardiac function after eight weeks. It implies that injuries could stimulate cardiomyocyte proliferation and generate certain amounts of new cardiomyocytes. However, this regenerative capacity diminishes within the first week after birth, injuries at P7 could not recover but instead replaced with scar tissue.

METHODS

Search strategy A comprehensive literature search was conducted through PubMed/Medline, Embase, and Web of Science databases from 1 January 2000 to 21 December 2023. Terms (Take PubMed/Medline as an example) included (((("Myocardial Infarction"[MeSH]) OR ("Myocardial Reperfusion Injury"[Mesh])) OR ((((cardiac) OR

(heart)) OR (myocardial)) AND (((infarction) OR (ischemia)) OR ("left anterior artery ligation")))AND (((((cardiac) OR (heart)) OR (myocardial)) OR (cardiomyocyte)) AND ((proliferation) OR (regeneration)))) AND ("Mice"[Mesh]) Filters: from 2000 - 2023.

Participant or population Adult mice.

Intervention Left anterior artery ligation.

Comparator Sham group.

Study designs to be included Animal experiment.

Eligibility criteria Studies were included if they met the following criteria: (1) MI models in adult mice were successfully completed; (2) There was information on cell cycle activity of cardiomyocytes in the MI group vs Sham group or infarct border zone vs remote zone in the same post-MI heart; (3) Outcome indicators of proliferative cell cycle must include at least one of followings: Ki67, PH3, BrdU/EdU and AurkB. Studies were excluded if they met any of the following criteria: (1) Studies were reviews, comments, or meeting abstracts; (2) Studies were conducted with animal models of neonatal mice; (3) there was missing data about predetermined outcome parameters.

Information sources A comprehensive literature search was conducted through PubMed/Medline, Embase, and Web of Science databases from 1 January 2000 to 21 December 2023. A series of in vivo studies on estimating the cell cycle markers after MI in adult mice were collected. We also checked reference lists of related reviews and all eligible studies for additional trials.

Main outcome(s) The proportions of Ki67+, PH3+, BrdU/EdU+ or AurkB+.

Quality assessment / Risk of bias analysis Two reviewers (L.Y. and Z.P.) independently appraised the potential risk of bias using SYRCLE's Risk of Bias tool, based on 10 domains: random sequence generation, baseline characteristics, allocation concealment, random housing, blinding, random outcome assessment, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias. Discrepancies were resolved by consensus.

Strategy of data synthesis Mean difference (MD) was used as a summary statistic, calculated for each comparison with 95% CI. The standard error (SE) in the study was converted to SD. The pooled effect was calculated by a random or common effect model in this meta-analysis accounting for potential heterogeneity. I2 statistic was used to evaluate the heterogeneity among studies. If I2 > 50%, a random effects model was applied.

Subgroup analysis Subgroup analysis was conducted for different time points for outcome measures post-MI (within 14 days or more than 14 days) and different mouse strains (C57BL/6J and other strains) considering potential causes of heterogeneity.

Sensitivity analysis Subgroup analysis was conducted for different time points for outcome measures post-MI (within 14 days or more than 14 days) and different mouse strains (C57BL/6J and other strains) considering potential causes of heterogeneity.

Country(ies) involved China.

Keywords Cardiomyocyte proliferation, myocardial infarction, cell cycle, heart, lineage tracing.

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