Pharmacological clearance of senescent cells improves cardiac remodeling andfunction after myocardial infarction in female aged mice

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Despite recent progress in identifying and narrowing the gaps in cardiovascular outcomes between men and women, general understanding of how cardiovascular disease presentations differ between the sexes remains limited. Accordingly, it is still unknown whether cell senescence, a main feature of cardiac male aging, is a significant feature also of the female aged mouse heart and whether senolytics, senescence- clearing compounds, promote myocardial repair and regeneration after myocardial infarction (MI) in aged female mice. To this aim, the combination of two senolytics, dasatinib and quercetin (D+Q) or just their vehicle was administered to 22-24 months old C57BL/6 female mice after MI. D+Q improved global left ventricle function and myocardial performance in aged female mice after MI whereby female cardiac aging is characterized by accumulation of cardiac senescent cells that are further increased by MI. Despite their terminal differentiation nature, also cardiomyocytes acquire a senescent phenotype with age in females. D+Q removed senescent cardiac non-myocyte and myocyte cells in aged female mice, ameliorating cardiac remodeling and regeneration in aged female mice. Furthermore, senolytics removed aged dysfunctional cardiac stem/progenitor cells (CSCs), relieving healthy CSCs with normal proliferative and cardiomyogenic differentiation potential. In conclusions, senescent cardiac non-myocyte and myocyte cells accumulate in the aged female hearts and these dysfunctional senescent cells are acutely increased by permanent coronary occlusion. Senolytycs therapy selectively remove senescent cells fostering efficient repair of the aged female heart after acute ischemic damage. Thus, cellular senescence represents a potential novel therapeutic avenue to improve female patient outcomes following myocardial infarction.