Aging is one of the main risk factors for cardiovascular diseases (CVD) where myocardial infarction (MI) prevalence reaches its peak in males over 80 years of age\(^1\). Current preclinical MI models that heavily rely on 12-week-old mice lack the ability to fully recapitulate the human disease condition, because of the species and the age mismatch. As such, an engineered tissue model of the aging heart microenvironment would be essential for an increased understanding of the MI. In this study, we combined both cellular and environmental aging towards creating an \textit{in vitro} model of the aging heart to study the effect of both biochemical and biophysical changes in an aging ECM on heart cells under normal and MI-mimicking conditions. To that end, we used mice heart tissues from three age groups corresponding human age groups of the early 20s, late 30s, and late 60s, respectively\(^2\), and cultured hiPSC-derived cardiomyocytes for either 35-60-days or 100-120-days to recapitulate chronological cellular aging\(^3\). After 3 weeks of culture, iCMs on different ECM age groups were assessed for aging-associated phenotype, cardiomyocyte maturity, as well as myocardial injury response. Cell senescence was evaluated by staining for senescence associated beta-galactosidase activity and lipofuscin accumulation in combination with the cell proliferation marker Ki67. Senescence associated phenotype increased when cells were cultured on aged ECM and proliferative ability increase d when cultured on young ECM. Strikingly, young ECM induced cell cycle re-entry in aged iCMs that had shown negligibly low Ki67 expression before 3-week incubation on ECM (Fig. 1A). Mechanical and functional maturity of iCMs were assessed through cardiac phenotype, contractile kinetics, and drug response. We observed improved contractile kinetics when cultured on adult ECM, where iCMs showed faster and stronger spontaneous beating (Fig 1B). MI-mimicking stress conditions were simulated, and cellular response was monitored by cell viability, cytotoxicity, and staining for mitochondrial ROS accumulation and apoptotic proteins. Aged iCMs cultured on aged ECM responded poorly to hypoxic stress, displaying significantly high apoptotic signals when compared to iCMs on young and adult ECMS. Even though the biochemical composition effect in 2D model system provides much useful information, we further integrated stiffness as a biophysical cue to better recapitulate \textit{in vivo} cardiac tissue microenvironment. We fabricated gels corresponding young and aged cardiac stiffnesses and cultured iCMs on ECM coated gels. We observed combinational effect of stiffness and ECM biocomposition on iCM cardiac survival and response upon MI.

**Conclusion:** In this study, we used different age human iCMs, mouse ECM and hydrogel system to study the effect of cell and ECM age on iCM maturation, senescence and response to MI/RI. Our results showed that cardiac aging is the cumulative result of both cellular and microenvironmental changes associated with aging and the paracrine factors held within ECM along with the stiffness alter iCM phenotype and stress response.

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**References:**
\(^1\) Heart Disease Facts & Statistics | cdc.gov
\(^2\) Life span as a biomarker \textit{The Jackson Laboratory}