News Release

Title

Cardiomyocytes capture stem cell-derived, anti-apoptotic microRNA-214 via clathrin-mediated endocytosis in acute myocardial infarction

Key Points

○Cardiovascular disease including ischemic heart disease remains the leading cause of mortality worldwide.

○Cell-based therapy represents a potential frontier to transform the treatment and prognosis of heart failure and acute myocardial infarction through repair of damaged cardiac tissue.

○Although mesenchymal stem cells produce and secrete paracrine factors in extracellular vesicles to improve cardiac function, the mechanisms by which cardiomyocytes effect transmembrane signaling in response to EVs remained unclear.

○Clathrin-mediated endocytosis in cardiomyocytes plays a critical role in their uptake of circulating, extracellular vesicle-associated microRNAs that inhibit apoptosis.

Summary

Dr. Shunsuke Eguchi, Dr. Mikito Takefuji and Prof. Toyoaki Murohara at Department of Cardiology, Nagoya University Graduate School of Medicine identified a mechanism by which cardiomyocytes respond to EVs.

Cardiovascular disease including ischemic heart disease is the leading cause morbidity and mortality worldwide. Cell-based therapy represents a potential frontier to transform the treatment and prognosis of heart failure and acute myocardial infarction through repair of damaged cardiac tissue. Recently, mesenchymal stem cells have served as alternate cellular sources of cell-based therapy. Although mesenchymal stem cells produce and secrete paracrine factors in extracellular vesicles (EVs) to improve cardiac function, the mechanisms by which cardiomyocytes effect transmembrane signaling in response to EVs remained unclear. The research team used adipose-derived regenerative cells (ADRCs) as mesenchymal stem cells. And then they cultured cardiomyocytes with EVs previously isolated from ADRC culture supernatant to examine the efficacy of cardiomyocyte endocytosis. The result showed that clathrin-mediated endocytosis in cardiomyocytes plays a critical role in their uptake of circulating, EV-associated microRNAs (miRNAs) that inhibit apoptosis. The date suggested that ADRC-derived EVs would serve as a useful tool to preferentially deliver miRNAs into the damaged cardiomyocytes. This work was published online in Journal of Biological Chemistry on August 16, 2019.

Research Background

Substantial improvements in primary-prevention efforts to reduce risk factors of cardiovascular disease including smoking, low-density lipoprotein cholesterol, and blood pressure have decreased the incidence of myocardial infarction; however, cardiovascular disease including ischemic heart disease remains the leading cause of mortality worldwide. Cell-based therapy represents a potential frontier to transform the treatment and prognosis of heart failure and acute myocardial infarction through repair of damaged cardiac tissue. Recently, mesenchymal stem cells have served as alternate cellular sources of cell-based therapy. Mesenchymal stem cells produce and secrete nucleic acids including miRNAs and proteins that are potentially involved in cytoprotection and angiogenesis. MiRNAs are small non-cording RNAs that regulate gene expression by suppressing their target mRNAs at post-transcriptional level. In cell-based therapy, mesenchymal stem cells secrete paracrine factors in EVs to improve cardiac function. Although EVs have emerged as key mediators of intercellular communication to improve cardiac function, the mechanisms by which cardiomyocytes effect transmembrane signaling in response to EVs remain unclear.

Research Results

They sought to clarify the role of EVs in improving cardiac function by investigating the effect of cardiomyocyte endocytosis of EVs from mesenchymal stem cells on acute myocardial infarction. Exposing cardiomyocytes to the culture supernatant of ADRCs prevented cardiomyocyte cell damage under hypoxia. The injection of ADRCs into the heart simultaneous with coronary artery ligation decreased overall cardiac infarct area and prevented cardiac rupture after acute myocardial infarction. Analysis of the expression of 35 known anti-apoptotic and secreted miRNAs in ADRCs revealed that ADRCs express several of these miRNAs, among which miR-214 was the most abundant. Of note, miR-214 silencing in ADRCs significantly impaired the anti-apoptotic effects of the ADRC treatment on cardiomyocytes. To examine cardiomyocyte endocytosis of EVs, we cultured the cardiomyocytes with ADRC-derived EVs labeled with the fluorescent dye and found that hypoxic culture conditions increased the levels of the labeled EVs in cardiomyocytes. An inhibitor of clathrin-mediated endocytosis significantly decreased hypoxia-induced cardiomyocyte capture of both labeled EVs and extracellular miR-214 secreted from ADRCs. Our results indicate that clathrin-mediated endocytosis in cardiomyocytes plays a critical role in their uptake of circulating, EV-associated miRNAs that inhibit apoptosis.

Research Summary and Future Perspective

The important achievement of this research is that miRNA-214 in EVs secreted from ADRCs prevents cardiac rupture induced by acute myocardial infarction; and that clathrin-mediated

endocytosis in cardiomyocytes plays a critical role in transporting the circulating miRNAs into the cell. The damaged cardiomyocytes with activated clathrin-mediated endocytosis may uptake EVs more aggressively than normal cardiomyocytes, suggesting that ADRC-derived EVs would serve as a useful tool to preferentially deliver miRNAs into the damaged cardiomyocytes.

Publication

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