Atrial fibroblasts secrete exosomal miR-21 that up-regulates KCa3.1 channels in atrial myocytes via the PI3K-Akt pathway

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Abstract

Background: Fibroblast-derived exosomes can regulate the electrical remodeling of cardiomyocytes, and the KCa3.1 channel is an important factor in atrial electrical remodeling; however, the underlying molecular mechanisms that influence the fibroblast-derived exosomes on the electrical remodeling of cardiomyocytes are blurry. Therefore, our objective is to study the regulation of cardiac electrophysiology by exosomes linked to KCa3.1. **Methods:** Atrial myocytes (AMs) and atrial fibroblasts collected from Sprague-Dawley suckling rats were isolated and cultured individually. The cellular atrial fibrillation (AF) model was then established via electrical stimulation (1.0 v/cm, 10 Hz), and fibroblast-derived exosomes were isolated via ultracentrifugation. Moreover, these exosomes were co-cultured with AMs to investigate their influences on KCa3.1 and its potential mechanism. Various techniques, such as nanoparticle tracking analysis, transmission electron microscopy, whole-cell patch clamp technique, reverse-transcription polymerase chain reaction (RT-PCR), Western blot, and immunofluorescence, were used. **Results:** Rapid pacing promoted the secretion of exosomes from atrial fibroblasts ($P < 0.05$), along with elevating the miR-21-5p expression level in atrial fibroblasts and exosomes ($P < 0.01$). The expression of protein and current density of the KCa3.1 channel significantly increased after rapid pacing in AMs (0.190 ± 0.010 vs. 0.513 ± 0.057, $P < 0.001$). The KCa3.1 channel expression and PI3K/AKT pathway were further amplified after co-culturing of AMs with exosomes secreted by atrial fibroblasts (0.513 ± 0.057 vs. 0.790 ± 0.020, $P < 0.001$). However, the KCa3.1 expression was reversed after the cells were co-cultured with exosomes secreted by atrial fibroblasts transfected with miR-21-5p inhibitors (0.790 ± 0.020 vs. 0.570 ± 0.056, $P < 0.001$) or after the use of LY294002, a PI3K/AKT pathway inhibitor (0.676 ± 0.025 vs. 0.480 ± 0.043, $P < 0.001$). **Conclusions:** Rapid pacing promoted the secretion of exosomes from fibroblasts, and the miR-21-5p was upmodulated in exosomes. Moreover, the miR-21-5p enriched in exosomes up-regulated the KCa3.1 channel expression in AMs via the PI3K/AKT pathway.

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