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Lipopolysaccharide exacerbates phenotypic changes of Brugada syndrome through autophagy

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Background: Brugada syndrome is an inherited arrhythmic disorder associated with an increased risk of ventricular fibrillation and sudden cardiac death. Autophagy is an intracellular process which can eliminate protein aggregates and damaged organelles to maintain cytoplasmic homeostasis. Inflammation is closely related to autophagy and can trigger the occurrence of arrhythmias in cardiovascular disorders. However, studies exploring the relationship among autophagy, inflammation and arrhythmogenesis of BrS are still lacking.
Objectives:
The aims of study are to investigate whether autophagy can contribute to the phenotypic changes of BrS, whether inflammation can further exacerbate the phenotypic changes of BrS by further activating autophagy in BrS, and which mechanism underlies the effects of autophagy and inflammation on BrS.
Methods: Human induced stem cell derived cardiomyocytes (hiPSC-CMs) were generated from two healthy donors (D1 and D2) and one BrS-patient with SCN5A-polymorphism (c.3148G>A). Autophagy levels were detected in hiPSC-CMS by western blot and immunofluorescence staining. 3-MA and BafA1 were used to inhibited the autophagy in hiPSC-CMs. LPS was applied to simulate inflammation in hiPSC-CMs. Western blot was applied to detect the protein levels of sodium channels (Nav1.5), and patch-clamp measurements were carried out to measure changes in the sodium channel currents and gating kinetics.
Results: Autophagy was enhanced in BrS-hiPSC-CMs compared to the healthy donor cells. Inhibition of autophagy could rescue the reduction of Nav1.5, peak sodium channel currents (I_{Na}) and maximal depolarization velocity (V_{max}) of action potentials (APs) in cardiomyocytes from the BrS-patient. PI3K/Akt/mTOR signaling pathway which played an important role in regulating autophagy was significantly reduced in BrS cell line. After activating PI3K by IGF-1 in BrS-hiPSC-CMs, autophagy levels were decreased and expression of Nav1.5, peak sodium currents and V_{max} of APs were increased. LPS treatment exacerbated the phenotypic changes of BrS and increased levels of autophagy in hiPSC-CMs from the BrS-patient. Inhibition of autophagy before LPS treatment increased the expression of Nav1.5, peak sodium currents and V_{max} of APs in BrS-hiPSC-CMs. LPS treatment also exacerbated the reduction of phosphorylation levels of PI3K/Akt/mTOR signaling pathway in BrS cell line. Application of IGF-1 before LPS treatment reduced autophagy levels and increased the Nav1.5 expression, peak sodium currents and V_{max} of APs in BrS-hiPSC-CMs.
Taken together, autophagy was activated and mediated the phenotypic changes of BrS. LPS could further increase the autophagy levels and exacerbate the phenotypic changes of BrS. The suppression of PI3K/Akt/mTOR signaling pathway contributed to autophagy activation with or without LPS in BrS-cells.
Conclusions: This study demonstrated that autophagy activation contributes to loss-of-function of SCN5A channels in BrS cardiomyocytes and inflammation can exacerbate the phenotype of BrS by enhancing autophagy.