Loss of MD1 increases vulnerability to ventricular arrhythmia in diet-induced obesity mice via enhanced activation of the TLR4/MyD88/CaMKII signaling pathway

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**Introduction** : Obesity is an important risk factor for ventricular arrhythmia (VA), and myeloid differentiation protein 1 (MD1) had been reported decrease in obese hearts. Nevertheless, underlying mechanisms linking MD1 and VA have not been fully studied. This study aims to investigate the regulatory role of MD1 in VA caused by diet-induced obesity.

**Methods** : MD1 knock-out (KO) and wild type (WT) mice from experimental groups were fed with a high-fat diet (HFD) from six-week-old for 20 weeks. The body weight gain, fast glucose and serum lipid levels were measured and recorded. In addition, pathological analysis, echocardiography, electrocardiography, langendorff-perfused heart and molecular analysis were performed to detect HFD-induced vulnerability to VA and its underlying mechanisms.

**Result** : After a 20-week HFD feeding, the mice showed an increase in body weight, glycemic, lipid levels, QTc interval, LVEDd, LVEDs and LVFS (table 1). HFD feeding also increased vulnerability to VA, as shown by the prolonged action potential duration (APD), enhanced APD alternans threshold and greater incidence of VA (figure 1). Moreover, HFD feeding caused LV hypertrophy and fibrosis (figure 2), and decreased the protein expressions of Kv4.2, Kv4.3, Kv1.5, Kv2.1 and Cav1.2 channels (figure 3). At last, above-mentioned HFD-induced adverse effects were further exacerbated in KO mice compared with WT mice. Mechanistically, the expressions of TLR4, MyD88, CaMKII and CaMKII phosphorylation (p-CaMKII) were obviously enhanced in KO-HFD mice, indicating MD1 deletion could strongly active the TLR4/MyD88/CaMKII signaling pathway (figure 4).

**Conclusion** : MD1 deficiency increased HFD-induced vulnerability to VA. This is mainly caused by the aggravated maladaptive LV hypertrophy, fibrosis and decreased protein expressions of ion channels, which are induced by the enhanced activation of the TLR4/MyD88/CaMKII signaling pathway.