The Role and Mechanism of Macrophage Colony-stimulating Factor (M-CSF) in Ventricular Electrical Remodeling after Myocardial Infarction in Mice by Regulating Cardiac Macrophages

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Introduction Inflammation plays an essential role in the occurrence and development of ventricular electrical remodeling after MI, and macrophage is one of the main regulatory cells of inflammatory response, it may play an important role in ventricular electrical remodeling after MI. Therefore, the main aim is to investigate the effect and mechanism of macrophage colony-stimulating factor (M-CSF) on ventricular arrhythmias after myocardial infarction in mice by regulating cardiac macrophages.

Methods Firstly, C57BL/6J wild type mice were randomly divided into Sham Group, MI/3d Group and MI/7d Group to investigate the relationship between M-CSF, different type macrophages and ventricular arrhythmias after MI. Then C57BL/6J wild mice were randomly divided into Sham group, MC group and MM group. The Sham group mice were given ligation line through LAD without ligation, the MC group and MM group were ligated with LAD to prepare MI model, the M-CSF (500 ug/kg/d) reagent was administered intraperitoneally for 5 consecutive days in MM group, and the Sham and MC group mice were given intraperitoneal injection of saline for 5 consecutive days. Three groups of mice were housed in the barrier environment for 1 week. At the end of the experiment, the relevant indexes of ventricular structural remodeling, serum and tissue inflammatory factors, M1 and M2
type macrophage levels were measured, and the ERP, the APD90, the threshold of action potential electrical alternating and the VAs inducibility were recorded. The concentrations of Cx43 and TH in myocardial tissues were also measured.

**Results** The levels of M-CSF significantly increased in the MI/3d group and the MI/7d group than that in the Sham group, and the level of M-CSF in MI/3d group was also significantly higher than that in the MI/7d group (all $P<0.05$). The M2 type macrophage increased continuously after MI, while the M1 macrophage increased significantly in the acute phase after MI (all $P<0.05$), then decreased timely. When compared with the MC group, the level of M2 type macrophage in the myocardial tissues in the MM group was significantly higher while the level of M1 type macrophage was significantly lower than that in the MC group (all $P<0.05$). The ventricular structural remodeling was significantly improved, the ventricular function were significantly increased and also the ventricular ejection fraction, the infarction size was significantly decreased. The levels of pro-inflammatory cytokines in serum and myocardial tissues all markedly decreased while the levels of anti-inflammatory cytokines significantly increased (all $P<0.05$). What’s more, the cell apoptosis, hypertrophy and fibrosis were all significantly improved. In addition, the ERP of the MM group was significantly longer than that in the MC group while the APD90 significantly shortened, and the threshold of action potential electrical alternating significantly increased, the VAs inducibility in the MM group was markedly lower than that in the MC group (all $P<0.05$). The TH level in the myocardial tissue of the infarction area of the MM group was significantly lower than that in the MC group while the Cx43 level significantly increased.

**Conclusion** M-CSF can significantly improve the ventricular electrical remodeling after MI in mice by regulating the levels of macrophages of different polarization types in heart tissue (increasing the level of M2 type macrophages and inhibiting the increase of M1 type macrophages), and then could inhibit the inducibility of VAs, which may have important relationship with M-CSF could significantly improve ventricular structural remodeling and function, inhibit sympathetic hyperdistribution in the peripheral area of infarction, and increase the expression level of Cx43.
**Keywords** macrophage colony-stimulating factor, ventricular electrical remodeling, ventricular arrhythmias, myocardial infarction.