Journal of Geriatric Cardiology | JGC
RESEARCH ARTICLE
J Geriatr Cardiol 2021; 18(4): 271–280

sDR5-Fc inhibits macrophage M1 polarization by blocking the glycolysis

Guang-Yao ZHAI[1,*], Shu-Yan QIE[2,*], Qian-Yun GUO[1], Yue QI[3], Yu-Jie ZHOU[1,✉]

1. Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, Beijing Institute of Heart Lung and Blood Vessel Disease, Beijing Key Laboratory of Precision Medicine of Coronary Atherosclerotic Disease, Clinical Center for Coronary Heart Disease, Capital Medical University, Beijing, China; 2. Department of Rehabilitation, Beijing Rehabilitation Hospital of Capital Medical University, Beijing, China; 3. Department of Epidemiology, Beijing Anzhen Hospital, Capital Medical University, Beijing Institute of Heart Lung and Blood Vessel Disease, Beijing, China

[*]The authors contributed equally to this manuscript

✉ Correspondence to: azzyj12@163.com

https://doi.org/10.11909/j.issn.1671-5411.2021.04.003

ABSTRACT

BACKGROUND M1 polarization of macrophages is an important pathological process in myocardial ischemia reperfusion injury, which is the major obstacle for the treatment of acute myocardial infarction. Currently, the strategies and mechanisms of inhibiting M1 polarization are poorly explored. This study aims to investigate the role of soluble death receptor 5-Fc (sDR5-Fc) in regulating M1 polarization of macrophages under extreme conditions and explore the mechanisms from the aspect of glycolysis.

METHODS Extreme conditions were induced in RAW264.7 cells. Real-time quantitative polymerase chain reaction and western blot were used to detect the expression of mRNA and proteins, respectively. Cell counting kit-8 was used to investigate the proliferation activity of cells. Expression levels of inflammatory cytokines were determined by enzyme-linked immunosorbent assay.

RESULTS We found that sDR5-Fc rescues the proliferation of macrophages under extreme conditions, including nutrition deficiency, excessive peroxide, and ultraviolet irradiation. In addition, administration of sDR5-Fc inhibits the M1 polarization of macrophages induced by lipopolysaccharide (LPS) and interferon-gamma (IFN-γ), as the expression of M1 polarization markers CD86, CXC motif chemokine ligand 10, matrix metalloproteinase 9, and tumor necrosis factor-α, as well as the secretion of inflammatory factors interleukin (IL)-1β and IL-6, were significantly decreased. By further investigation of the mechanisms, the results showed that sDR5-Fc can recover the LPS and IFN-γ induced pH reduction, lactic acid elevation, and increased expression of hexokinase 2 and glucose transporter 1, which were markers of glycolysis in macrophages.

CONCLUSIONS sDR5-Fc inhibits the M1 polarization of macrophages by blocking the glycolysis, which provides a new direction for the development of strategies in the treatment of myocardial ischemia reperfusion injury.

Acute myocardial infarction (AMI) is one of the leading causes of death worldwide. More than ten million people around the world die of cardiovascular diseases every year, and about seven million people die of AMI.[1] At present, the treatment of AMI mainly depends on drugs, coronary artery bypass surgery and interventional treatment, which significantly enhances the perfusion of myocardial tissues and improves the prognosis of patients. However, reperfusion can lead to injury of myocardial cells, even irreversible damages, which is known as myocardial ischemia reperfusion injury (MIRI).[2] MIRI is a major obstacle in the treatment of cardiovascular diseases, which can cause damage of oxidative stress to myocardial cells, lead to changes in myocardial ultrastructure, abnormal energy metabolism, cardiac function and electrophysiological disorders, or even sudden death of patients due to malignant arrhythmia.[3,4] Although the adverse effect of MIRI has been recognized for a long time, few applicable methods have been developed for promotion in clinical practice.[3,5] Thus, it is in urgent need to develop appropriate strategies to alleviate the MIRI.

Macrophages play important roles in the physiology