



Role of glycogen synthase kinase following myocardial infarction and ischemia–reperfusion

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Dear Editor,

We presume that the following three limitations might cast suspicion on the conclusions made by Ghaderi et al. [1] in their paper entitled “Role of glycogen synthase kinase following myocardial infarction and ischemia–reperfusion” after reading their article carefully.

Glycogen synthase kinase-3 beta (GSK-3 β) is a serine/threonine kinase widely expressed *in vivo*, which phosphorylates substrates through multiple signaling pathways, thereby regulating many cellular functions, including development, metabolism, gene transcription, protein translation, cytoskeleton tissue, cell cycle regulation and apoptosis [2]. Although GSK-3 β exists in a variety of tissues, it plays very important roles in the heart, such as regulating cardiac development, myocardial cell proliferation, myocardial hypertrophy, myocardial fibrosis and a series of physiological and pathological processes. Notably particularly, increasing evidence has shown that GSK-3 β plays an important role in myocardial ischemia–reperfusion injury by regulating inflammatory response and the opening of mitochondrial permeability transition pore (MPTP) [1]. Therefore, it is of significance to study the specific mechanism of GSK-3 β in myocardial ischemia–reperfusion injury, which is expected to be an attractive target for the development of new drugs for the treatment of MI-R.

This study, concentrating on GSK-3 β interactions with mitochondria, adds further knowledge to the relationship between GSK-3 β and myocardial ischemia–reperfusion

injury. The authors demonstrated that inhibition of GSK-3 β can reduce myocardial ischemia–reperfusion injury and apoptosis to play a cardioprotective role during reperfusion. Some aspects, however, need to be discussed.

First, there is a problem in describing the molecular structures of GSK-3 α and GSK-3 β . Ghaderi et al. [1] described that the GSK-3 family encodes two genes, GSK-3 α (51 kDa) and GSK-3 β . Additionally, GSK-3 β has alternative splice variants that encode two different protein products, GSK-3 β 1 (47 kDa) and GSK-3 β 2 (49 kDa). They also reported that the catalytic domain was highly conserved between the two isoforms, but compared with GSK-3 α , GSK-3 β 2 occupies a domain with a 13 amino acid insert consisting of a glycine-rich domain at the N-terminal. In 2001, Frame and Cohen [2] have reported that proteins of GSK-3 α and GSK-3 β have 97% sequence similarity within their kinase catalytic domains, but differ significantly from one another outside this region, with GSK-3 α possessing an extended N-terminal glycine-rich tail. Besides, detailed information about GSK-3 α and GSK-3 β proteins is obtained from The UniProt Knowledgebase (UniProtKB), which is a central hub for the collection of functional information and amino acid sequence on proteins, with accurate, consistent and rich annotation. In the Compositional bias of Family and Domains of UniProtKB, it is clearly described that GSK-3 α has a Gly-rich domain at the N-terminal rather than GSK-3 β .

Second, Ghaderi et al. [1] stated that the determinant role of GSK-3 β inhibitors is to reduce the MPTP opening threshold in regards to the impact of GSK-3 β on cell death and survival. However, to the best of my knowledge, such a conclusion is wrong. A large number of studies have shown that inhibition of GSK-3 β elevate the threshold of MPTP and suppress its opening during myocardial ischemia–reperfusion injury, which is cardioprotective. GSK-3 β , as a determinant factor of MPTP opening threshold, was first reported by Juhaszova et al. [3]. They confirmed that inactivation of GSK-3 β can increase threshold of MPTP and thus play a protective role in isolated cardiomyocytes in response to

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the excessive production of ROS. Besides, Yang et al. [4] also suggested that GSK-3 β inhibition increases the opening threshold of MPTP to reduce mitochondrial permeability, promotes mitochondrial biogenesis and improve mitochondrial-related apoptosis. What's more, Hurst et al. [5] showed that phospho-GSK-3 β (inactivation of GSK-3 β) plays a key role in inhibition of MPTP opening and protection of cardiomyocytes, and its phosphorylation level is a crucial factor for myocardial survival in lethal ischemia–reperfusion injury. Therefore, we thought that inhibition of GSK-3 β increases the opening threshold of MPTP rather than reduces as suggested by Ghaderi et al. [1].

Third, in our view, the authors indicated that GSK-3 β is phosphorylated at Tyr 216 residue after reperfusion due to an excessive amount of ROS, which may be not so accurate. All the references cited above [3–5] indicated that GSK-3 β is phosphorylated at Ser9 residue site rather than Tyr 216 residue site to inhibit the opening of MPTP during myocardial ischemia–reperfusion injury.

Therefore, we conclude that inhibition of GSK-3 β elevate the opening threshold of MPTP, and the inhibition of GSK-3 β was due to its phosphorylation at Ser9 residue during myocardial ischemia–reperfusion injury.

Compliance with ethical standards

Conflicts of interest None disclose.

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