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Inflammation Research

COMMENTARY

Evolution of β-catenin-independent Wnt–GSK3–mTOR signalling in regulation of energy metabolism in isoproterenol-induced cardiotoxicity model

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Abstract

Objective [illegible]

Method [illegible]

Result [illegible]

Conclusion [illegible]

Keywords [illegible]

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Introduction

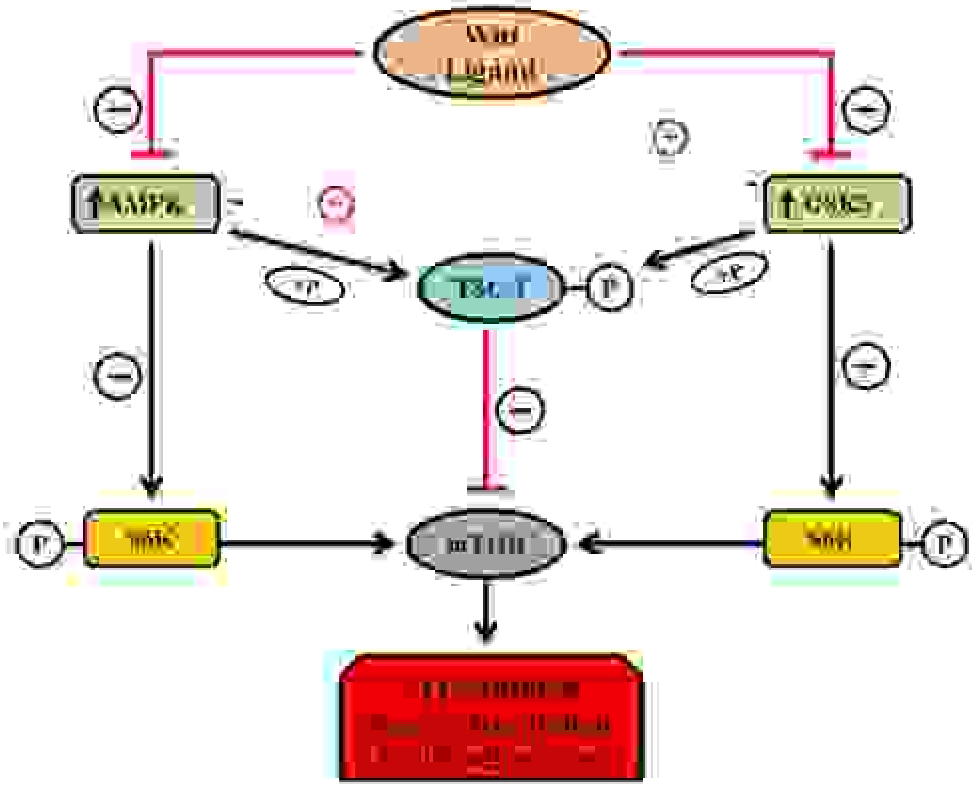

Fig. 1 GSK-3 and AMPK coordinately exert inhibitory effects on mTOR activation by phosphorylating TSC-2 and reducing phosphorylation of S6K which is responsible for activation of mTOR signaling. Stimulation of Wnt receptor induces mTOR activation by reverting the phosphorylation events on TSC-2 and S6K

kg body weight for 7 days lead to reduction in rate–pressure relationship, phosphocreatine/adenosine triphosphate ratio in isolated perfused rat heart suggesting an imbalance of energy status in this model [22]. In addition, 7 day post-isoproterenol injection increased cardiac workload and associated with normal myocardial blood flow depicting a mismatch between oxygen demand and supply. Biochemical evaluation of isolated heart from isoproterenol injected rats also revealed increased oxidative stress, cardiac hypertrophy. Though both of these studies observed partial recovery in ventricular structural changes and function, but energy dysregulation was clearly evident at the end. Thus, it is clear that myocardial hypoxia induced by isoproterenol results in permanent state of energy imbalance and mitochondrial dysfunction which triggers various pathological cascades leading to cardiac dysfunction and remodeling.

Wnt signaling protein has been observed to be directly implicated in mediating β-adrenergic stimulation-induced hypertrophic changes in cardiomyocytes. In a study, silencing of Wnt-signaling complex subunit dishevelled (Dvl) resulted in the regression of hypertrophic changes in cardiomyocytes exposed to isoproterenol insult. This suggests that the activation of canonical Wnt/β-catenin pathway is essential for promoting isoproterenol-induced cardiac structural alterations [23]. However, as discussed above, the non-β-catenin dependent Wnt signaling pathway is involved in regulation of cellular energy status by suppressing GSK-3β-mediated inactivation of Akt and mTOR signaling. It is worth mentioning here that isoproterenol administration resulted in decreased mitochondrial energy charge and creatine phosphate/creatine ratio (an indicator of reduced ATP synthesis) in heart at an early period of 3 h. This suggests that cardiac energy imbalance and mitochondrial dysfunction are early pathogenic events which might result in cardiac dysfunction and structural damage at later stages in isoproterenol model. Therefore, interventions which maintain the cellular ATP levels by improving mitochondrial function will delay the development of cardiac functional and structural damage in isoproterenol injected rats. We hereby propose a novel Wnt β-catenin-independent mechanism whose activation could be important for regulation of myocardial ATP levels in early stage of isoproterenol-induced cardiac necrosis. Importantly, the Wnt-mediated GSK-3 inhibition will stimulate key energy sensor and regulator molecule mTOR by involving Akt activation thus preserving the ATP levels in myocardium and hence prevent the development of cardiac dysfunction and necrosis at later stages in isoproterenol model. While inhibition of Wnt/β-catenin signaling is important for preventing the late stage cardiac remodeling, but transient Wnt-mediated GSK-3 inhibition and activation of mTOR signaling would exert cardioprotective effects during the initial period of ISO model by conserving the oxygen and energy

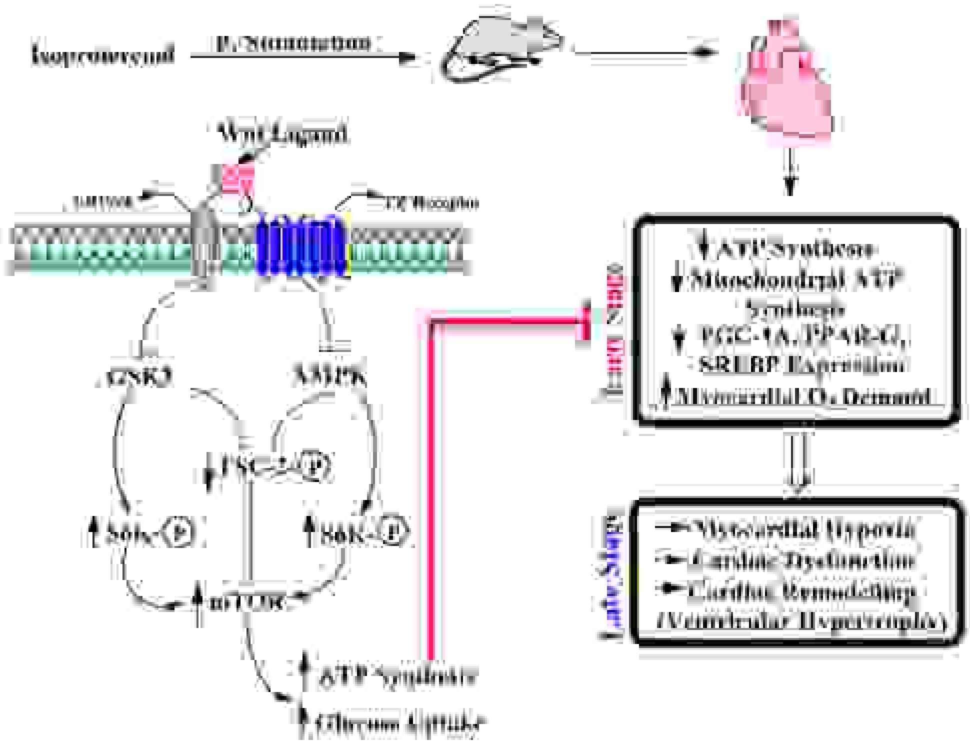

Fig. 2 Alterations in myocardial ATP [illegible] mitochondrial dysfunction in early phase of the [illegible] cardiac dysfunction, ventricular hypertrophy and hypoxia. Activation of β-catenin-independent Wnt signalling [illegible] energy and [illegible] by targeting GSK3/mTOR pathway during early phase and prevent cardiomyopathy in late stage

dysregulation. Finally, we discussed a new therapeutic role of non-canonical Wnt/GSK3/mTOR axis in ISO-induced myocardial infarction model. We propose that the short term and early activation of Wnt/GSK3/mTOR axis could exert cardioprotective effects in ISO model by sustaining myocardial tissue energy levels and thereby preventing mitochondrial dysfunction and histological damage. Further experiments are required to distinguish the temporal effects of activating Wnt/GSK3/mTOR axis in isoproterenol-induced cardiotoxicity model. If this hypothesis withstands experimental testing, it might offer a new dimension to harness the therapeutic potential of non β-catenin dependent Wnt/GSK3/mTOR axis in cardiac diseases associated with hyper-adrenergic syndrome. Effect of Wnt/GSK3/mTOR axis on energy dysregulation induced by Iso is diagrammatically represented in Fig. 2. This study discussed the possible cardioprotective role of Wnt/GSK3/mTOR axis in preventing early pathological changes in isoproterenol heart failure model. However, how the temporal succession of changes in this axis during pathological condition in ISO-induced cardiac toxicity model needs to be determined. Therefore, it would be important to study the impact of pharmacological modulation of this axis on various pathological outcomes including energy dysregulation, cardiac dysfunction and fibrosis underlying high-dose ISO administration.

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Declarations

Conflict of interest The authors declare that there is no conflict of interest.

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