0335
Reduced scar maturation and contractility lead to exaggerated left ventricular dilation after myocardial infarction in mice lacking AMPKα1

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Objective: Cardiac fibroblasts (CF) are crucial in left ventricular (LV) remodelling after myocardial infarction (MI). They predominantly express the α1 catalytic subunit of AMP-activated protein kinase (AMPKα1), while AMPKα2 is the major catalytic isoform in cardiomyocytes. AMPKα2 is known to protect the heart by preserving the energy charge of cardiac myocytes during injury, but whether AMPKα1 interferes with maladaptive heart responses remains unexplored. In this study, we aim at further substantiating the role of this AMPK isoform in the post-MI LV remodelling and more particularly in the regulation of fibrotic properties of CF.

Methods: AMPKα1 knockout (KO) and wild type (WT) mice were subjected to permanent ligation of the left anterior descending coronary artery to mimic MI. Cardiac fibrosis was monitored using qRT-PCR analysis, histology and immunohistofluorescent staining. LV function and remodelling was assessed by echocardiography.

Results: In the absence of AMPKα1, the CF proliferative response was increased in infarcted myocardia. It resulted in elevated levels of fibrotic factors but did not lead to excessive matrix deposition or degradation in KO infarcts. While CF proliferation was increased, expression of the myodifferentiation marker α-smooth muscle actin was decreased. This faulty maturation of myofibroblasts might derive from down-regulation of the transforming growth factor-β1/p38 mitogen-activated protein kinase pathway in KO infarcts. Although infarct size was similar in KO and WT hearts subjected to MI, these changes resulted in defective scar collagen maturation. This was associated with an exacerbated adverse remodelling as indicated by increased LV diastolic 30 days after MI.

Conclusion: Our data genetically demonstrate the centrality of AMPKα1 in post-MI scar formation and highlight the specificity of this catalytic isoform in cardiac fibroblast/myofibroblast biology.

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Glucagon-like peptide 1 or GLP-1 counters NADPH oxidase activation during hyperglycemia through an AMPK-dependent pathway in adult cardiomyocytes

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Background and objective: Exposure to high glucose (HG) stimulates NADPH oxidase (NOX2) dependent-ROS production in cardiomyocytes. NOX2 activation is not triggered by an increased glucose metabolism but results from a glucose transport through a sodium-glucose co-transporter (SGLT). The aim of this work is to identify potential therapeutic approaches to counteract glucotoxicity.

Methods and results: Primary cultures of adult rat cardiomyocytes were exposed to high glucose concentration (HG, 21mM). AMP-activated protein kinase (AMPK) activation by A769662 or Phenformin nearly suppressed ROS production under hyperglycemia. GLP-1, a new anti-diabetic drug, exerted a similar effect, blocking hyperglycemia-mediated ROS production. Interestingly, GLP-1 treatment induced an AMPK activation, the maximal activation being observed at 100 nM. α2AMPK, the major isoform expressed in cardiomyocytes (but not α1AMPK) was activated in response to GLP-1. Anti-ROS properties of AMPK were not related to change in glucose uptake or glycolysis. Using in situ proximity ligation assay technology, we demonstrated that AMPK activation prevented p47phox translocation to the caveolar structure after high glucose concentration exposure, whatever the AMPK activators used. NOX2 activation by α-methyl-D-glucopyranoside, a glucose analog exclusively transported through SGLT, or by Angiotensin 2 was also counteracted by GLP-1. The crucial role of AMPK in limiting glucotoxicity was demonstrated by overexpressing a constitutively active form of AMPK using adenoviral infection. This overexpression prevented NOX2 activation in response to HG. Finally, in mice cardiomyocytes, GLP-1 did not exert protective action in the absence of α2AMPK.

In conclusion, GLP-1 induces α2AMPK activation and blocks HG-induced p47phox translocation to the plasma membrane, limiting glucotoxicity.

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The estrone receptor alpha C451 palmitoylation site is absolutely required for vascular membrane-initiated action of estrogens in mice


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