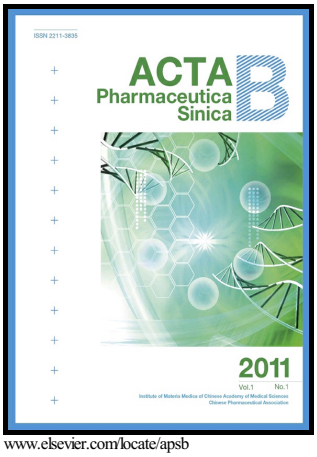
Author's Accepted Manuscript



www.elsevier.com/locate/apsb

Hypoxia-stressed cardiomyocytes promote early cardiac differentiation of cardiac stem cells through HIF-1α/Jagged1/Notch1 signaling

Keke Wang, Ranran Ding, Yanping Ha, Yanan Jia, Xiaomin Liao, Sisi Wang, Rujia Li, Zhihua Shen, Hui Xiong, Junli Guo, Wei Jie

PII: S2211-3835(18)30009-1
DOI: https://doi.org/10.1016/j.apsb.2018.06.003
Reference: APSB561

To appear in: *Acta Pharmaceutica Sinica B*

Received date: 15 January 2018
Revised date: 27 February 2018
Accepted date: 8 June 2018

Cite this article as: Keke Wang, Ranran Ding, Yanping Ha, Yanan Jia, Xiaomin Liao, Sisi Wang, Rujia Li, Zhihua Shen, Hui Xiong, Junli Guo and Wei Jie, Hypoxia-stressed cardiomyocytes promote early cardiac differentiation of cardiac stem cells through HIF-1α/Jagged1/Notch1 signaling, *Acta Pharmaceutica Sinica B,* https://doi.org/10.1016/j.apsb.2018.06.003

Original article

Hypoxia-stressed cardiomyocytes promote early cardiac differentiation of cardiac stem cells through HIF-1α/Jagged1/Notch1 signaling

Keke Wang[a,†], Ranran Ding[a,c,†], Yanping Ha[a], Yanan Jia[a], Xiaomin Liao[a], Sisi Wang[a], Rujia Li[a], Zhihua Shen[a], Hui Xiong[a], Junli Guo[b*], Wei Jie[a*]

[a]*Department of Pathology, Guangdong Medical University, Zhanjiang 524023, China*

[b]*Cardiovascular Institute of First Affiliated Hospital, Hainan Medical University, Haikou 570102, China*

[c]*Department of Pathology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China*

Received 15 January 2018; received in revised form 26 February 2018; accepted 26 April 2018

[*]Corresponding author. Tel. +86 754 2388584.

E-mail address: wei.jie@gdmu.edu.cn (Wei Jie), guojl79@163.com (Junli Guo).

[†]These authors made equal contributions to this work.

Running title: HIF-1α/Jagged1/Notch1 signaling in CSCs differentiation

Abstract Hypoxia is beneficial for the differentiation of stem cells transplanted for myocardial injury, but mechanisms underlying this benefit remain unsolved. Here, we report the impact of hypoxia-induced Jagged1 expression in cardiomyocytes (CMs) for driving the differentiation of cardiac stem cells (CSCs). Forced hypoxia-inducible factor 1α (HIF-1α) expression and physical hypoxia (5% O_2) treatment could induce Jagged1 expression in neonatal rat CMs. Pharmacological inhibition of HIF-1α by YC-1 attenuated hypoxia-promoted Jagged1 expression in CMs. An ERK inhibitor (PD98059), but not inhibitors of JNK (SP600125), Notch (DAPT), NF-κB (PTDC), JAK (AG490), or STAT3 (Stattic) suppressed hypoxia-induced Jagged1 protein expression in CMs. c-Kit$^+$ CSCs isolated from neonatal rat hearts using a magnetic-activated cell sorting method expressed GATA4, SM22α or vWF, but not Nkx2.5 and cTnI. Moreover, 87.3% of freshly isolated CSCs displayed Notch1 receptor expression. Direct co-culture of CMs with BrdU-labeled CSCs enhanced CSCs differentiation, as evidenced by an increased number of BrdU$^+$/Nkx2.5$^+$ cells, while intermittent hypoxia for 21 days promoted co-culture-triggered differentiation of CSCs into CM-like cells. Notably, YC-1 and DAPT attenuated hypoxia-induced differentiation. Our results suggest that hypoxia induces Jagged1 expression in CMs primarily through ERK signaling, and facilitates early