Title

‘Youthful’ phenotype of c-Kit+ cardiac fibroblasts

Journal

Cellular and Molecular Life Sciences, 79(8)

ISSN

1420-682X

Authors

Firouzi, Fareheh

Echeagaray, Oscar

Esquer, Carolina

et al.

Publication Date

2022-08-01

DOI

10.1007/s00018-022-04449-1

Peer reviewed

Cellular and Molecular Life Sciences (2022) 79:424
https://doi.org/10.1007/s00018-022-04449-1

Cellular and Molecular Life Sciences

ORIGINAL ARTICLE

'Youthful' phenotype of c-Kit$^+$ cardiac fibroblasts

Fareheh Firouzi[1] · Oscar Echeagaray[1] · Carolina Esquer[1] · Natalie A. Gude[1] · Mark A. Sussman[1]

Received: 17 March 2022 / Revised: 4 June 2022 / Accepted: 24 June 2022

Abstract

Cardiac fibroblast (CF) population heterogeneity and plasticity present a challenge for categorization of biological and functional properties. Distinct molecular markers and associated signaling pathways provide valuable insight for CF biology and interventional strategies to influence injury response and aging-associated remodeling. Receptor tyrosine kinase c-Kit mediates cell survival, proliferation, migration, and is activated by pathological injury. However, the biological significance of c-Kit within CF population has not been addressed. An inducible reporter mouse detects c-Kit promoter activation with Enhanced Green Fluorescent Protein (EGFP) expression in cardiac cells. Coincidence of EGFP and c-Kit with the DDR2 fibroblast marker was confirmed using flow cytometry and immunohistochemistry. Subsequently, CFs expressing DDR2 with or without c-Kit was isolated and characterized. A subset of DDR2$^+$ CFs also express c-Kit with coincidence in ~ 8% of total cardiac interstitial cells (CICs). Aging is associated with decreased number of c-Kit expressing DDR2$^+$ CFs, whereas pathological injury induces c-Kit and DDR2 as well as the frequency of coincident expression in CICs. scRNA-Seq profiling reveals the transcriptome of c-Kit expressing CFs as cells with transitional phenotype. Cultured cardiac DDR2$^+$ fibroblasts that are c-Kit$^+$ exhibit morphological and functional characteristics consistent with youthful phenotypes compared to c-Kit$^-$ cells. Mechanistically, c-Kit expression correlates with signaling implicated in proliferation and cell migration, including phospho-ERK and pro-caspase 3. The phenotype of c-kit$^+$ on DDR2$^+$ CFs correlates with multiple characteristics of 'youthful' cells. To our knowledge, this represents the first evaluation of c-Kit biology within DDR2$^+$ CF population and provides a fundamental basis for future studies to influence myocardial biology, response to pathological injury and physiological aging.

Keywords Fibroblast · Cardiac · c-Kit · DDR2 · Youthful

Abbreviations

BSA	Bovine serum albumin
cCICs	C-Kit$^+$ cardiac interstitial cells
Ccl3	C–C motif ligand 3
CCN2	Cellular communication network factor 2
CF	Cardiac fibroblast
CICs	Cardiac interstitial cells
Ctsb	Cathepsin B
Cxcl	C-X-C motif chemokine
DAPI	4′,6-Diamidino-2-phenylindole
DDR2	Discoidin domain-containing receptor 2
DEGs	Differentially expressed genes
DMEM/F12	Dulbecco's modified eagle medium: nutrient mixture F-12
ECM	Extracellular matrix
EGFP	Enhanced green fluorescent protein
EMT	Epithelial–mesenchymal transition
EPDCs	Epicardial-derived cells
ERK	Extracellular signal–regulated kinase
FACS	Fluorescence-activated cell sorting
FBS	Fetal bovine serum
GEO	Gene expression omnibus
GM	Growth medium
GO	Gene ontology
H2B	Histone H2B
H2O2	Hydrogen peroxide

✉ Mark A. Sussman
heartman4ever@icloud.com

Fareheh Firouzi
ffirouzi@sdsu.edu

Oscar Echeagaray
oecheagaray@sdsu.edu

Carolina Esquer
carolina.esquer@sdsu.edu

Natalie A. Gude
ngude@sdsu.edu

[1] SDSU Integrated Regenerative Research Institute and Biology Department, San Diego State University, 5500 Campanile Drive, San Diego, CA 92182, USA

Published online: 16 July 2022