Molecular and Cellular Neuroscience 75 (2016) 1–13

Contents lists available at ScienceDirect

Molecular and Cellular Neuroscience

journal homepage: www.elsevier.com/locate/ymcne

Linckosides enhance proliferation and induce morphological changes in human olfactory ensheathing cells

Johana Tello Velasquez [a], Rebecca-Qing Yao [a], Filip Lim [b], Chunguang Han [c], Makoto Ojika [d], Jenny A.K. Ekberg [a,e], Ronald J. Quinn [a], James A. St John [a,*]

[a] Eskitis Institute for Drug Discovery, Griffith University, Brisbane, Australia
[b] Universidad Autónoma de Madrid, Madrid, Spain
[c] Research Center for Materials Science, Nagoya University, Nagoya, Japan
[d] Graduate School of Bioagricultural Sciences, Nagoya University, Nagoya, Japan
[e] School of Biomedical Sciences, Queensland University of Technology, Brisbane, Australia

ARTICLE INFO

Article history:
Received 17 November 2015
Revised 22 May 2016
Accepted 21 June 2016
Available online 22 June 2016

Keywords:
Glia
Natural compound
Transplantation
Neural regeneration
Starfish

ABSTRACT

Linckosides are members of the steroid glycoside family isolated from the starfish *Linckia laevigata*. These natural compounds have notable neuritogenic activity and synergistic effects on NGF-induced neuronal differentiation of PC12 cells. Neurogenic factors or molecules that are able to mimic their activities are known to be involved in the survival, proliferation and migration of neurons and glial cells; however how glial cells respond to specific neurogenic molecules such as linckosides has not been investigated. This study aimed to examine the effect of three different linckosides (linckoside A, B and granulatoside A) on the morphological properties, proliferation and migration of human olfactory ensheathing cells (hOECs). The proliferation rate after all the treatments was higher than control as detected by MTS assay. Additionally, hOECs displayed dramatic morphological changes characterized by a higher number of processes after linckoside treatment. Interestingly changes in microtubule organization and expression levels of some early neuronal markers (GAP43 and βIII-tubulin) were also observed. An increase in the phosphorylation of ERK 1/2 after addition of the compounds suggests that this pathway may be involved in the linckoside-mediated effects particularly those related to morphological changes. These results are the first description of the stimulating effects of linckosides on hOECs and raise the potential for this natural compound or its derivatives to be used to regulate and enhance the therapeutic properties of OECs, particularly for cell transplantation therapies.

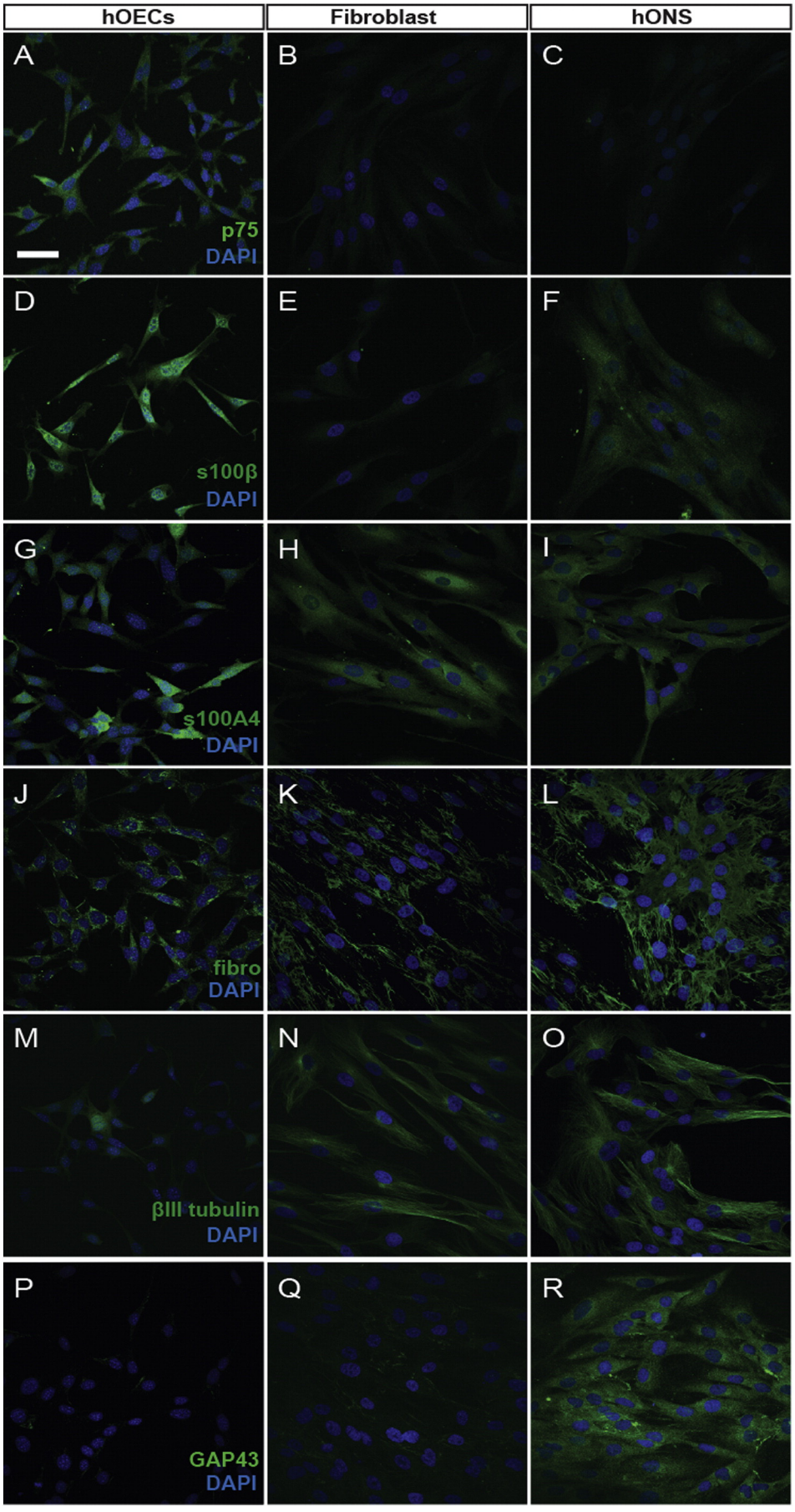
1. Introduction

The glia of the primary olfactory system, olfactory ensheathing cells (OECs), promote axonal regeneration in vivo and in vitro (Barnett, 2004; Moreno-Flores et al., 2003; Raisman, 2001) and their neuro-regenerative potential in the treatment of spinal cord injuries has been broadly studied in the last two decades (Thuret et al., 2006; Li et al., 2014). Factors that can be addressed to improve the use of OECs for spinal cord repair include the proliferation of OECs in vitro to generate sufficient numbers of cells prior to transplantation, as well as the need to improve their proliferation, migration and integration within the host tissue post-transplantation. The challenge of overcoming these limiting factors needs to be addressed in order for OECs to be more widely and effectively used in the development of neural repair therapies (Barnett and Riddell, 2007; Raisman, 2001; Thuret et al., 2006).

Neurotrophic factors have been used to regulate and enhance OEC therapeutic properties (Woodhall et al., 2001; Kim et al., 1996; Bianco et al., 2004), but the large molecule size and potential side-effects have limited their use as an effective option. The discovery and development of low molecular weight natural products that are able to mimic growth factors to stimulate the activity of OECs, or to alter the properties of OECs to improve neural regeneration, is an avenue with high potential. We have recently shown that the polyphenol compound curcumin potently stimulates phagocytic activity of OECs and increases their migration by stimulating the dynamic movement of peripheral lamellipodial waves (Tello Velasquez et al., 2014). Natural compounds that are neurogenic or neuritogenic are also of potential use for neural repair as promoting the growth of neurons is crucial for regeneration. However, due to the essential close relationship between neurons and

* Corresponding author at: Institute for Drug Discovery, Griffith University, 170 Kessels Road, Nathan 4111, Queensland, Australia.
E-mail addresses: j.tellovelasquez@griffith.edu.au (J. Tello Velasquez), rebecca.yao@griffithuni.edu.au (R.-Q. Yao), filip.lim@uam.es (F. Lim), hanc@cic.nagoya-u.ac.jp (C. Han), ojika@agr.nagoya-u.ac.jp (M. Ojika), jenny.ekberg@qut.edu.au (J.A.K. Ekberg), r.quinn@griffith.edu.au (R.J. Quinn), j.stjohn@griffith.edu.au (J.A.S. John).

http://dx.doi.org/10.1016/j.mcn.2016.06.005
1044-7431/


hOECs
Fibroblast
hONS
A
p75
DAPI
B
C
D
s100β
DAPI
E
F
G
s100A4
DAPI
H
I
J
fibro
DAPI
K
L
M
βIII tubulin
DAPI
N
O
P
GAP43
DAPI
Q
R