European Journal of Pharmacology 734 (2014) 83–90

Contents lists available at ScienceDirect

European Journal of Pharmacology

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

Review

Reversal of myofibroblast differentiation: A review

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ARTICLE INFO

Article history:
Received 25 January 2014
Received in revised form
2 April 2014
Accepted 3 April 2014
Available online 15 April 2014

Chemical compounds studied in this article:
Capsaicin (PubChem CID: 1548943)
S-Nitroso-N-acetylcysteine
(PubChem CID: 10313479)

Keywords:
Myofibroblast differentiation
Dedifferentiation
Molecular mechanisms
Mediators
Drugs

ABSTRACT

It has long been considered that fibrosis and fibroblast-to-myofibroblast differentiation are irreversible processes. However, recent data obtained indicates that tissue fibrosis and fibroblast-to-myofibroblast differentiation can indeed be reversed, which offers the possibility of a new therapeutic approach for fibrotic disorders. Here, we discuss the origin of the myofibroblasts and different aspects of their differentiation, especially the key mediators and TGFβ-induced signaling pathways. We also report here a few factors involved in myofiroblast dedifferentiation and several compounds which can reverse the established dedifferentiated myofibroblast, as examples that provide the reader a glimpse of the current trends of approach for discovering useful anti-fibrotic drugs.

Contents

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http://dx.doi.org/10.1016/j.ejphar.2014.04.007
0014-2999/

1. Introduction

The fibrotic diseases encompass a wide spectrum of clinical entities such as systemic sclerosis (SSc), sclerodermatous graft *versus* host disease, nephrogenic systemic fibrosis, as well as pulmonary, liver, and kidney fibrosis (Rosenbloom et al., 2010, 2012; Beyer et al., 2012; Wynn and Ramalingam, 2012). Approximately 45% of all deaths in the western developed countries can be attributed to fibrotic disease (Wynn, 2008) and the mortality in underdeveloped or developing countries is likely to be even much higher (Rosenbloom et al., 2012). Although these diseases pose a serious threat to health, an enormous challenge to health services, and a enormous economic burden to society, unfortunately, there is currently no accepted effective treatment for fibrosis disease (Wynn and Ramalingam, 2012).

Fibrosis results from the excess accumulation of extracellular matrix (ECM) macromolecules by activated mesenchymal cells, known as myofibroblasts, which distinguishes controlled repair occurring during normal wound healing from the uncontrolled fibrosis that is the hallmark of fibrotic disease (Hinz and Gabbiani, 2010; Hinz et al., 2012). Myofibroblasts are multifunctional cells derived from mesenchymal progenitors (fibroblasts), which play critical roles in both wound healing and fibrosis (Hinz et al., 2007), and the accumulation of myofibroblasts within pathologic lesions is a pivotal feature of many fibrotic disorders (Wynn, 2008). In addition, fibroblasts possess the potential to differentiate into myofibroblasts and this process is generally considered irreversible (Ryu and Daniels, 2010). Moreover, many patients with fibrosis diseases reach clinical attention only after significant fibrosis has already occurred (Garrison et al., 2013), so inhibition of the fibroblast-to-myofibroblast differentiation process may serve as a invalid means to prevent the progression of disease.

Fortunately, in recent years, many research groups have found that fibroblast-to-myofibroblast differentiation can in fact be reversed in phenotype and gene expression (Hecker et al., 2011; Garrison et al., 2013). And this reversible phenomenon offers a new therapeutic target and brings new hope for the fibrotic patients. Herein, we will briefly review the origin of myofibroblasts, their differentiation, and several factors or drugs for reversing myofibroblasts differentiaton. Finally, our perspectives on this research area are provided.

2. Myofibroblasts

2.1. Roles of myofibroblasts in health and disease

The myofibroblast is an intermediate cell between the fibroblast and the smooth muscle cell (Gabbiani et al., 1971) and myofibroblasts have been demonstrated as the main effectors of fibrosis in all tissues (Shirol and Shirol, 2012). Myofibroblasts are associated with wound healing and commonly present in fibrotic organs with high remodeling capacity such as kidneys (LeBleu et al., 2013), lungs (Phan, 2002) and liver (Lemoinne et al., 2013). Activated myofibroblasts express α-smooth muscle actin (α-SMA) and display increased proliferation, migratory ability, production of cytokines and interstitial matrix (Shirol and Shirol, 2012); however, myofibroblasts often create a collagenous and stiff scar that frequently disrupts the function of intact residual tissues and alters the biochemical and biophysical microenvironment, so pathological and persistent myofibroblast activation makes healthy neighboring cells into fibrotic and dysfunctional cells (Kis et al., 2011). Therefore, myofibroblasts play crucial roles in growth, development, wound healing as well as disease in most tissues and organs.

2.2. Origins of myofibroblasts

It has been demonstrated that myofibroblasts are derived from different precursor cells in both normal and pathological tissues (Fig. 1). Myofibroblasts are present in few normal tissues, such as alveolar septa, intestinal pericryptal cells, and bone marrow stroma (Tomasek et al., 2002; Wynn and Ramalingam, 2012). In injured tissues undergoing repair, quiescent fibroblasts, such as resident fibroblasts or perivascular and vascular adventitial fibroblasts, are activated and then differentiate into a myofibroblast phenotype (Li and Wang, 2011). In skin wounds, myofibroblasts originate from local recruitment of fibroblasts in the dermis and subcutaneous tissues surrounding the wound (Desmouliere et al., 2005). It has been shown that pericytes and vascular smooth muscle cells (SMCs) are also potential sources of myofibroblasts in vascular wound healing (McAnulty, 2007).

Another important cellular source for myofibroblasts is epithelial to mesenchymal transition (EMT) and endothelial to mesenchymal transition (EndMT). Numerous studies have described the occurrence of EMT in the course of renal, pulmonary, and liver fibrosis (Liu, 2004; Willis et al., 2006; Xu et al., 2009; Iwaisako et al., 2012). During EMT, differentiated epithelial cells lose expression of their epithelial characteristics such as E-cadherin, zona occludens 1, mucin 1, desmoplakins, cytokeratin 18, and gain mesenchymal cell markers such as vimentin, fibroblast-specific protein-1, α-SMA, N-cadherin, type I/III collagen, fibronectin and snail (Kalluri and Weinberg, 2009). Endothelial cells have been demonstrated to undergo a similar process called EndMT which is observed during cardiovascular development as well as in pathological cancer and fibrosis (Kovacic et al., 2012; Yu et al., 2014). In EndMT, endothelial cells gradually lose their endothelial markers such as VE-cadherin, CD31, von willebrand factor, TIE1 and TIE2 (Garcia et al., 2012; Ghosh et al., 2012), and also acquire fibroblastic markers like EMT process. In addition, some tissue specific stem cells in response to certain stimuli or specific signals, may differentiate into myofibroblasts (Cho et al., 2012; Yang et al., 2012).

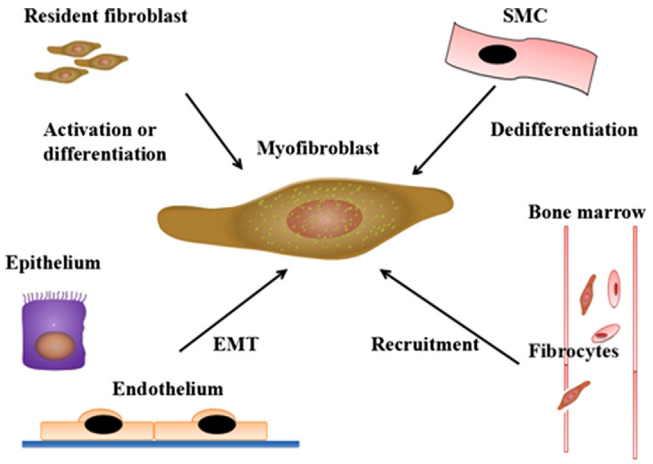

Fig. 1. Multiple origins of myofibroblasts.