Biochemistry & Pharmacology: Open Access

Riobo and Galdo, Biochem & Pharmacol 2013, 2:2
DOI: 10.4172/2167-0501.1000e141

Editorial Open Access

Hedgehog Dysfunction in Fibrosis: Insights in the Pathogenesis of Scleroderma

Natalia A Riobo[1]* and Francesco Del Galdo[2]

[1]Department of Biochemistry and Molecular Biology, Thomas Jefferson University, Philadelphia, USA
[2]LMBRU and Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, UK

Introduction

The Hedgehog (HH) pathway has been repeatedly linked to the development of fibrosis in different tissues in conditions like liver fibrosis, pancreatic cancer, idiopathic pulmonary fibrosis and more recently Scleroderma. Transforming growth factor-β (TGF-β) is the main signal that activates fibroblasts to contract and deposit collagen and other extracellular matrix proteins. These specialized cells, myofibroblasts, are very abundant in fibrotic conditions. In this commentary we will discuss the evidences that link the HH and TGF-β pathways and will discuss their potential dysfunction during the pathogenesis of Scleroderma.

Aberrant Activation of the HH Pathway in Fibrotic Conditions

In human idiopathic pulmonary fibrosis there is a paradoxical reduction of expression of the HH proteins SHH and IHH in the alveolar and bronchiolar epithelia with a specific increase of SHH in fibroblast in the fibrotic regions [1]. Nuclear staining of Gli1 and Gli2, the transcription factors that mediate the canonical HH pathway [2], and the pattern of expression of negative regulators of HH signaling in idiopathic pulmonary fibrosis indicates activation of the pathway in the fibrotic loci and the surrounding alveolar epithelium by the paracrine action of SHH secreted by activated fibroblasts. Studies in primary lung fibroblasts indicate that SMO, the central transducer of the HH pathway, and Gli activity are required to induce the expression of α-smooth muscle actin (αSMA), colagen1a (COL1a), and fibronectin-1 (FN1), markers of TGF-β induced fibroblast activation. Interestingly, TGF-β treatment of lung fibroblasts isolated from patients affected by pulmonary fibrosis undergo myofibroblastic differentiation in a Gli-dependent manner but partially independently of SMO, suggesting an alternative pathway leading to Gli activation in a pro-fibrotic environment. Interestingly, this observation was limited to profibrotic fibroblasts and not reproducible on fibroblasts subcultured from healthy lungs.

Activation of the HH pathway has also been implicated in the desmoplastic response in pancreatic cancer [3]. Expression of SHH in an orthotopic model of pancreatic cancer in mice contributes to the fibrogenic reaction, as administration of SHH blocking antibody almost prevented the resulting fibrosis [3]. SHH enhanced pancreatic stellate cell proliferation and differentiation and enhanced pancreatic myofibroblast invasion in a paracrine manner. As a proof of principle, developmental overexpression of SHH or IHH in acinar cells in zebrafish also leads to a dramatic fibrotic response [4]. In this model, the fibrotic regions contained elevated numbers of proliferating myofibroblasts characterized by expression of αSMA and proliferating cell nuclear antigen (PCNA). The fibrotic region also showed an increase in TGF-β in ductular cells and of αSMA and Gli1 and Gli2 in the myofibroblasts. SHH and IHH also increased the expression of some matrix metalloproteases (MMPs), which are necessary for the extracellular matrix remodeling that promotes migration of activated HH-responsive fibroblasts. This study also revealed that Hh ligands recruit and activate myofibroblasts from several sources, which is in agreement with the reported migratory and chemotactic effect of SHH on fibroblasts [5,6].

Similar studies on post injury liver fibrosis indicated that deletion of SMO in liver fibroblasts was sufficient to suppress the fibrotic reaction [7]. Moreover, HH proteins mediate liver fibrosis in conditions as diverse as radiation injury, schistosomiasis, and fatty liver disease [8-10].

Altogether, these and several other studies in the literature indicate that regardless of the cause leading to tissue fibrosis or the organ affected, HH pathway plays a central role in the activation of tissue fibroblasts, the key cellular elements of fibrosis, and that this activation is selective and not does not extend to other cell types such as epithelial or endothelial cells.

Regulation of HH Signaling by TGF-β

One of the key cytokines upregulated during tissue fibrosis is TGF-β. The HH pathway transcription factor Gli2 is one of the targets of TGF-β signaling, providing a direct way to stimulate Gli-dependent transcription even in the absence of HH ligands. Upregulation of Gli2 leads to induction of Gli1 for a strong activation of HH-target genes in normal fibroblasts and other cell types [11]. The mechanism involves recruitment of Smad3 and β-catenin to distinct elements of the gli2 gene promoter in response to TGF-β and is blocked by ALK5 inhibitors or Smad3 siRNA [11,12].

Dysfunctional SHH Activation in Scleroderma

Besides its role in the activation of tissue fibroblasts, SHH is a key signaling molecule for epithelial cell proliferation and angiogenesis [13]. The discovery of this common pathway in the function of epithelial cells, endothelial cells and fibroblasts led to implement therapeutic approaches using recombinant SHH to improve tissue regeneration during wound healing [14,15].

Indeed, during wound healing the activation of tissue fibroblasts and deposition of extracellular matrix is finely tuned with epithelial cells proliferation and angiogenesis [16]. In contrast, during tissue fibrosis in Scleroderma both epithelial cell proliferation and angiogenesis

***Corresponding author:** Natalia A Riobo, Department of Biochemistry and Molecular Biology, Jefferson Medical College, Thomas Jefferson University, USA, E-mail: Natalia.Riobo@jefferson.edu

Received June 24, 2013; **Accepted** June 27, 2013; **Published** July 01, 2013

Citation: Riobo NA, Galdo FD (2013) Hedgehog Dysfunction in Fibrosis: Insights in the Pathogenesis of Scleroderma. Biochem & Pharmacol 2:e141. doi:10.4172/2167-0501.1000e141

are impaired in favor of aberrant fibroblast activation. In this sense it is rather intriguing to note that the activation of SHH pathway, noted in Scleroderma as well as in many other fibrotic conditions, it is not accompanied by increased proliferation of epithelial cells and angiogenesis [17-19].

If SHH is clearly activated during tissue fibrosis, why angiogenesis and epithelial cell proliferation are impaired? Does TGF-β play any role in the cell-type selective SHH function during fibrosis?

Indeed, the work of Jung et al. [4] clearly demonstrates that during fibrogenesis there is an intricate paracrine signaling involvingfibroblasts and epithelial cell types.The study of the cell specific crosstalk of TGF-β and SHH will shed light in the complex molecular events leading to fibrosis in Scleroderma and other fibrotic diseases.

References

1. Cigna N, Farrokhi Moshai E, Brayer S, Marchal-Somme J, Wémeau-Stervinou L, et al. (2012) The hedgehog system machinery controls transforming growth factor-β-dependent myofibroblastic differentiation in humans: involvement in idiopathic pulmonary fibrosis. Am J Pathol 181: 2126-2137.
2. Robbins DJ, Fei DL, Riobo NA (2012) The Hedgehog signal transduction network. Sci Signal 5: 6.
3. Bailey JM, Swanson BJ, Hamada T, Eggers JP, Singh PK, et al. (2008) Sonic hedgehog promotes desmoplasia in pancreatic cancer. Clin Cancer Res 14: 5995-6004.
4. Jung IH, Jung DE, Park YN, Song SY, Park SW (2011) Aberrant Hedgehog ligands induce progressive pancreatic fibrosis by paracrine activation of myofibroblasts and ductular cells in transgenic zebrafish. PLoS One 6: 27941.
5. Polizio AH, Chinchilla P, Chen X, Kim S, Manning DR, et al. (2011) Heterotrimeric Gi proteins link Hedgehog signaling to activation of Rho small GTPases to promote fibroblast migration. J Biol Chem 286: 19589-19596.
6. Bijlsma MF, Borensztajn KS, Roelink H, Peppelenbosch MP, Spek CA (2007) Sonic hedgehog induces transcription-independent cytoskeletal rearrangement and migration regulated by arachidonate metabolites. Cell Signal 19: 2596-2604.
7. Michelotti GA, Xie G, Swiderska M, Choi SS, Karaca G, et al. (2013) Smoothened is a master regulator of adult liver repair. J Clin Invest 66904.
8. Wang S, Hyun J, Youn B, Jung Y (2013) Hedgehog signaling regulates the repair response in mouse liver damaged by irradiation. Radiat Res 179: 69-75.
9. Pereira TA, Xie G, Choi SS, Syn WK, Voieta I, et al. (2013) Macrophage-derived Hedgehog ligands promotes fibrogenic and angiogenic responses in human schistosomiasismansoni. Liver Int 33: 149-161.
10. Syn WK, Agboola KM, Swiderska M, Michelotti GA, Liaskou E, et al. (2012) NKT-associated hedgehog and osteopontin drive fibrogenesis in non-alcoholic fatty liver disease. Gut 61: 1323-1329.
11. Dennler S, André J, Alexaki I, Li A, Magnaldo T, et al. (2007) Induction of sonic hedgehog mediators by transforming growth factor-beta: Smad3-dependent activation of Gli2 and Gli1 expression in vitro and in vivo. Cancer Res 67: 6981–6986
12. Dennler S, André J, Verrecchia F, Mauviel A (2009) Cloning of the human GLI2 Promoter: transcriptional activation by transforming growth factor-beta via SMAD3/beta-catenin cooperation. Journal J Biol Chem 284: 31523-31531.
13. Chinchilla P, Xiao L, Kazanietz MG, Riobo NA (2010) Hedgehog proteins activate pro-angiogenic responses in endothelial cells through non-canonical signaling pathways. Cell Cycle 9: 570-579.
14. Asai J, Takenaka H, Kusano KF, Ii M, Luedemann C, et al. (2006) Topical sonic hedgehog gene therapy accelerates wound healing in diabetes by enhancing endothelial progenitor cell-mediated microvascular remodeling. Circulation 113: 2413-2424.
15. Park HJ, Lee J, Kim MJ, Kang TJ, Jeong Y, et al. (2012) Sonic hedgehog intradermal gene therapy using a biodegradable poly(β-amino esters) nanoparticle to enhance wound healing. Biomaterials33: 9148-9156.
16. Deonarine K, Panelli MC, Stashower ME, Jin P, Smith K, et al. (2007) Gene expression profiling of cutaneous wound healing. J Transl Med 5: 11.
17. Zerr P, Palumbo-Zerr K, Distler A, Tomcik M, Vollath S, et al. (2012) Inhibition of hedgehog signaling for the treatment of murine sclerodermatous chronic graft-versus-host disease. Blood 120: 2909-2917.
18. Horn A, Palumbo K, Cordazzo C, Dees C, Akhmetshina A, et al. (2012) Hedgehog signaling controls fibroblast activation and tissue fibrosisin systemic sclerosis. Arthritis Rheum 64: 2724-2733.
19. Horn A, Kireva T, Palumbo-Zerr K, Dees C, Tomcik M, et al. (2012) Inhibition of hedgehog signalling prevents experimental fibrosis and induces regression of established fibrosis. Ann Rheum Dis 71: 785-789.