Roles of Pancreatic Stellate Cells in Pancreatic Inflammation and Fibrosis

ATSUSHI MASAMUNE, TAKASHI WATANABE, KAZUHIRO KIKUTA, and TOORU SHIMOSEGAWA

Division of Gastroenterology, Tohoku University Graduate School of Medicine, Sendai, Japan

Over a decade, there is accumulating evidence that activated pancreatic stellate cells (PSCs) play a pivotal role in the development of pancreatic fibrosis. In response to pancreatic injury or inflammation, quiescent PSCs are transformed (activated) to myofibroblast-like cells, which express α-smooth muscle actin. Activated PSCs proliferate, migrate, produce extracellular matrix components, such as type I collagen, and express cytokines and chemokines. Recent studies have suggested novel roles of PSCs in local immune functions and angiogenesis in the pancreas. If the pancreatic inflammation and injury are sustained or repeated, PSC activation is perpetuated, leading to the development of pancreatic fibrosis. In this context, pancreatic fibrosis can be defined as pathologic changes of extracellular matrix composition in both quantity and quality, resulting from perpetuated activation of PSCs. Because PSCs are very similar to hepatic stellate cells, PSC research should develop in directions more relevant to the pathophysiology of the pancreas, for example, issues related to trypsin, nonoxidative alcohol metabolites, and pancreatic cancer. Indeed, in addition to their roles in chronic pancreatitis, it has been increasingly recognized that PSCs contribute to the progression of pancreatic cancer. Very recently, contribution of bone marrow–derived cells to PSCs was reported. Further elucidation of the roles of PSCs in pancreatic fibrosis should promote development of rational approaches for the treatment of chronic pancreatitis and pancreatic cancer.

Fibrosis is a characteristic feature of chronic pancreatitis (CP) and of the desmoplastic reaction associated with pancreatic cancer. Until recently, however, the molecular mechanisms of pancreatic fibrosis remained largely unknown at least in part as a result of the lack of appropriate in vitro models. In 1998, star-shaped cells in the pancreas, called pancreatic stellate cells (PSCs), were identified and characterized.[1,2] Over a decade, there is accumulating evidence that activated PSCs play a pivotal role in the development of pancreatic fibrosis in CP and in pancreatic cancer.[1–8]

Activation of Pancreatic Stellate Cells

In normal pancreas, stellate cells are quiescent and can be identified by the presence of vitamin A–containing lipid droplets in the cytoplasm.[1–5] PSCs show mainly a periacinar distribution and constitute 4% of all pancreatic cells.[1,2] Expression of the intermediate filament proteins, desmin and glial fibrillary acidic protein (GFAP), is also used as a marker of quiescent PSCs. The expression and activation of GFAP have been confirmed in transgenic GFAP-*LacZ* mice where 2.2 kilobase of the GFAP promoter activity was associated exclusively with PSCs.[9] The cell functions of quiescent PSCs remain largely unknown, but periacinar localization suggests a role in maintaining pancreatic acinar cells. In addition, their periductal and perivascular localization suggests that quiescent PSCs might play a role in the regulation of ductal and vascular functions in the pancreas.

The physiologic consequences of vitamin A storage in PSCs remain unclear, but it might have a role in maintenance of the quiescent state. McCarroll et al[10] showed that retinol and its metabolites inhibited the induction of α-smooth muscle actin (α-SMA) expression in quiescent PSCs and induced quiescence in culture-activated PSCs. It is, therefore, tempting to speculate that retinoic acids are involved in the maintenance of a quiescent phenotype through the binding to their nuclear receptors and the regulation of gene expression. In this scenario, the loss of retinoids in the course of PSC activation might not be an epiphenomenon but essential for senescence.

In response to pancreatic injury or inflammation, quiescent PSCs undergo morphologic and functional changes to become myofibroblast-like cells, which express α-SMA (Figure 1). This step is called activation. The critical regulatory events that induce PSC activation in vivo are likely to be similar, at least in part, to the events that regulate the activation of primary PSCs in culture in vitro.[1–8] Studies of rat and human primary PSCs in culture have identified a variety of soluble factors, such as cytokines (interleukin [IL]-1, IL-6, and tumor necrosis factor [TNF]–α) and growth factors (platelet-derived growth factor [PDGF], transforming growth factor [TGF]–β1, and activin A), ethanol and its metabolites, oxidative stress, and pressure, as well as extensive changes in the composition and organization of extracellular matrix (ECM), as regulators of PSC activation.[11–19] Potential sources of these activating factors include activated macrophages, platelets, pancreatic acinar cells, ductal cells, and endothelial cells in inflamed pancreas. It has been shown that pancreatic cancer cells can also be a source of PSC-activating factors.[6–8] Importantly, PSCs by themselves are capable of synthesizing cytokines such as TGF-β1, activin A, and IL-1, suggesting the existence of autocrine loops that might

Abbreviations used in this paper: BM, bone marrow; CP, chronic pancreatitis; ECM, extracellular matrix; GFAP, glial fibrillary acidic protein; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; PDGF, platelet-derived growth factor; MMP, matrix metalloproteinase; NADPH, nicotinamide adenine dinucleotide phosphate; PSCs, pancreatic stellate cells; SMA, smooth muscle actin; TGF, transforming growth factor; TIMP, tissue inhibitor of metalloproteinase; TLR, Toll-like receptor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

© 2009 by the AGA Institute
1542-3565/09/$36.00
doi:10.1016/j.cgh.2009.07.038

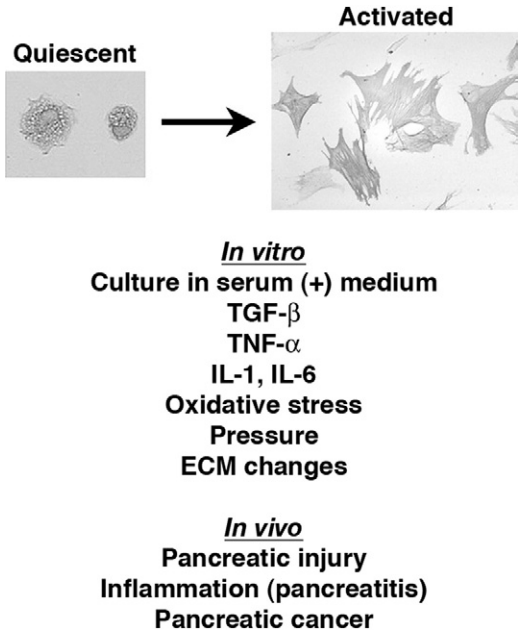

Figure 1. Stimulants of PSC activation. Quiescent PSCs undergo morphologic and functional changes to become activated myofibroblast-like cells. In vitro studies have identified a variety of soluble factors such as cytokines and growth factors, ethanol and its metabolites, oxidative stress, and pressure, as well as extensive changes in the composition and organization of ECM, as regulators of PSC activation. During pancreatic injury, inflammation, and pancreatic cancer in vivo, PSCs are likely to be exposed to these stimuli.

contribute to the perpetuation of PSC activation after stimulation by an initial exogenous signal, thereby promoting the development of fibrosis.[11–17]

Functions of Pancreatic Stellate Cells

On activation, PSCs lose lipid droplets, more actively proliferate, migrate, produce ECM components, and secrete proinflammatory cytokines and chemokines.[1–8,19] Cytokines and growth factors produced by acinar cells, inflammatory cells, platelets, ductal cells, endothelial cells, cancer cells, and PSCs by themselves could activate PSCs and induce these cell responses in paracrine and autocrine manners.[1–8] Accumulating evidence supports major roles for PDGF, which induces proliferation and migration of PSCs, and TGF-β1, which induces PSCs to express α-SMA and ECM proteins, as mediators of the persistently activated and profibrogenic phenotypes of PSCs.[11–19] In addition, recent studies have revealed that PSCs have a variety of cell functions (Table 1). Not only do PSCs produce ECM components, they also produce matrix-degrading enzymes of the matrix metalloproteinases (MMPs) family and their inhibitors (tissue inhibitors of metalloproteinases [TIMPs]). PSCs have been shown to secrete MMP-2, MMP-9, and MMP-13 and to express TIMP-1 and TIMP-2.[20] Thus, PSCs might be involved in the maintenance of normal tissue architecture by regulating ECM turnover. In this scenario, resolution of cerulein-induced pancreatitis in mice involves transient activation of PSCs and deposition of ECM proteins, as well as transient up-regulation of MMPs and TIMPs.[21] On the other hand, MMP-2 produced by PSCs might contribute to the progression of pancreatic cancer.[22]

The increased expression of the cytoskeletal protein α-SMA confers increased contractile potential, which is further enhanced by endothelin-1.[23] As mentioned, PSCs are located around the ductal and vascular structures[1–5]; PSC contraction could regulate vascular and ductal tone in the pancreas.

PSCs have the ability to produce a wide variety of cytokines and growth factors. PSCs produce IL-1β, IL-6, TNF-α, TGF-β1, and PDGF-BB, all of which contribute to perpetuation of PSC activation.[3–5,11–19,24,25] Chemokines (IL-8, monocyte chemoattractant protein [MCP]-1, and RANTES) produced by PSCs contribute to the recruitment of inflammatory cells to the inflamed pancreas.[24,25] Expression of cell adhesion molecules, such as intercellular adhesion molecule-1 in PSCs, also contributes to the adhesion of recruited inflammatory cells.[26] Very recently, we and others have shown that PSCs express Toll-like receptors (TLRs), proteins involved in the activation of innate immunity.[27,28] PSCs express TLR2, which recognizes pathogen-associated molecular patterns of gram-positive bacteria, and TLR4, which recognizes lipopolysaccharides of gram-negative bacteria. PSCs also express TLR3, which recognizes double-stranded RNA produced during viral replication, and TLR5, which recognizes flagellin, the major component of bacterial flagella. In addition, PSCs endocytose and phagocytose foreign bodies, necrotic debris, and aged polymorphonuclear cells, suggesting that PSCs might have a role in the local immune functions in the pancreas.[28,29] Thus, it is likely that PSCs play a "macrophage-like" role in the pancreas, comparable to the role of Kupffer cells in the liver. PSCs might contribute to organ restitution and homeostasis by engulfing pancreatic acinar cells undergoing apoptosis and necrosis.[30]

A novel function we recently identified in PSCs is related to angiogenesis.[31] PSCs constitutively produce vascular endothelial growth factor (VEGF), and its generation is increased by hypoxia. In addition to VEGF, PSCs express several angiogenesis-regulating molecules including VEGF receptors (Flt-1 and Flk-1), angiopoietin-1 and its receptor Tie-2, and vasohibin-1. Conditioned media of hypoxia-treated PSCs induced angiogenesis in vitro and in vivo; it increased tube formation on Matrigel (BD Biosciences, Franklin Lakes, NJ) and directed vessel formation in nude mice (Figure 2).[31] A significant association between fibrosis, angiogenesis, and higher VEGF expression has been reported in pancreatic cancer and in CP.[32] Thus, PSCs might play profibrogenic and proangiogenic roles during the development of pancreatic fibrosis, where they are subjected to hypoxia. Although further in vivo studies are needed for a more detailed characterization of this scenario, these findings suggest a novel mechanism linking hypoxia, inflammatory responses, angiogenesis, and fibrosis in the pancreas.

Table 1. Responses of PSC to Stimulation and Activation

α-SMA expression
Proliferation
ECM production (type I, type III collagen, etc)
Cytokine, chemokine production (IL-8, MCP-1, etc)
Adhesion molecule (ICAM-1) expression
Migration/chemotaxis
Contractility
Matrix degradation (MMPs expression)
TLRs expression
Endocytosis and phagocytosis
Angiogenic responses

Download English Version:

https://daneshyari.com/en/article/3284041

Download Persian Version:

https://daneshyari.com/article/3284041

Daneshyari.com