1. ABSTRACT

Liver fibrosis represents a major medical problem with significant morbidity and mortality. Worldwide hepatitis viral infections represent the major cause liver fibrosis; however, within the United States chronic ethanol consumption is the leading cause of hepatic fibrosis. Other known stimuli for liver fibrosis include helminthic infection, iron or copper overload and biliary obstruction. Fibrosis can be classified as a wound healing response to a variety of chronic stimuli that is characterized by an excessive deposition of extracellular matrix proteins of which type I collagen predominates. This excess deposition of extracellular matrix proteins disrupts the normal architecture of the liver resulting in pathophysiological damage to the organ. If left untreated fibrosis can progress to liver cirrhosis ultimately leading to organ failure and death if left untreated. This review will discuss the molecular events leading to liver fibrosis. The discussion will include collagen gene regulation and proliferative signals that contribute to the amplification of the hepatic stellate cell, the primary fibrogenic cell type that resides in the liver.

2. INTRODUCTION

The hepatic stellate cell (HSC) (formerly called the Ito cell, fat storing cell, perisinusoidal cell, and lipocyte) is the primary cell-type in the liver responsible for excess collagen synthesis during hepatic fibrosis (1-10). Following a fibrotic stimulus, such as excess ethanol consumption, the HSC undergoes a complex transformation or activation process where the cell changes from a quiescent vitamin A storing cell to that of an activated myofibroblast-like cell (11-13). Cellular changes accompanying HSC activation include morphological changes to a myofibroblast-like cell that is associated with the appearance of the cytoskeletal protein smooth muscle α-actin, a loss in the cellular vitamin A stores, and an increase in the appearance of rough endoplasmic reticulum (2,5,8,10,14-21). Metabolically an increase in DNA synthesis and cellular proliferation occurs with HSC activation. Altered collagen synthesis, at both the mRNA and protein levels, is observed with a dramatic increase in type I collagen, and smaller but significant increases in type III and type IV collagens (3,5,8,10,14,15,17-23). Expression of HSP47, a collagen-binding stress protein believed to act as a collagen-specific molecular chaperone during collagen biosynthesis, is induced in the HSC during hepatic fibrosis (24). In addition, expression of all three isoforms of TGF-β, the most potent fibrogenic cytokine for HSCs, and its receptors are increased following HSC activation (25-27). Furthermore, the synthesis of platelet-derived growth factor-beta (PDGF-β), the most potent mitogen for HSCs is increased following HSC activation (6,24,25,28,29). In accordance, the PDGF-β receptor is also increased in activated HSCs (30,31).

Activation of HSCs results in two major events that promote the fibrogenic response of these cells. First, HSCs change their pattern of gene expression that results in an increase in synthesis and deposition of extracellular matrix proteins; hence these cells become directly fibrogenic. Secondly, the proliferation rate of HSCs increases following cellular activation. This effectively amplifies the number of fibrogenic cells present in the liver. Therefore, it is believed that effective treatment regimes aimed at reducing or inhibiting either the fibrogenic or
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Figure 1. PDGF-Induced Proliferation Signaling in the Hepatic Stellate Cell. Following binding of PDGF to the PDGF cell surface receptor several signaling cascades are activated in the HSC. Activation of the MAPK-JNK pathway has been demonstrated as well as activation of the Ras-MEK-ERK pathway. In addition FAK has been shown to be involved in HSC proliferation which signals through the PI3-kinase-AKT-p70S6 kinase pathway. Cross-talk between the different signaling pathways also occurs.

proliferative responses of HSCs would reduce the deleterious effects of HSCs in the progression of fibrosis.

3. FIBROGENESIS

The molecular mechanisms underlying hepatic fibrosis are under extensive investigation. In the normal liver the turnover of the extracellular matrix (ECM) is maintained in a homeostatic equilibrium between ECM synthesis and degradation. During fibrosis an imbalance between ECM synthesis and degradation occurs. This imbalance results in a net increase in the synthesis and deposition of extracellular matrix proteins accompanied with an increase in tissue inhibitor of matrix metalloproteinase (TIMP) expression that inhibits collagenase activity.

The molecular mechanisms responsible for the increase in ECM components is best understood for type I collagen. Regulation of type I collagen during the fibrogenic response has shown to be a complex process. Type I collagen is the product of two genes, the \( \alpha_1(I) \) and \( \alpha_2(I) \) genes and although located on different chromosomes these genes are coordinately regulated in a tissue specific, developmental, and inducible manner. Increased type I collagen synthesis is due to both transcriptional and posttranscriptional mechanisms. An increase in the transcription rate of the \( \alpha_1(I) \) collagen gene is observed accompanied with an increase in Sp1 binding activity to the promoter (32-35). Sp1 is a potent transactivator of the \( \alpha_1(I) \) collagen gene (36). In addition, post-transcriptional regulation of the type I collagen takes place following HSC activation. An increase in the stability of the \( \alpha_1(I) \) collagen mRNA occurs that is mediated through protein interactions in the 3’ untranslated region of the mRNA molecule. Increased translation of the \( \alpha_1(I) \) collagen message is noted following HSC activation that is mediated by protein binding to a conserved stem loop structure within the 5’ region of the mRNA encompassing the translational start site (8,9,33,37-39). In addition to increased expression of collagen and other ECM components an increase in TIMP gene expression occurs as well as a decrease in matrix metalloproteinase gene expression.

There are several mediators that can influence the fibrogenic response of HSCs. These include retinoids, interleukin-1\( \beta \), tumor necrosis factor, and acetaldehyde. However, transforming growth factor – beta (TGF-\( \beta \)) is the most potent fibrogenic cytokine known for the HSC. Exogenous administration of TGF-\( \beta \) induces fibrosis in the lung, kidney, and liver (40). During experimental models of hepatic fibrosis, including bile duct ligation, CCl\( _4 \) administration, and schistosomiasis infection, a prolonged increase in TGF-\( \beta \) expression is observed (41-44). In addition, patients with alcohol-induced and viral-induced cirrhosis also exhibit increased TGF-\( \beta \) mRNA levels that correlate with the extent of fibrosis (45-47). Studies using transgenic mice have provided strong evidence for a fibrogenic role of TGF-\( \beta \) in the development of liver fibrosis. A constitutively expressing form of active TGF-\( \beta \) resulted in increased levels of TGF-\( \beta \) with the development of hepatic fibrosis and increased type I collagen deposition (40,48,49).

4. PROLIFERATION

In addition to the molecular events leading to the excess synthesis and remodeling of the extracellular matrix, proliferation of activated HSCs amplifies the fibrogenesis. Quiescent HSCs reside in the liver in a non-proliferative state; however, once activated, either when cultured on plastic cellular or in vivo following a fibrogenic response, HSCs proliferate (50,51). Although several factors are mitogenic for HSCs the most potent mitogenic factors for the HSC is platelet-derived growth factor (PDGF) (52-58). PDGF is a heterodimeric protein composed of two polypeptide chains (A and B chains) that can combine into three different combinations, AA, BB, or AB. For the HSC, PDGF-BB is the most potent at stimulating cellular proliferation (32,53,59). The PDGF receptor is a transmembrane dimeric complex composed of \( \alpha \alpha \), \( \alpha \beta \), or \( \beta \beta \) subunits (60). Binding of PDGF to its receptor results in receptor dimerization and activation by autophosphorylation of tyrosine residues (61). The phosphoryrosines on the activated receptor operate as high affinity binding sites for several molecules, mediated by either src homology domains (SH-2 domains) or phosphotyrosine binding domains that propagate the signals of receptor activation stimulating several signaling cascades (62,63) (see Figure 1).

4.1. MAPK signaling

Activation of Ras followed by the sequential activation of Raf, MEK, and ERK is one signaling cascade that is activated by PDGF stimulation of HSCs (54,64,65). ERK activation results in the phosphorylation of several transcription factors, including SAP and ELK-1. Activation of ERK is observed following PDGF stimulation in cultured HSCs and in HSCs isolated from animals treated with a single dose of CCI(4) (66). The
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The anti-proliferative effects of PDGF may be mediated by ERK inhibition or by up-regulation of endothelin B receptors (ETB-R) amplifying the anti-proliferative effect of endothelin-1 in HSCs.

4.3. PI3-kinase – Akt signaling

The phosphatidylinositol 3-kinase (PI3-kinase) – Akt pathway is also activated following PDGF stimulation of HSCs (58,85). PI3-kinase is a heterodimeric protein that possesses lipid and protein kinase activity. It is composed of a regulatory 85 kDa subunit and a 110 kDa catalytic subunit. After PDGF stimulation, the 85 kDa subunit of PI3-kinase associates with the activated PDGF receptor through two SH-2 domains and becomes phosphorylated. Activation of PI3-kinase results in the generation of several phosphorylated inositol lipids (PtdIns3P, PtdIns(3,4)P₂, PtdIns(3,5)P₂, and PtdIns3,4,5P₃), from phosphoinositols that are essential for intracellular signaling (86,87). The generated phosphorylated inositol lipids bind to the pleckstrin homology domain of Akt and induces Akt translocation to the plasma membrane. Once located at the plasma membrane, conformational changes occur that permit phosphoinositide-dependent kinase 1 (PDK-1) to phosphorylate Akt at Thr 308 and Ser 473 residues, followed by PKA, which in turn is activated by cAMP (77).

Activation of PI3-kinase is important for HSC proliferation and chemotaxis (85; our unpublished observations). A role for PI3-kinase in HSC proliferation is supported by in vivo studies in rats where CCl₄ treatment leads to autophosphorylation of the PDGF receptor and increased PI3-kinase activity. Furthermore, inhibition of PI3-kinase by wortmannin blocked mitogenesis in response to PDGF supporting the involvement of this pathway in HSC proliferation (85). Similar results are obtained using a more specific PI3-kinase inhibitor LY294002 (65). Inhibition of PI3-kinase by wortmannin also reduces ERK and JNK activity (80). Another possible mechanism by which PDGF can inhibit its own proliferative response is the ability of cAMP to block activation of Raf-1, MEK, and MAPK by phosphorylation of Raf-1, thereby inhibiting its binding affinity to Ras (81). Phosphorylation of Raf-1 is mediated by PKA, which in turn is activated by cAMP (77).

Activation of PI3-kinase including integrin and stimulators of G-protein-coupled receptors (87,94-97).

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collagen protein levels, implicating its participation in HSC proliferation. Both inhibition of PI3-kinase with LY and inhibition of Akt by adenoviral mediated transduction of a dominant negative form of Akt markedly reduced HSC proliferation, α1(I) collagen mRNA, and protein levels. Transduction of HSCs with an adenovirus expressing a constitutively active form of Akt induced HSC proliferation in low serum conditions. Thus, it is concluded that Akt is positioned downstream of PI3-kinase (our unpublished observations).

4.4. FAK signaling

PDGF also activates focal adhesion kinase (FAK), a member of the focal adhesion complex (98). This complex interacts with extracellular matrix proteins through integrin interactions, providing a direct sensor to the integrity of the extracellular environment. PDGF treatment of HSCs leads to FAK phosphorylation, which is blocked by a dominant negative form of ras (99,100). We have shown that PDGF treatment activates and requires focal adhesion kinase (FAK) and PI3-kinase for HSC proliferation (unpublished observations). Blocking FAK activity using a dominant negative form of FAK (Ad-FAK-C) inhibits HSC proliferation and PI3-kinase activity following PDGF treatment. We have also demonstrated that FAK is positioned upstream of PI3-kinase in the proliferative response of HSCs to PDGF. Additionally, blocking FAK inhibits cell migration (unpublished observations).

4.5. p70S6 kinase signaling

Another downstream target in the PI3-kinase pathway via Akt is p70 S6 kinase (p70S6 kinase). The p70S6 kinase is a 70 kDa protein that is activated by mitogens and growth factors, several hormones including insulin, amino acids, and by intracellular calcium (101-105). A primary target of p70S6 kinase is the ribosomal S6 protein of the 40S ribosomal subunit (106,107). p70S6 kinase exists in two different isoforms, a 70 kDa cytoplasmic and an 85 kDa nuclear form. It is a key regulatory element of mRNA translation and protein synthesis. Furthermore, it is required for cell cycle progression, cell differentiation and cell growth. Both isoforms are in the mitogen-activated pathway, downstream of PI3-kinase. Activation of p70S6 kinase occurs through a complex series of phosphorylation events on several serine or threonine residues via the Aku/PDK1 pathway (108,109). Phosphorylation of Thr 229 and Thr 389 are most critical or threonine residues via the Akt/PDK1 pathway (108,109). These data indicate that p70S6 kinase is positioned downstream of Akt in the PI3-kinase pathway and is strongly involved in HSC proliferation. We have shown that PDGF activates FAK and PI3-kinase in HSC proliferation (unpublished observations). Taken together, we have also shown FAK signals to PI3-kinase leading to Akt activation and subsequent p70S6 kinase activation. Furthermore, rapamycin modulates the proliferative response in HSCs by inhibiting p70S6 kinase (unpublished data). The likely mechanisms by which rapamycin blocks p70S6 kinase activity is either by direct inhibition of p70S6 kinase phosphorylation in the PI3-kinase pathway or by inhibition of the mTOR/FRAP induced phosphorylation (112,113).

4.6. Signaling complexity

In general, one signaling factor can be responsible for a wide range of possible biologic effects. This may be due to the complexity of intracellular signaling, because one signal does not strictly stimulate only a single cascade but more likely cross-talk with other pathways, therefore modulating a broad spectrum of signaling kinases. On the other hand a single signaling factor may have several biologic functions, indicating the diversity of cellular metabolism. However, pharmacologic blockade of one specific signaling step several hours after growth factor stimulation still can result in abrogation of the biologic response. This suggests that a stimulus needs a distinct amount of time until it results in the desired action. An early stage is probably the association of the growth factor with its receptor, followed by intermediate and late phase until completion of the biologic effect (114). In fact, it has been demonstrated that growth-factor-dependent mitogenesis requires two specific phases of signaling in the Ras/ERK pathway for progression in the cell cycle (101). This accounts also for PDGF-induced PI3-kinase activation, where only the late wave of activation is required for progression through G1 (102). Similar results were obtained in human HSCs, showing that PDGF-induced stimulation resulted in a biphasic stimulation of ERK activity, which was related to the stimulation of cell proliferation (103).

A proper intracellular milieu is essential for the correct execution of the biological function of all the described kinase pathways. Therefore, it is not surprising that pH and intracellular calcium concentration play a very important role in preserving homeostasis and kinase integrity in HSCs. For example, the mitogenic potential of the different isoforms of PDGF correlated with their
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potential to increase intracellular Ca\(^{2+}\) in activated rat and human HSCs (104). Furthermore, the ability of PDGF to induce a proliferative response was associated with the capability to maintain an increased intracellular Ca\(^{2+}\) concentration due to Ca\(^{2+}\) entry (105,118). Accordingly, PDGF stimulation of HSCs in the absence of Ca\(^{2+}\) did not result in HSC proliferation (115). Regulation of the intracellular pH by modulating the activity of the Na\(^+/\)H\(^+\) exchanger is another facet of PDGF (116,117). Pharmacologic inhibition of the Na\(^+/\)H\(^+\) exchanger resulted in an inhibition of PDGF-induced mitogenesis, indicating that changes in the intracellular pH by this growth factor are essential for its proliferative activity (119). Furthermore, it has been proposed that PDGF-induced amplification of the Na\(^+/\)H\(^+\) exchanger activity is linked to the activation of PI3-kinase and inhibition of the Na\(^+/\)H\(^+\) exchanger lead to the disruption of downstream signaling events, such as PDGF-induced FAK phosphorylation (109). Indeed, we have demonstrated that FAK is involved in cell adhesion, cell migration and more importantly in HSC proliferation, because blocking FAK or PI3-kinase resulted in a marked reduction of these phenomena.

Finally, other mitogenic growth factors include angiogenic growth factors, such as basic fibroblast growth factor (b-FGF) and vascular endothelial growth factor (VEGF). In stellate cells b-FGF has a similar mitogenic and chemoattractant activity as PDGF (120). VEGF signaling in HSCs via its receptors includes activation of ERK, protein-kinase C and e-Akt. Activation of HSCs is associated with increased expression of VEGF and its receptors, which may again result in more cross-talk signals in the complex signal transduction pathways of hepatic stellate cells (121,122).

5. PERSPECTIVE

In summary, proliferation in hepatic stellate cells is regulated via different signaling cascades (see Figure 1). Recent research has led to better understanding of how HSCs change from a quiescent to an activated and proliferating cell type. However, further research needs to address the question of how the cell-cycle is targeted by these signaling pathways. It is anticipated that an understanding of the molecular events leading to fibrogenesis and HSC proliferation may lead to the development of effective therapies for hepatic fibrosis.

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