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# Roles Of The Gh-Igf-Igfbp Axis In Hepatic Fibrosis

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## ABSTRACT

Hepatic fibrosis refers to the excessive deposition of collagen fibers and subsequently evolves liver cirrhosis to HCC. Currently, there is not successful therapeutic approach to liver fibrosis in addition to liver transplantation for patients with decompensate liver cirrhosis. Therefore, it is important to identify cellular and molecular mechanism that promote liver damage or provide hepatoprotection for development of therapeutic approaches. The GH-IGF-IGFBP axis consists of growth hormone (GH), two growth factors (IGF-I and IGF-II), their receptors (IGF-IR and IGF-IIR) and a group of binding proteins (IGFBP1-7). In the recent years, accumulating evidences have demonstrated that the elements of this axis play the important roles in the pathogenesis of liver fibrosis. In this review, we first summarize genomic and pathological information of the IGF-IGFBP axis and further review the roles of each element of this axis in the pathogenesis of liver fibrosis.

## KEYWORDS:

Growth hormone; Hepatic fibrosis; Insulin-like growth factor; Insulin-like growth factor receptor; Insulin-like growth factor binding protein

## INTRODUCTION

Hepatic fibrosis refers to the extracellular matrix (ECM) caused by various reasons, such as hepatitis B and C virus infections, cholestasis, alcohol abuse, drugs, metabolic, autoimmune and congenital diseases. In general, these factors can lead to development of severe liver damage then can progress to liver fibrosis and subsequently evaluates liver cirrhosis to HCC [1]. There are more than 600,000 HCC cases each year so it has been the 5th most common neoplasm globally and the 3rd leading cause of cancer-related death [2, 3]. At the present, in addition to liver transplantation for patients with decompensate liver cirrhosis; there is not successful therapeutic approach to liver fibrosis. Less than 40% of the patients with HCC are eligible

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for curative treatments including surgical resection as the option, liver translation and percutaneous ablation. Unfortunately there is either a high frequency of tumor recurrence after surgical or resistance to conventional chemotherapy and radiotherapy [4]. Even much worse was that about 21% of patients with nonalcoholic steatohepatitis (NASH) will have some regression of fibrosis while 38% patients will progress over 5.3 years follow-up, and alcoholic hepatitis is a necroinflammatory process associated with the rapid progression of fibrosis and leads to cirrhosis in 40% of case in recent study. With the increase of nonalcoholic fatty liver disease (NAFLD) and alcoholic liver disease (ALD), the trend is still developing [5]. Therefore, it is important to identify cellular and molecular mechanism that promotes liver damage from fibrosis in order to provide hepatoprotection for development of therapeutic approaches.

The GH-IGF-IGFBP axis consists of GH, two growth factors (IGF-I and IGF-Ⅱ), their receptors (IGF-IR and IGF-Ⅱ) and a group of binding proteins (IGFBP1-7), parts of their biological functions listed in table 1. In the recent years, the accumulating evidences have demonstrated that the GH-IGF-IGFBP axis plays important roles in the pathogenesis of liver fibrosis and carcinoma. For instance, GH resistance and low serum levels of IGF-1 are common features in human liver fibrosis and cirrhosis [6]. IGFBPs are modified in cirrhosis patient especially increased IGFBP1 and reduced IGFBP3 levels subsequently lead to change this hormone bioavailability in liver tissues [7, 8]. In this article, we aimed to summarize genomic and pathological information of the GH-IGF-IGFBP axis and further to review the roles of each element of this axis in the pathogenesis of hepatic fibrosis.

**Hepatic fibrosis in humans**

Chronic liver diseases and its complications constitute one of the major causes of mortality worldwide. Liver fibrosis namely hepatic fibrosis refers to the ECM caused by various reasons, such as hepatitis B and C virus infections, cholestasis, alcohol abuse, drugs, metabolic, autoimmune and congenital diseases, especially the excessive deposition of collagen fibers, subsequently evolves liver cirrhosis to HCC [1]. The increasing prevalence of liver cirrhosis makes it one of the major medical hot points in the 21st century. At present, in addition to liver transplantation for patients with decompensate liver cirrhosis, there is not successful therapeutic approach to liver fibrosis.

HCC (HCC) is one of the most common malignant tumors. Necrosis and inflammation of the liver caused by chronic liver damage are key driving forces in the progression of hepatocarcinogenesis. It is reported about 5% of patients with compensated liver cirrhosis eventually develop liver cancer each year [2]. Recent study suggests that about 21% of patients with nonalcoholic steatohepatitis (NASH) will have some regression of fibrosis while 38% patients will progress over 5.3 years follow-up, and alcoholic hepatitis is a necroinflammatory process associated with the rapid progression of fibrosis and leads to cirrhosis in 40% of case. Therefore with the increase of NAFLD and ALD the trend is developing [3]. Moreover, in the liver related cause of death, which the patients with compensated cirrhosis died of, liver cancer accounts for 50-70%

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[5, 6]. The morbidity of liver cancer is gradually increasing around the world annually (dead patient over super 625thousand per year), ranking the fifth of the malignant tumors. Liver cancer include different types, histologically distinct primary hepatic neoplasms including HCC, intrahepatic bile duct carcinoma (cholangiocarcinoma), hepatoblastoma,bile duct cystadenocarcinoma, and haemangiosarcoma and epitheliod haemangioendothelioma. In developing countries HCC accounts for 85-90% of primary liver cancers and is the fifth most common cancer in all global [9].After experienced aggressive conventional therapy the five-year survival rate of patients with HCC is not more than 10% yet, which make the malignancy become the second cancer killer after pancreatic ductal adenocarcinoma. Up to today surgical resection and liver transplantation are still the optimal selection for treatment of liver cancer but they can only be offered to a small subgroup of patients with early stages of disease. The five-Recurrent rate of HCC is 50-70% following surgery operation and the five-year survival rate is only 80% [10].

**Cellular basis and molecular pathways in hepatic fibrosis**

The liver is a complex organ, which makes up of parenchymal cells such as hepatocytes and non-parenchymal cells such as bile duct epithelial cells (BEC), hepatic stellate cells (HSC), liver sinusoidal endothelial cells, resident macrophages (Kupffer cells) and other immune cells, such as B-cells, T-cells and natural killer (NK) cells. Remarkably, the progression and resolution of fibrosis also is a complex process involving parenchymal and non-parenchymal cells as well as infiltrating immune cells, which can directly or indirectly contribute to liver fibrosis. Chronic hepatocyte death caused by apoptosis, necrosis or necroptosis is a most vital step. Cell death induces activation of inflammatory and profibrogenic pathways in non-parenchymal cells infiltrating immune cells, which on one hand initiate the fibrosis progression, on the other hand which also may promote the fibrosis resolution [11].

In the past decade, researches have focused on HSCs and analyzed its characteristic features like plasticity and transdifferentiation to myofibroblasts, which can be readily recapitulated in tissue culture. The activation of HSC represents the vital event of liver fibrosis since this cell type is the major producer of ECM [12], which is the essential step that culminates in major changes in liver architecture. So current concepts envision activated HSCs as a crucial profibrogenic source and key fibrogenic effector cell type; the majority of hepatocytes are thought to undergo necrosis or apoptosis, thereby providing space for proliferating cells, although the other cells also involve the procedure of the liver fibrosis, as point of fact macrophages, infiltrating neutrophils, T and B cells, and eosinophils participate in the inflammatory response and may continue to cause the damage, whereby activated macrophages and neutrophils clean up tissue debris, dead cells and invading organisms [13,14].

More recent work regarding liver fibrosis is progressively shifting towards the myofibroblast as a pivotal cell type due to its contractile nature and

RA Journal of Applied Research
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synthesis repertoire [15, 16]. Result from the animal and human studies suggested that activation of hepatic myofibroblasts plays a critical role in development of liver fibrosis, in which the increased amount of myofibroblasts correlates with the severity of liver fibrosis in patients [17]. Although evidence hints at HSCs and PFs as a major source [14, 15], the source of the myofibroblasts is not completely understood and the composition may vary depend on the cause lead to liver fibrosis. All myofibroblasts share some common characterizations, for example expression of Col1α1, α-SMA, fibronectin, TIMP1, TGFβRI, PAI-1, activin, vimentin, activation of TGFβ1 signaling pathway. Myofibroblasts can up regulate expression in liver ,which stand for a wide spectrum of functions such as the dynamic nature in the wound-healing response, synthesis of fibrillar collagens, contractile and migratory activities, secretion of chemotactic and vasoactive factors, and the secretion of matrix metalloproteinases (MMPs) and tissue inhibitor of metalloproteinases (TIMPs) [17].

Substantial progress has been achieved in delineating the molecular mechanisms underlying liver fibrosis in the last decade which have been described in excellent reviews [18-20]. Using experiment model in vitro and in vivo the researchers proved again that PI3K/Akt signaling pathway involved in the progression of the liver fibrosis and carcinogenesis [21, 22]. And hepatoma-derived growth factor/nucleolin axis represents a novel diagnostic and therapeutic target [23].

Inflammation and activation of the immune system are also critical steps in liver fibrosis. In this respect, more recent study show that Insulin-like growth factor binding protein- related protein (IGFBPrP1) can initiate the liver fibrosis by inducing inflammation, HSC activation and EMC deposition through the ERK 1/2 pathway[24]. In addition, lipopolysaccharide (LPS) originated from the gut is very important for the production of interleukin 6 (IL-6) by Kupffer cells thereby linking liver regeneration, fibrosis and cancer development [25, 26].

Moreover, recruitment of inflammatory cells from the bone marrow to the injured liver that is mediated by chemokines or growth factors has been shown to be another critical step for fibrosis progression [27]. Additional factors that have played the important part in the pathogenesis of liver fibrosis are represented by adipokines [28], especially leptin that signals through the gp130 co-receptor and activates the JAK-STAT pathway [29]. More recently, Gankyrin promotes liver fibrosis/cirrhosis progression into hepatocarcinoma relying on a persistent liver injury and inflammatory microenvironment, hence the inhibition of gankyrin and Rac1/JNK as a potential prevention mechanism for cirrhosis transition [30].The renin-angiotensin system also has emerged as a key system in tissue remodeling of the liver and represents a promising target for therapeutic intervention [31].

## Genetic and chemical animal models for research in hepatic fibrosis

Several animal models have been established and employed to identify molecular mechanisms

RA Journal of Applied Research
||Volume||1||Issue||08||Pages-277-312||Sept -2015|| ISSN (e): 2394-6709
www.rajournals.in

underlying liver fibrosis. These animal models reflecting toxic liver injury were set up commonly by repeatedly application of hepatotoxic substances such as carbon tetrachloride (CCl4) or dimethylnitromine (DMN), diethylnitrosamine (DEN), thioacetamide (TAA), DEN plus CCl4. In addition, surgical ligation of the common bile duct (BDL) or cholic acid (CA) feeding resulting in bile acid overload mouse model is often used to mimic cholesteric liver injury. Certainty many special animal model were established for the special purpose in the study of liver fibrosis Table 1.

To identify vital effecter pathways in hepatic fibrosis many genetic models, gene transduction models and gene knock-down models for liver fibrosis have been established in recent years, such as classic transforming growth factor beta (TGF-beta) [37], platelet-derived growth factor B (PDGF-B) [38], PDGF-C[39] and tissue inhibitor of metalloproteinase 1 (TIMP-1) [40]. Mice with targeted deletion of the multidrug resistance 2 (Mdr2) gene represent a genetic model for sclerosing cholangitis and cholestasis-induced hepatic fibrosis. Although chronic liver injury is rather mild in Mdr2-deficient mice, they develop HCC and represent a genetic model for inflammatory liver cancer [41]. Mdr2 deficient mice have been used to identify liver tumorpromoting functions of nuclear factor kappa B (NFkappaB) [42]. Axl-/- mice, a gene transduction models, were set up by injecting an adenoviral vector IGFBPrP1 via their tail vein thereby overexpressed IGFBPrP1 in rat liver [43]. More recent Gankyrinhep transgenic mice were generated, which characterized by hepatocyte-specific gankyrin overexpression and malignant transformation from liver fibrosis to tumors obviously. This new transgenic mouse strain shares typical features of the majority of human HCC development, and it faithfully recapitulates the natural history of chronic injury, inflammation and fibrosis [30].

**The GH-IGF-IGFBP axis and its role in hepatic fibrosis**

The GH-IGF-IGFBP axis consists of GH (GH), two growth factors (IGF-I and IGF-II), their receptors (IGF-IR and IGF-Ⅱ) and a group of binding proteins (IGFBP1-7). To systematically describe each element of the GH-IGF-IGFBP axis in genetics and biology, bioinformatics of all members in this axis is summarized in Table 2. In the recent years, accumulating evidence has demonstrated that GH resistance and low serum levels of IGF-1 are common features in human liver fibrosis and cirrhosis [6]. Furthermore, IGFBPs are also modified in cirrhosis patient. Especially increased IGFBP1 and reduced IGFBP3 levels lead to change this hormone bioavailability in liver tissues [7, 8]. IGFBP7 induces liver fibrosis by inducing hepatic stellate cell activation and hepatocyte apoptosis [44]. Therefore, the GH-IGF-IGFBP axis plays important roles in the pathogenesis of liver fibrosis or liver carcinoma. In the recent years, several animal models have been developed to investigate pathophysiology of hepatic fibrosis in relation with the GH-IGF-IGFBP axis. These animal models are described briefly in Table 3. The molecular defect of each element of this axis is discussed as following.

RA Journal of Applied Research
||Volume||1||Issue||08||Pages-277-312||Sept -2015|| ISSN (e): 2394-6709
www.rajournals.in

**GH**

This hormone is produced and secreted by the pituitary gland to induce body growth by binding to the GH receptor in liver and activating a signaling pathway leads to transcription of several genes, including IGF. Its main process as follow, GH binds to its cognate GH receptor thereby leading to receptor dimerization and Janus kinase 2(JAK2) activation. The activated JAK2 phosphorylates the signal transducer and activator of transcription 5(STAT5), which form a dimerization then translocates to nucleus therefore ultimately control the expression of genes by acting as a transcription [49].

GH deficiency patient have very low levels of GH, as well as low IGF-1 due to the impaired hepatic synthesis. IGF-1 inhibits GH secretion by acting on the pituitary directly or by stimulating somatostation secretion in the hypothalamus, which in turn suppress GH release. So a negative feedback circuit forms. Insulin and amino acids are needed for post signaling to induce IGF-1synthesis [50]. GH resistance and low serum levels of IGF-1 are common features in human liver fibrosis and cirrhosis [6] and mounting evidences have manifested that the GH plays important roles in the pathogenesis of liver fibrosis or liver carcinoma in the recent years.

Adams L.A. et al. have reported an obvious development of NAFLD in patients with hypothalamic and pituitary dysfunction [51]. Furthermore, liver cirrhosis is found to be companied with IGF-1 deficiency and become more severe with the disease progression [52-55]. Interestingly IGF-1 levels are reduced in cirrhotic patients while GH levels are increased [56]. Another study further proven that GH, IGF-I, and IGF-binding protein 3 (IGFBP3) were closely associated with hepatic steatosis and fibrosis in patients with NAFLD even in non-GH-deficient control population [57].

On one hand, GH resistance dramatically exacerbates liver fibrosis in a mouse model of inflammatory cholestasis [58]. On the other hand, recombinant human GH can influence the GH/IGF-1 axis in rats with liver cirrhosis [59], at the same time regardless its side effects, GH replacement therapy can reverse NASH in patients with adult growth hormone deficiency [60] and improve the GH resistance in cirrhosis patients significantly increasing levels of IGF-1, IGFBP-3 and ALS were measured [6]. Abrogation of GH signaling in male liver leads to metabolic syndrome, hepatic steatosis, increased inflammation and fibrosis, and development of hepatic tumor [61]. Also more recent a good review pointed out that GH resistance plays a causal role in the development of liver fibrosis and abrogation of growth hormone signaling render the liver cells more susceptible to insults therefore contributes to the progression of liver fibrosis, but the mechanism underlies is still unknown [62]. From all mentioned above, it is obvious that the GH is closely related to the procedure of liver fibrosis.

**GHR**

The growth hormone receptor (GHR) gene located in human chromosome 5q13.1. Liver cells have GH receptors that upon stimulation by the hormone

RA Journal of Applied Research
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increase IGF-1 gene transcription, once synthesized IGF-1 is released into plasma. In GH resistance, GH receptors in the liver are unresponsive to GH and result in decreased IGF-1production, and subsequently lead to hyper secretion of GH [63].

Researchers spare no effort to uncover the function of GH signaling in liver. They generated several strain of mice with GH receptor gene knockout. Surprisingly the GH receptor (GHR) gene-disrupted mouse (GHR-/-), characterized by dwarf and GH insensitive resulting in low serum IGF-1 and increased levels of GH, are long lived and hold the record for the longest-lived laboratory mouse. Although the reason behind it is not unclear, there is evidence of decreased rates of diabetes and cancer [64, 65].The similar results in Ecuadorian patients with Laron syndrome have been reported [66].

It is apparent that liver-specific GHR knockout or deficient mice (GHRLD) is very important model as liver play a key role in the GH/IGF-1 axis, more factors could contribute to the tumorigenesis in GHRLD mice. GHR-LD mice have a fourfold increase in serum GH levels and a more than 90% reduction in circulating IGF-1 thereby developing hyperglycemia, hyperinsulinemia, and marked insulin resistance as a result of high circulating GH acting on tissues such as muscle and fat but GH signaling has remained intact in it [67]. Of particular interest, although GHRLD mice have no change in body size and body composition, as early as 6-8 weeks of life these mice had catch severe hepatic steatosis despite on a normal diet, largely owing to increased triglyceride (TG) synthesis together with less excretion of TG and elevated supply of free fatty acids [67, 68]. More recently a study by Edward O. list, et al.come to the same result in a separate independent study [69]. Furthermore, accumulating evidence implicated that hyperinsulinema and insulin-resistance in GHR-LD mice could lead to deregulation of insulin receptor (IR) in malignant cells and promote tumor progression [70, 71].

Similarly, an examine show that in GHR-LD mice, in addition to the abnormal glucose tolerance, impaired insulin secretion, and hyperlipidemia, key markers of inflammation , fibrotic markers (such as Col1A2 and Col3A1), Mup1 and Selenbp2 were significantly increased, together with a two- to threefold increase in TGF-β transcripts. The expression of cell cycle and growth relevant genes (such as Ccnd1, Socs2, Socs3, and Egfr) was markedly affected in GHR-LD liver. Microscopic analyses of GHR-LD livers further revealed the presence of hepatic adenomas of different stages of malignancy. Hence abrogation of GH signaling in male liver leads to metabolic syndrome, hepatic steatosis, increased inflammation and fibrosis, and development of hepatic tumor [72].

**IGF-1**

IGF-I is a polypeptide and produced by several tissues including liver ,bone muscle and brain with endocrine, paracrine, and autocrine effects whose structure is 50% similar to that of insulin. Although many tissues secrete it, more than 90% of circulating IGF-I is synthesized in the liver, of which accounting for about 75% of circulating IGF- I level secondary to the GH stimulation, which is the main

RA Journal of Applied Research
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www.rajournals.in

mediator of GH function in normal embryonic development and postnatal growth [73].

GH is produced and secreted by the pituitary gland to induce body growth by binding to the GH receptor in the liver and activating a signaling pathway leads to transcription of several genes, including IGF-I. Human IGF-I gene is located on chromosome 12q23.2 consisting of six exons and several introns and can be transcribed from two alternative promoters. These different mature IGF-I transcripts, produced by alternative splicing and polyadenylation, encode for different preproteins that undergo post-translational modifications and mature by proteolytic cleavage at both ends, thereby resulting in a single polypeptide of 70 amino acids residues (7.5 kDa) cross-linked by 3 disulfide bonds and share homology with insulin, but the impact on IGF-I functionality of such a complex mRNA and protein procession is not completely understood [73, 74].

As mention above, IGF-I is produced by several tissues, including the liver, bone, muscle and brain. The IGF-I produced in these organs acts locally, with the exception of the liver, the most secreted hormone producer. Interestingly, although that Hepatocytes are the main producers of IGF-I in the liver and the liver-originated IGF-I has endocrine effects on the extrahepatic tissues, no local effects of this hormone in the liver has been reported. The cause may be due to the low amount of IGF-I receptors expressed on the hepatocytes membranes. However, there are IGF-I receptors expressed in the liver in non-abundant non-parenchymal cells such as Kupffer cells, hepatic stellate cells (HSCs) and myofibroblasts cells thereby make a minimal contribution [74,75].

Circulating IGF-I levels increase from birth to puberty and reach their maximum value then decline with age thereafter. When circulating IGF-I increases and reaches certain high level, it inhibits the synthesis of GH thus IGF-I production is controlled by negative feedback. Functionally IGF-I can increase glucose use by stimulating its peripheral uptake and inhibits liver glucose-lowering effect that is similar to insulin. IGF-I exerts its function by binding to its principal receptor (IGF-IR) with high affinity. In addition, it can also bind to IR with 100-fold less affinity. IGF-I binding to IGF-IR promotes anabolic processes such as DNA, RNA, protein and glycogen synthesis and produces proliferative and differentiating effects. The following tables summarize the IGF-I physiological effects [75].

There is little IGF-I receptors on the hepatocytes, suggesting that during the adulthood IGF-I from liver would be unable to stimulate liver growth. However, IGF-I may play an important role in promoting hepatocyte proliferation and accelerating DNA synthesis together with cytokines as IL-6, TGF-α, HGF and TNF-α,although the mechanism of IGF-I stimulating liver regeneration more effectively than growth of intact liver is unclear [76,77].

IGF-I is a major ligand of the IGF pathway, highly expressed in the liver. But some work showed that IGF-I serum levels were associated with variables related to liver dysfunction and to

RA Journal of Applied Research
||Volume||1||Issue||08||Pages-277-312||Sept -2015|| ISSN (e): 2394-6709
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more advanced liver disease and seem to undergo little influence from other clinical and laboratory variables, therefore mainly reflecting hepatic functional status. Even some other work show that IGF-I may be a protumorigenic factor for several cancer, such as prostate cancer [78],colon adenocarcinoma [79], breast cancer in premenopausal women [80],colorectal and lung cancer [81],but all these studies establish no cause-effect relationship between IGF-I level and tumor development. However, majority of studies show that IGF-I expression may be antitumorigenic in the case of HCC. Firstly, in patients of chronic liver damage and functional insufficiency, such as liver cirrhosis, the secretion IGF-I is reduced or even totally suppressed in the most severe cases [81-83]. So IGF-I levels are negatively related to the level of clinical impairment and can be used as an index for evaluating the severity of cirrhosis; also it can be used for determining the severity of the disease, when liver biopsy is not possible [84, 85]. A recent survey supports this conclusion [86]. As the cirrhotic liver is the substrate for HCC development, in turn the decreased IGF-I levels could help to hepatocarcinogenesis. In fact, in patients with chronic hepatitis, decreased levels of IGF-I are associated with HCC incidence [87]. In contrast, IGF-I plays an essential role to prevent the development of NASH [88]; Secondly, amounting study data prove that patients with HCC also show lower levels of circulating IGF-I when compared with healthy controls[89,90,91]. In fact, as the previous serum IGF-I levels is preceded by a significant reduction with the progression of hepatic dysfunction in patients with HCC [90, 91, 92, 93], independently of the etiology [91]. More recent study supports this view [91]. Thus, a precocious diagnosis of HCC could be performed based on a decrease in serum IGF-I levels [86, 95, 96], IGF-I could represent a good, noninvasive marker of liver fibrosis [96]. Moreover, transcriptome analysis reveals that IGF-I mRNA levels are decreased in HCC human samples compared to normal livers tissue [97]. This can also be observed when liver tumors develop in mouse models after a single exposure to DEN hepatotoxic. In this case, mouse HCC is induced in a non-cirrhotic liver [98]; and furthermore, bioactive IGF-I also declined significantly after an oral glucose load in patients with liver cirrhosis, despite unchanged concentrations of total and free IGF-I [99].Thirdly decreased levels of IGF-I are associated with higher tumor invasiveness and poor prognosis [98]. Baseline levels of plasma IGF-1 and VEGF correlated significantly with survival in patients with HCC, Integrating IGF-1 and VEGF into HCC staging significantly enhanced prognostic stratification of patients [100] that seems to be validated by another more recent work. The combination of low IGF-I and high VEGF predicts median overall survival of 2.7 mo compared with 19 mo for patients with higher IGF-I and lower VEGF. Serum IGF-I levels also predict tumor progression and overall survival in patients with HCC who undergo transarterial chemoembolization [101]. High pretreatment IGF-1 levels were associated with better DCR, PFS and OS of patients who received antiangiogenic therapy for advanced HCC [102]. Fourthly, lack of liver IGF-I mRNA increases

RA Journal of Applied Research
||Volume||1||Issue||08||Pages-277-312||Sept -2015|| ISSN (e): 2394-6709
www.rajournals.in

the risk of HCC recurrence after curative resection [103, 104].

**IGF-IR**

IGF-IR is a transmembrane tyrosine kinase receptor that is structurally similar to insulin receptor, composed of two homodimers, connected by disulfide bond, two extracellular α subunits forming the receptor for ligand binding and two β subunits comprising the transmembrane and tyrosine kinase domains. IGF-I, IGF-Ⅱ and insulin bind to IGF-1R, however, IGF-Ⅱ and insulin bind to IGF-IR with 2-5 fold and 100-1000 fold less affinity, respectively, thereby IGF-IR is mainly activated by IGF-Ⅰ[105].After IGF ligand binding, IGF-IR undergoes a conformational change that activates the tyrosine kinase domain, which causes autophosphorylation of specific tyrosine thereby full activation of the IGF-IR and recruitment of specific docking proteins, including insulin receptor substrate proteins (IRS-1 to -4) and an adaptor protein Shc[106]. Insulin receptor substrate proteins (IRS) are the most important substrates of IGF-IR and play a prominent role in exerting the activity of IGF-IR by activating downstream signals. Following IGF-IR activation, additional tyrosine residues are then phosphorylated, which act as docking stations for substrates such as the insulin receptor substrate IRS and Shc adaptor proteins, then recruit additional factors to yield activations of many signaling cascades, of which the phosphatidyl inositol 3-kinase (PI3K) and the mitogen-activated protein kinase (MAPK) are two very important signaling cascades, both result in cell differentiation, proliferation and anti-apoptosis. Thus, in summary, IGF-IR activation leads to differentiation or to increased cell proliferation and migration [107].

Signaling through IGF-IR plays an important role in tumorigenesis because of its ability to promote proliferation, anti-apoptosis and increase cell mobility [107]. IGF-IR is highly activated in HCC tumors and it is the activation of IGF-1R, but not insulin receptor that is associated with the activation of ribosomal protein S6 (RPS6) and an increase in IGF-Ⅱ level [108], which suggests that IGF-Ⅱ may be responsible for IGF-IR activation. Subsequent signaling is transduced mainly through PI3K/Akt/mTOR pathway thereby mediating cell survival and the RAS/RAF/MAP kinases that predominates cell proliferation [109]. It is reported that IGF-IR gene expression levels were higher in adjacent normal mucosa than in cancer tissue and were significantly related to venous invasion and liver metastasis. IGF-IR gene expression is thus considered a useful predictor of liver metastasis from colorectal cancer.CM-MSCs secreted high levels of insulin binding proteins (IGFBPs), as well as, exerted an inhibitory effect on HCC proliferation. The antitumor effect was mediated through dysregulation of IGF signaling cascade; specifically, the activation of IGF-IR on HCC was inhibited which disrupted the downstream phosphatidylinositol 3-kinase (PI3K)/Akt signaling events [110].IGF-IR signaling via the PI3K and Akt axis also involves NF-κB signaling which upon chronic activation can lead to fibrosis and cirrhosis, thus increasing the risk of HCC [111].

IGF-IR overactivation is one of the hallmarks of HCC and can be mediated by increased levels of

RA Journal of Applied Research
||Volume||1||Issue||08||Pages-277-312||Sept -2015|| ISSN (e): 2394-6709
www.rajournals.in

IGF-IR protein and/or excess of IGF ligands. IGF-IR overexpression promotes tumor growth, progression, invasion and metastasis [112].Healthy mature hepatocytes do not express IGF-IR. In liver cirrhosis the condition is not completely clear as some authors' report that IGF-IR is unregulated while others consider it is just opposite [97,113]. Increased IGF-IR expression were observed after both acute and chronic hepatic damage, an increase of IGF-IR mRNA content was also observed in hepatic tissue obtained from all CHC patients as well as from 6 cadaveric liver donors following orthopic transplantation in comparison to normal liver, while no relevant modifications were detected in IGF-I mRNA content. The immunohistochemical results showed that the raise in IGF-IR mRNA content was related both to ductular reaction and to increased IGF-IR expression in hepatocytes. So the author thought that the up-regulation of IGF-IR expression in hepatocytes of patients with CHC could constitute an attempt to stimulate hepatocyte regeneration. Another work proved that High IGF-IR immunohistochemical expression correlated with the tumor grade and cirrhosis in a univariate analysis in HCC. The up-regulation of IGF-IR expression in hepatocytes of patients with CHC could constitute an attempt to stimulate hepatocyte regeneration [114]. Interestingly, in this study the IGF-I mRNA levels decrease from 4.95 ± 1.8 in normal livers to 1.22± 0.69 in the diseased livers with either chronic hepatitis or cirrhosis, IGF-I receptor levels also decrease from 1.15 ±0.83 in the normal to 0.31 ± 0.22 in the liver disease group [97].

**IGF-Ⅱ**

IGF-Ⅱ shares about 70% amino acid identity with IGF-I. Similar to IGF-I, IGF-Ⅱ can be produced by several tissues, but most comes from both parenchymal and non-parenchymal liver cells and acts in an autocrine, paracrine and endocrine fashion. It is abundant in fetal development, yet its quantity sharply diminishes after birth. IGF-Ⅱ knockout mice develop normally except all of them have stunted growth after birth, indicating that IGF-Ⅱ is critical in growth. The igf2-/-mice are born 40% smaller than the control mice, but the growth rate after birth is similar between knockout and control animals, indicating IGF-Ⅱ is more important for fetal growth [77].

IGF-Ⅱ expression is not regulated by GH like IGF-I, whose main transcriptional regulator is still not clearly understood. During fetal life the liver is the major organ for IGF-Ⅱ synthesis and secretion. Interestingly, neither normal liver tissue nor tissue of patients with chronic active hepatitis expressed IGF-Ⅱ in adult liver in immunohistochemical analysis [115], but more recent study showed that in all patients with HCC, IGF-Ⅱ expression was upregulated in tumor and adjacent non-neoplastic liver [116]. And overexpression of IGF-Ⅱ has been found in liver tumor tissue in both different animal models of hepatocarcinogenesis and approximate mannose-6-phosphately (M6P) 30-40% patient with HCC. These data suggest that IGF-Ⅱ plays an important role in cell proliferation of regenerating nodules and in HCC cells. IGF-Ⅱ also is a potent autocrine and paracrine mitogen for HCC cell proliferation [117].

RA Journal of Applied Research
||Volume||1||Issue||08||Pages-277-312||Sept -2015|| ISSN (e): 2394-6709
www.rajournals.in

IGF-Ⅱ gene encodes a pre-pro-IGF-Ⅱ protein of 180 amino acids that transforms to a 156 amino acid-long pro-IGF-Ⅱ upon peptide signal loss [118]. Most of the proIGF-Ⅱ is cleaved and glycosylated to yield the 67 amino acid-long mature IGF-Ⅱ [119]. IGF-Ⅱ can binds to IGF-1receptor/ IGF-Ⅱ receptor and hybrid receptor. The M6P/ IGF-Ⅱ receptor mediates the action of IGF-Ⅱ on exocytosis in insulin secreting cells. IGF-Ⅱ can stimulate the insulin release from β-cells at basal concentration of glucose, but inhibit glucose-induced insulin release [120, 121]. IGF-Ⅱ is able to bind with high affinity to IGF-IR just like IGF-I, to regulate cell proliferation and differentiation [122]. IGF-Ⅱ can also bind to IGF-ⅡR thereby inducing IGF-Ⅱitself internalization and degradation. Finally, IGF-Ⅱ can bind to insulin receptor subtype A (IR-A) to display mainly mitogenic effects [123]. It is very interesting that both IR-A and IGF-Ⅱ have been found increase in several tumors [124].

## IGF-IIR AND HEPATIC FIBROSIS

The IGF-ⅡR gene is located on chromosome 6q26 and an SNP with guanine to adenine (G to A) at position 1619 was implicated in IGF-Ⅱ-dependent growth, so it is not surprising that IGF-ⅡR gene expression in humans present polymorphism namely most humans are bi-allelic but some show imprinted expression [125]. IGF-ⅡR gene expression results in a transmembrane glycoprotein containing 2491 amino acids and about 90% locates in the Golgi apparatus and the other in the cell surface [126]. The extracellular domain consists of 15 homologous tandem repeats, able to bind with different affinities to mannose 6-phosphate (M6P)-containing proteins or M6P free factors. The 300 kDa protein contains 15 extracellular domains, which are the main binding sites for IGF-Ⅱ, M6P, and M6P analogues. IGF-ⅡR is an essential receptor to regulate the mannose-6 phosphate tagged lysosomal enzymes by transferring the enzymes from the secret sites to lysosome/endosome. The domains 3, 5, and 9 form the binding pocket for M6P.The main function of IGF-ⅡR is to transport extracellular and Golgi derived-acid hydrolases and other ligands to lysosomes [127]. Upon IGF-Ⅱ binding, the entire complex is internalized in clathrin-coated vesicles that travel to the endosomal compartment, where the ligand is degraded and the receptor is recycled to the cell membrane. IGF-ⅡR can bind IGF-Ⅱ with high affinity but has no tyrosine kinase activity and thereby does not transduce any signal to IGF-Ⅱ, so it is postulated that IGF-ⅡR may function as a tumor suppressor and plays a key role in regulating cell growth by contributing to the activation of TGF-Band inactivating the IGF-Ⅱ. Therefore, in the IGF axis, IGF-ⅡR acts as a scavenger receptor lacking intrinsic signaling and functions as tumor suppressor [125]. But another opinion thought that IGF-ⅡR may be cleaved from the cell membrane to act as a truncated soluble form [128].

IGF-ⅡR is a negative mediator for carcinogenesis and highly expressed in fibrotic HSCs and several cancers. For example, IGF-ⅡR was found high expression in HCC tissues and melanoma [129]. some authors thought that the IGF-ⅡR-specific peptide-431 may be used as a targeting ligand for HCC, melanoma, hemangioma, [130,131,132,134].In one hand, inhibition of

RA Journal of Applied Research
||Volume||1||Issue||08||Pages-277-312||Sept -2015|| ISSN (e): 2394-6709
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IGF-ⅡR expression increases cellular proliferation both in vitro and in vivo[135,136], even mannose 6-phosphate/ IGF-ⅡR gene can act as the tumor suppressor in cancer. M6P/ IGF-ⅡR are found inactivated in prostate cancer [137]. On other hand, the expression of IGF-II and IGF-IIR is obviously decreased in carcinomas and metastatic breast cancer, but has been found increase in normal gland and adenomas [138]. M6P/ IGF-II reduce tumorigenicity and invasive potential of HCC, but knockdown of M6P/ IGF-ⅡR enhances cell motility and invasiveness [139].

In addition, the experiment in vitro suggested overexpression of full length IGF-ⅡR into IGF-ⅡR deficient cells decreases cell growth and increases apoptosis [140] and decreases tumor growth in vivo [141]. The work manifested that overexpression of IGF-IIR has also been associated with an increase in cell number, because overexpression of IGF-ⅡR may affect the signaling of other relevant molecules, for example TGF-β thereby resulting in proliferative effects [141,142]. But antiproliferative effects of overexpressed IGF-IIR may only present in cell lines or tumors, and this increased proliferation depends on increased IGF-II levels. IGF-IIR also functions in the degradation of its ligand IGF-II peptide and in capture / activation/degradation of extracellular M6P-bearing ligand. IGF-IIR not only reduces the bioavailability of IGF-II but also inhibit IGF-II-mediated DNA synthesis [143]. From the mention above, we can conclude that the deficiency or loss of the IGF-ⅡR function will cause a decreased degradation of IGF-Ⅱ thereby an increase in the bioavailability of IGF-II.

**IGFBP-1**

IGFBP-1 is located on the chromosome 7q12.3, gene size 5312.Most of the IGFs (approximately 99%) in circulation bind to a group of binding proteins, termed as IGF binding proteins (IGFBPs). There are six IGFBPs (IGFBP-1 to -6) with conserved structure binding to IGFs with high affinity, while IGFBP-7 binds to IGFs with low affinity [144].IGFBPs are present in body fluids and tissue, varying in molecular size, biological function and hormone regulation. IGFBPs are involved in several biological functions, e.g. prolong the IGFs half-life, store and transport IGFs, modulate the activity of IGFs, as well as IGF-independent actions on cellular proliferation and migration [145]. Generally IGFBPs decrease the bioactivity of IGFs by competing with IGF receptors for binding. Posttranslational modifications of IGFBPs can affect their IGF affinity and thus regulate IGFs actions. For example, phosphorylation of IGFBP-1 increases its IGF binding affinity and promotes the inhibitory effect of IGFBP-1 on IGF actions. Serum proteolysis of IGFBPs, particularly proteolysis of IGFBP-3 can reduce the IGF binding affinity and thereby increase the IGF bioactivity [146].

IGFBP-1 is considered to be the acute regulator of IGF-Ⅰ bioavailability and a marker of peripheral insulin sensitivity. It stimulates cell migration and proliferation by its IGF independent effect. It also is thought to be most metabolically regulated IGFBP. Hepatic IGFBP-1 production, which is the major source of circulating IGFBP-1, is inhibited by insulin and stimulated by glucogen, cortisol, fasting or cytokines [147,148]. In the circulation, similar to

RA Journal of Applied Research
||Volume||1||Issue||08||Pages-277-312||Sept -2015|| ISSN (e): 2394-6709
www.rajournals.in

IGFBP-2,-4, and -6, IGFBP-1 forms a binary complex with IGFs, which is able to cross the vessel wall to transport IGFs into target tissues. IGFBP-1 has been considered to be the acute regulator of IGFs bioavailability by regulating the unbounded free IGF- I levels in vivo [149]. It has demonstrated that the Arg-Gly-Asp (RGD) conserved sequence in IGFBP-1 binds to the alpha 5 beta 1 integrin (α5β1 integrin) and stimulates the cell migration and proliferation, indicating IGFBP-1 has IGF independent effect [150].

IGFBP-1 plays an important role in the development and progression of HCC. The data showed that IGFBP-1was detected in cytoplasm as well as nucleus and down-regulated in HCC tissue compared to the adjacent non-cancerous liver tissue. These decreased expressions of IGFBP-1 were correlated with tumor differentiation, liver cirrhosis, microvascular invasion or metastasis [151,152]. Another study showed that IGFBP-1 can at least partly prevent liver fibrosis and improve cirrhotic liver regeneration by regulating the expression of the immediate-early gene [153]. Interestingly, the serum level of IGFBP-1 in patients with alcoholic liver cirrhosis was elevated [154]. Another work also found the same result in the patients with liver cancer, and postulated that increased synthesis of certain IGFBPs is necessary to compensate decreased production of the others or increased IGF production, determination of serum IGF-II, IGFBP-1 and their ratio may aid in estimating the compensatory capacity of the liver affected by cancer [155].

**IGFBP2**

IGFBP-2 is located on the chromosome 2q35, gene size 31609. It is the principal IGFBP secreted by white adipose tissue. It is regulated by leptin and has an anti-diabetic effect. IGFBP-2 and -5 seem to increase the bioavailability of IGF ligands therefore producing function against that of IGFBP-3 [156]. Furthermore there are evidences both in vitro and in vivo showing that antisense strategy targeting IGFBP-2 or 5 decreases neoplastic growth [156,157]. But IGFBP-2 and the other family members also have been proposed to suppress tumor development through binding IGFs preventing binding to their receptor and thereby preventing IGF driven tumorigenesis [158]. Conversely, there are also studies that demonstrate oncogenic functions including promoting proliferation, driving invasion, and suppressing apoptosis [159]. These effects appear to be independent of its ability to bind the IGFs and instead promote invasion and proliferation through interaction with integrin [160]. Studies have identified down-regulation in liver cirrhosis and hepatitis B virus-developed HCC tissue levels of IGFBP-2 protein respectively, which may be potential diagnostic makers or therapeutic targets for HBV-related HCC [161]. Extensive studies are needed to evaluate the role of IGFBP-2 in each group to provide a better understanding of it oncogenic and tumor suppressive potential.

**IGFBP3**

IGFBP-3 is located on the chromosome 7q12.3, gene size 9630. It is the predominant form and most abundant IGFBPs in circulation, account for 90% of all IGFBPs in serum. It binds to IGFs together with an acid-labile subunit (ALS) to form a stable ternary

RA Journal of Applied Research
||Volume||1||Issue||08||Pages-277-312||Sept -2015|| ISSN (e): 2394-6709
www.rajournals.in

complex. This 150kDa complex is not able to cross the vascular endothelium. Both IGFBP-3 and ALS are mainly produced from liver and regulated by GH .One of the key regulators of IGF expression is IGFBPs, it binds to the majority of circulating IGF-I and IGF- II ligands with high affinity, thus limit IGF access to IGF-I receptor, therefore reduce the availability of IGFs for signaling through IGFs receptors and diminish their effects on the cancer progression. On the other hand, the ternary complex increases the IGF-I half-life up to about twenty hours and keeps it in the circulation. Once the ternary complex is cleavaged into binary complex by a protease, IGF-I is released and able to cross the vasculature then leave the circulation and enter target tissues with the help of other IGFBPs thereby regulating the function and bioavaility of IGF-I [162].

Many studies have proven that IGFBP-3 involves in liver cirrhosis and hepatocellur carcinoma. In HCC patients with cirrhosis, IGFBP-3 mRNA of tumor or adjacent non-tumor tissues was lower than the normal liver tissue [163]. IGFBP-3 levels were significantly lower in cirrhotic patients compared to the healthy subjects and were correlated with the degree of liver dysfunction, and IGFBP-3 levels in patient with HCC were significantly lower than that in both the healthy subjects and patient with liver cirrhosis [164].Downregulation of IGFBP-3 in human HCC samples has been linked to promoter hypermethylation [165]. IGFBP-3 serum IGFBP-3 level were also significantly reduced in patients with cirrhosis or HCC[81,82,83,154,]and may be considered as the most promising serological marker for the prediction of the development of HCC in the HCV patients with cirrhosis [166,167]. The culture-activated HSCs migration can be reduced after IGFBP-3 knock-down therefore IGFBP-3 knock-down is thought to be a marker for culture-activated HSCs and play a role in HSC migration. An in vitro study suggested that IGFBP-3 had IGF-independent function that inhibited the cellular proliferation in breast cancer cells [168].

**IGFBP4**

IGFBP-4 is located on the chromosome 17q12.3, gene size 14308.Six high affinity IGFBPs (IGFBP1-6) have been described sharing 36% homology. IGFBP-4 mainly originates from the liver but it is widely expressed in different tissues. It has been found in all biological fluids and its serum level in human ranges between 300 and 700ng/ml [169]. IGFBP-4 expression is regulated by different hormones, cytokines, and other substances and by developmental aspects. Among the six IGFBPs, IGFBP-4 is the smallest in size and is unique in two aspects: it contains two extra cysteine residues in the variable L domain and it has been consistently shown to inhibit IGF action. IGFBP-4 contains an N-linked glycosylation site and weight a 24-kDa on nonglycosylated form and a 28-kDa glycosylated form [158,170].

IGFBP4 show lower expression in tumor cells of several neoplasms such as neuroblastoma, colon, lung, breast, and thyroid, respectively compared to their normal tissues [171-175]. But in breast cancer patients, IGFBP4 expression was viewed as an independent prognostic factor indicating better outcome in patients with ER (+) breast tumors [176]. Generally, Insulin like growth factor binding protein

RA Journal of Applied Research
||Volume||1||Issue||08||Pages-277-312||Sept -2015|| ISSN (e): 2394-6709
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4 (IGFBP4) regulates growth and development of tissues and organs by negatively regulating IGF signaling suggesting growth inhibitory role and as a down-regulated gene in most cancers. Recent reports have shown that IGFBP-4 inhibits the growth of cultivated cancer cells and tumor growth in vivo [177,178]. In cultured cells, adding purified IGFBP-4 can inhibit IGF actions by preventing the binding of IGFs to their receptors [179-181]. Furthermore, overexpression of IGFBP-4 demonstrated an inhibition to the growth of colon and prostate cancer cells in vivo [182, 183]. However, IGFBP-4 also shown an adverse effect on renal cell carcinoma, glioma in vitro and in vivo studies [184-186]. Study found that an increase in liver and kidney IGFBP-4 production in PHx rats, resulting in elevated serum IGFBP-4 levels, which suggest that IGFBP-4 involve in liver regeneration [187]. As for the effect of IGFBP-4 on liver cirrhosis and HCC, little has been reported.

**IGFBP-5**

IGFBP-5 is located on the chromosome 2q3.5, gene size 23445. IGFBP-5 binds to IGFs with high affinity as ternary complex together with ALS. IGFBP-5 is associated with IGF activation and seems to increase the bioavailability of IGF ligands thereby playing a role contrary to that of IGFBP-3 [188]. By measuring serum sample from 92 patients with biopsy-proven NAFLD and 51 healthy controls, the researchers come to a conclusion that serum IGFBP-5 levels were correlated with liver steatosis, fibrosis, and nonalcoholic steatohepatitis scores and may be useful to differentiate both advanced fibrosis and definite nonalcoholic steatohepatitis from other NAFLD groups [90].

A great deal of evidences indicated that IGFBP-5 involve in fibrosis, such as increased expression in both SSc and IPF [189, 190], inducing collagen and fibronectin production from fibroblast [191], inducing dermal fibrosis with an increase in the number and vimentin andα-SMA expression [192]. IGFBP-5 induces epithelial and fibroblast responses consistent with the fibrotic response [193]. All these suggest that IGFBP-5 induces myofibroblast differentiation and its upregulated expression could be an initiating event in the overproduction of ECM components and the development of fibrosis. Furthermore, overexpression of IGFBP-5 increases the survival of partially activated hepatic stellate cells and myofibroblasts by lowering apoptosis via an IGF1-independent mechanism, and enhances the expression of profibrotic genes [194]. Therefore, its lowered expression may reduce the progression of liver fibrosis, suggesting its profibrotic role in liver. But IGFBP-5 overexpression in skin and lung promotes the progression of fibrosis [189, 190]. Interestingly, the same researcher later found another converse fact that overexpression of IGFBP-5 in the abcd4-/- mice can reduces hepatocyte proliferation , inflammation , oxidative stress and ECM deposition thereby evidently reducing liver fibrosis in chronic cholangiopathy, totally showing a protective effect on liver pathology [195]. In order to clarify the differential role and expression of IGFBP-5 in liver and other organ, by analyzing IGFBP-5 steady-state expression in the BXD genetic reference population

RA Journal of Applied Research
||Volume||1||Issue||08||Pages-277-312||Sept -2015|| ISSN (e): 2394-6709
www.rajournals.in

and the correlation with clinical features, the authors come to a conclusion that IGFBP-5 has an organ specific regulation and a role that differ between organs, therefore explain why it was found as a profibrotic factor in lung and skin whereas protective effect in liver fibrosis [190, 191]. In addition, a protective effect of IGFBP-5 on hepatocyte in vivo is consistent with its prosurvival effect in activated HSC in vitro [195].

**IGFBP-6**

IGFBP-6 is a member of the insulin-like growth factor-binding protein family , located on the chromosome 12q13.13, gene size 4910. IGFBP-6 and -4 binds to IGFs as a binary complex. It is unique because of its N-terminal disulfide linkages and obvious binding preference for IGF-Ⅱ thereby involving in the systemic and local regulation of IGF-Ⅱ actions, functioning as a potent inhibitor of interaction between IGF-Ⅱ and its receptor thus preventing major functions of IGF-Ⅱ, such as induction of proliferation, differentiation, cell adhesion, or colony formation [196]. Data showed that IGFBP-6 abnormal regulation is involved in tumorigenesis through IGF-Ⅱ [197]. IGFBP-6 inhibits tumor cell proliferation and induces apoptosis thereby attenuating tumor growth [198]. Another work showed IGFBP-6 function as an oncosuppressor in NPC pathogenesis through regulating EGR-1 expression [199]. On the contrary, IGFBP-6 also induced cancer cell migration in an IGF-independent manner [200]. IGFBP-6 attenuation in ACTH-secreting pituitary adenomas is associated with tumor growth by activating the PI3K-AKT-mTOR pathway [201]. IGFBP-6 also inhibits the proliferation of primary cells from contracture tissue [202].As for the effect of IGFBP-6 on the liver fibrosis or HCC, there are few reports.

**IGFBP-7**

IGFBP -7 is located on chromosome 4q12. Oh et al. showed that IGFBP-7 contains an IGFBP conserved motif at the $NH_2$ terminal and is expressed in different tissues. IGFBP-7 differs from the other six members of this family by lacking the C-terminus. IGFBP-7 can bind to IGF-Ⅰ, IGF-Ⅱ and insulin. Comparing with the other six IGF binding proteins, IGFBP-7 binds the IGFs with 5- to 25-fold lower affinity, whereas it binds insulin with 500-fold higher affinity [203].

IGFBP-7 has been implicated in several cellular processes such as proliferation, senescence and apoptosis and demonstrating tumor suppressive activity through the induction of apoptosis and it is downregulated in some cancers including liver fibrosis and HCC [204-209]. More studies showed that IGFBP-7 expression is significantly downregulated in HCC sample and cells lines compared to normal liver and hepatocyte respectively [207, 208], and inversely correlate with the stage and grades of HCC [207], namely associated with both tumor progression and clinical outcome in HCC [82], suggesting that IGFBP-7 function as a potential tumor suppressor for HCC and a useful predict prognosis marker so targeting overexpression of IGFBP-7 might be a novel therapy for it [207]. In addition, IGFBP-7 also profoundly inhibited viability and induced apoptosis in multiple human HCC cell lines by inducing

RA Journal of Applied Research
||Volume||1||Issue||08||Pages-277-312||Sept -2015|| ISSN (e): 2394-6709
www.rajournals.in

reactive oxygen species and activating a DNA damage response and p38 MARK. Thus it might be potent therapeutic eradicating both primary HCC and distant metastasis [208].

Interestingly there are many of works suggesting that IGFBP-7 contributes to liver fibrosis. The experiments in vitro showed that IGFBP-7 expression increases in the activated HSC and induces liver fibrosis by mediating the activation and transdifferentiation of HSC and hepatocyte apoptosis [210, 211].and another studies in vivo proven that IGFBP-7 contributes to the development of liver fibrosis and may involve in the progression of hepatic fibrogenesis [212-214]. In fact anti-IGFBP-7 antibody may ameliorate liver fibrosis in mice by suppressing the activation of hepatic stellate cells, inhibiting the synthesis of major components of the ECM, whose mechanism associated with the TGF-β1/Smad3 signaling pathways [213].

## CONCLUSIONS AND PERSPECTIVES

As we discussed above, the GH-IGF-IGFBP axis is associated with several processes in liver fibrosis and cancer including growth, differentiation, proliferation and metastasis. The tissue expression and serum levels of IGF-I, IGFBP-3 and IGFBP-7 markedly decline respectively [207, 215]. The marked decline of IGF-I, IGFBP-3 and IGFBP-7 serum levels may serve as markers for clinical prediction, diagnose and prognosis of hepatic fibrosis [207]. Regardless disputation, more recent study show the expression of IGFBP-7 gradually decreases with the stages and grades of HCC and a significant proportion of HCC patients with IGFBP-7 gene deletion, and the experiment *in vivo* and *vitro* suggested that IGFBP-7 function as a novel tumor suppressor for HCC and its inhibitory effect was more pronounced than the in vitro effect, whose mechanism *in vitro* growth inhibitory effect might be mediated by its ability to interfere with IGF-I signaling. Therefore, targeting IGFBP-7 overexpression might be a promising novel therapy for HCC [216]. Further investigation is needed to completely understand physiology and pathology relevance of IGFBP-7, which may be a study hot point in the future.

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