Role of MMP-13 in Remodeling of Hepatic Fibrosis

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Abstract

Matrix metalloproteases (MMP) are responsible for degradation of ECM components in fibrotic tissues. It is thought that especially MMP-13, a homolog of human MMP-1, may be the key for reversal of liver cirrhosis. This is because it is able to degrade the collagens found in fibrotic ECM. However, this MMP is only found in the early phase of hepatic fibrosis. Both overexpression of MMP-13 and apoptosis of hepatic stellate cells (HSC), which are the major collagen producing cells, have shown promising results in remodeling to a near-normal liver architecture. Therapeutic treatment of the fibrotic tissue with both these methods, might result in a clearance of the hepatic cirrhosis. However, a lot is not yet known about this enzyme, and a lot of research needs to be done.

Introduction

Fibrosis is a wound-healing response to a variety of continuous stimuli. Development of fibrosis can be divided into four phases. The first phase is getting the injury. The second phase is the induction of an inflammation by the immune system. The third phase is the activation and differentiation of fibroblasts and other structural resident cells into α-smooth muscle actin (αSMA)-positive, interstitial-collagen-producing myofibroblasts. As last is the remodeling or the clearance of the fibrotic matrix. In chronic fibrotic situations, such as liver cirrhosis, the remodeling or clearance is defective. This is due to an imbalance between extracellular matrix (ECM) production and degradation. (Giannandrea & Parks, 2014; Hernandez-Gea & Friedman, 2011; Tsukada et al., 2006)

Hepatic fibrosis is characterized by an accumulation of ECM in parenchyma cells. The normal ECM is responsible for maintaining homeostasis of the liver cells. This accumulation can thus lead to organ dysfunction, and eventually death (Louka & Ramzy, 2016; Uchinami et al., 2006). The healthy liver consists mostly out of collagens type IV and IV. However, during fibrosis, the ECM is replaced by types I and III interstitial collagens with fibrous septa surrounding regenerating nodules (Endo et al., 2011; Hernandez-Gea & Friedman, 2011; Iredale et al., 2013). This reconstruction results in an altered architecture and functionality.

The primary cause of hepatic fibrosis is a hepatitis viral infection, including hepatitis B and C. Other causes are toxic/alcohol-induced, autoimmune diseases, and metabolic changes (Elsharkawy et al., 2005). If the liver suffers from an acute injury, the fibrosis will be short-termed and restore to the normal architecture. However, during chronic injury, accumulation of the ECM and the imbalance will endure, leading to the substitution of the parenchyma. Eventually, this will lead to cirrhosis, which consists out of extensive fibrosis, loss of metabolic function, and has a high mortality rate. Over 200 million patients suffer from liver cirrhosis worldwide (Endo et al., 2011; Giannandrea & Parks, 2014; Hernandez-Gea & Friedman, 2011). Although progression to this phase is slow and can take up to 20 or 40 years, there is no therapeutic therapy for liver cirrhosis (Hernandez-Gea & Friedman, 2011). This thesis will talk about a possible drug, MMP-13, which is involved in the balance between ECM production and degradation.

The last stage in the development of fibrosis is an important one. This revolves around the biosynthesis of cross-links (Slot-Verhoeven et al., 2005). These cross-links are necessary for the stabilization of the collagen fibrils and fibers and also seems to play a role in the collagen accumulation. The enzyme required for the formation of the cross-links is called lysyl oxidase (LOX), which is an extracellular amine oxidase. Its main function is to post-translationally modify collagens, in particular, collagen type I and elastin. Another indirect function is to establish the microenvironment through these modifications. (Cox et al., 2013)

The biosynthesis of the cross-links can take place through one of two pathways, The allysine or the hydroxyallysine pathway. LOX will convert the amide side chain in the collagen telopeptide into aldehydes. In the allysine pathway, amide lysine (Lys) will be converted into allysine. In the other pathway, the hydroxyallysine pathway, hydroxylysine (Hyl) will be converted into hydroxyallysine (Eyre et al., 1984; Slot-Verhoeven et al., 2005). However, Lys can also be hydroxylated, and in this case, LOX will form a hydroxyallysine instead of an allysine. After formation of the aldehydes, di-, tri-, or tetra-functional cross-links get formed when the aldehydes react with either a Lys, Hyl, or histidine residue in the triple helix (Slot-Verhoeven et al., 2005). Depending on the tissue, either allysine or hydroxyallysine is dominant (Eyre et al., 1984). In fibrotic tissue, hydroxyallysine is known to be the dominant aldehyde (Slot-Verhoeven et al., 2005).

The imbalance in ECM production and degradation during fibrosis is due to an imbalance in levels of matrix metalloproteinases (MMP) and tissue inhibitors of metalloproteinases (TIMP) (Slot-Verhoeven et al., 2005). When MMP production is not enough to exceed the inhibitory effects of the TIMPs, the balance will shift toward ECM production, and with that remodeling into fibrotic tissue (Elsharkawy et al., 2005). MMPs are able to degrade the ECM components. TIMPs are responsible for controlling the activity of these MMPs in different tissues. There are four different TIMPS. TIMP-1, TIMP-2, TIMP-3, and TIMP-4. Out of all these, TIMP-1 is able to inhibit the most MMPs (Iredale et al., 2013). Overexpression of TIMP-1 can lead, because of this, to more severe fibrosis, without there being an increase in collagen synthesis (Giannandrea & Parks, 2014).

For the longest time, it has been thought that hepatic fibrosis is irreversible. Around half a century ago, scientists believed that the only way to save a patient was to perform a liver transplantation (Bonis et al., 2001). However, now it is believed that the process of fibrosis is bidirectional and dynamic. Research in small rodents has shown promising results in remodeling fibrotic ECM to a near-normal architecture in the liver (Ellis & Mann, 2012). In order for fibrosis to be reversible, ECM degradation must be higher than ECM production. The cleavage of collagen type I seems to play a key role in this process. In studies using mice with a cleavage-resistant mutant of this collagen, fibrotic tissue could not be resolved (Hemmann et al., 2007).

Even a lot of clinical evidence has been observed concerning the reduction of hepatic fibrosis, especially for patients treated for chronic hepatitis B or C. In order for the liver to return to a near-normal architecture, the underlying problem needs to be treated first. Only then the patients can recover from this chronic disease. (Issa et al., 2004; Tacke & Trautwein, 2015)

MMP Family

Around 28 types of human MMP are known at this time. These are all members of a family of Zn^{2+} and Ca^{2+} depending endopeptidases (Iredale et al., 2013). Their structure consists out of a N-terminal pro domain, blocking the catalytic domain containing the Zn^{2+} and Ca^{2+} binding sites, and a C-terminal hemopexin domain. This pro-domain is about 80 amino acids long and contain the sequence PRCXXPD, with the exception of MMP-23. MMPs will be secreted as zymogens, and (Hemmann et al., 2007) when the pro-domain is removed, revealing the catalytic domain, the MMP becomes activated. In order for the pro-domain to be removed, Ca^{2+} needs to be

present and the pH needs to be neutral (Vincenti & Brinckerhoff, 2002). The catalytic domain contains three conserved histidines in its sequence, namely HEXGHXXGXXHS (Hemmann et al., 2007), which are responsible for the ligation of the active Zn^{2+} site. It is thought that the C-terminal is able to recognize its substrates, meaning it is able to bind the fibrillar collagens. (Ra & Parks, 2007; Yu et al., 2012). However, MMPs can have both stimulating and inhibitory effects on fibrosis (Giannandrea & Parks, 2014).

All MMPs can be divided into one out of six groups: collagenases, gelatinases, stromelysins, matrilysins, membrane-type MMPs, or non-classified MMPs. In this thesis, the focus is on the collagenase group, specifically MMP-13. This subgroup consists, besides MMP-13, out of MMP-1, MMP-8, and MMP-18 (Gupta & Patil, 2012). This group, with the exception of MMP-18, is able to cleave the triple helix of collagens type I, II and III, (Slot-Verhoeven et al., 2005). This triple helix structure has three polyproline II-like chains tightly wound around a common axis, being the reason why other proteases are not able to cleave these collagens. Once these chains are unwound, the collagens become susceptible for MMPs from the gelatinase groups (Ravanti et al., 2001; Vincenti & Brinckerhoff, 2002). The collagens get cleaved at a specific site around ¾ from the N-terminus at a unique glycine (Gly)-leucine (Leu)/isoleucine (Ile) bond (**Figure 1**) between amino acids 775 and 776. (Gupta & Patil, 2012; Ravanti et al., 2001; Yu et al., 2012).

What makes MMP-13 unique is its ability to act, besides a collagenase, as a gelatinase. Because of this ability, this MMP is able to cleave even smaller collagen fragment that can be used for following metabolism

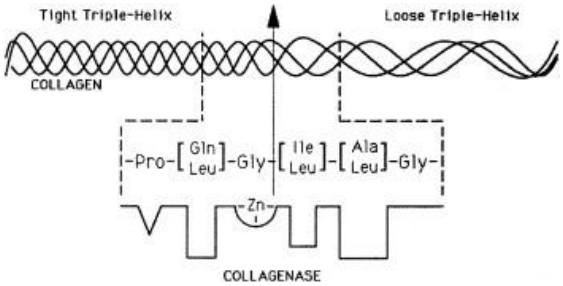

Figure 1: Cleavage site of collagenases. MMP-1, -8, and -13 are able to cleave triple helices between a specific Gly – Leu/Ile bond. (Lauer-Fields et al., 2002)

(Pendás et al., 1997; Uría et al., 1998). It has a 40-fold stronger gelatinolytic activity than the other collagenases (Ravanti et al., 2001). For this reason, MMP-13 is able to cleave collagen more effectively than the other collagenases (Vincenti & Brinckerhoff, 2002). Furthermore, MMP-13 is also able to cleave other ECM components, such as collagens type IV, X, and XIV and fibronectin (FN) (Uría et al., 1998). Although MMP-13 is able to cleave all these kinds of collagens, its preference is to cleave collagen type II. Because of this, there are different expression levels of MMP-1 and MMP-13 expression in skin wound healing, since degradation of collagens type I and III seem to be more important in this location. The structure of the ECM thus influences what types of collagen and with that MMPs are present in the healing process (Ravanti et al., 2001). Differences with the other collagenases are that MMP-1 is able to degrade interstitial collagens more effectively (Vincenti & Brinckerhoff, 2002). MMP-8 has the same specificity for the collagens as MMP-1, it is also able to cleave interstitial collagens type I and III (Giannandrea & Parks, 2014). However, in contrast to MMP-1 and MMP-13, MMP-8 is not expressed in the early phase of recovery of liver cirrhosis (Endo et al., 2011).

Besides their role in fibrosis, MMPs are also involved in other physiological processes. They play a major role in other forms of remodeling in connective tissues, such as embryonic growth and development, pregnancy, and bone growth (Gupta & Patil, 2012; Pendás et al., 1997). However, these types of degradation are essential for development and repair. Abnormal degradation, on the other hand, can lead to diseases such as cancer, arthritis, or atherosclerosis (Yu et al., 2012).

MMP-13

PATHWAY

After liver injury, hepatic fibrosis will develop. During this development, MMP-13 mRNA expression is increased. Hepatic stellate cells will activate, and at the early stage of this activation, they will express MMP-13 (Han, 2006). In acute injuries, this expression is

enough to clear the fibrosis and return to a near-normal liver architecture. However, during cirrhosis, this MMP-13 is only increased in the early phase and will destroy surrounding tissue in order to deposit de altered ECM (Uchinami et al., 2006).

Degradation of the ECM will lead to secretion of ECM-bound cytokines, under which transforming growth factor (TGF)-β, which will, together with interstitial collagenase, induce the fibrogenesis (Hemmann et al., 2007; Uchinami et al., 2006). In absence of TGF-β, MMP-13 levels are decreased during the fibrolysis. Also, TIMP-1 mRNA expression seems to be directly associated with TGF-β (Hemmann et al., 2007).

Once the HSCs are fully activated, they will stop producing MMP-13 and with that, the ability to degrade ECM and cleave collagens is lost. On top of that, they will start producing TIMPs, especially TIMP-1, shifting the balance even further towards ECM production (Han, 2006). Furthermore, reactive oxygen species (ROS) secreted by neutrophils help the HSC by stimulating collagen synthesis (Uchinami et al., 2006).

Besides the HSCs, the hepatic parenchyma consists out of standard hepatocytes, endothelial cells and non-parenchymal cells, under which immune cells such as Kupffer cells (KC) (Hernandez-Gea & Friedman, 2011). KCs are also able to release cytokines that increase the fibrogenesis. They secrete IL-1 and TGF-β, which stimulate the production in the inactive HSCs (Uchinami et al., 2006).

MMP-13 is thought to play a major role in the initial inflammation response. Activation of MMP-13 will lead to a reduction of the inflammation process, which means less severe fibrosis (Uchinami et al., 2006). Activation of MMP-13 takes place in a two-step mechanism, through a plasmin and MMP-3 or MMP-14 and MMP-2 in absence of TIMP-2. However, activation through MMP-14 will lead to a disruption between HSCs and the ECM, which creates an environment for the HSC to proliferate and migrate (Hemmann et al., 2007). The inflammation response will thus lead to changes in the liver which results in fibrogenesis (Uchinami et al., 2006).

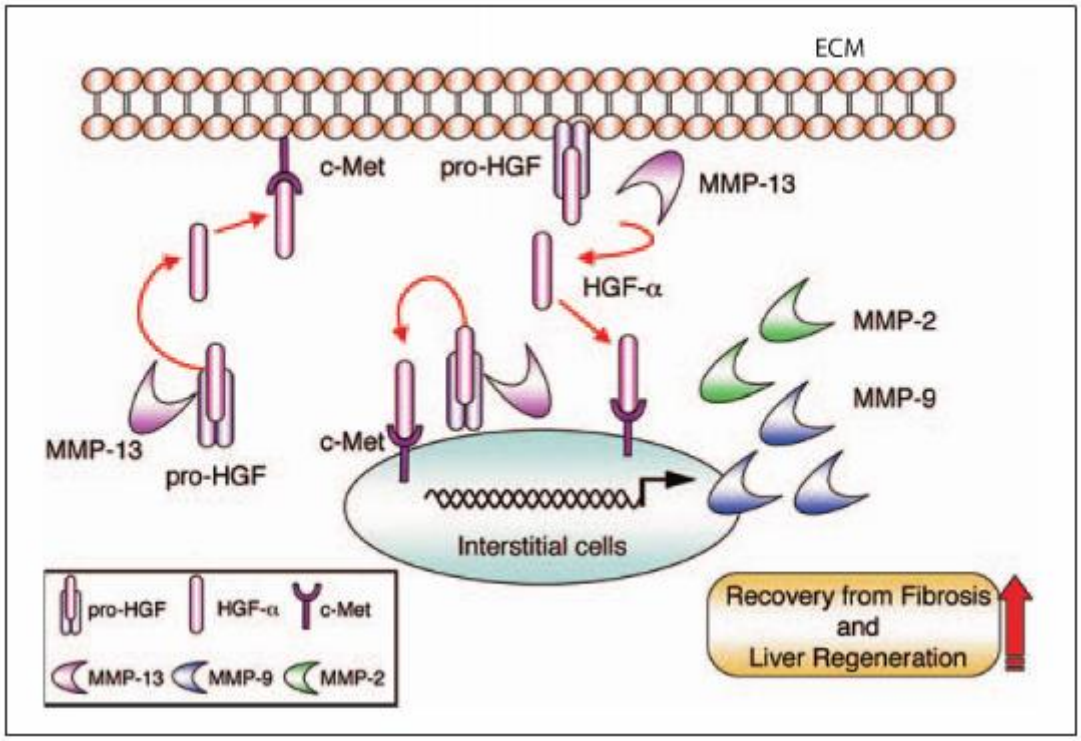

Figure 2: Schematic representation of the mechanisms of MMP-13 mediated HGF activation and MMP-2 and MMP-9 induction. MMP-13 converts pro- hepatic growth factor (HGF) into the activated form α-HGF through c-Met. α-HGF then helps MMP-13 to activate MMP-2 and -9, which help with the collagen degradation. This degradation contributes to the restoration of the ECM and thus recovery of liver cirrhosis. (Endo et al., 2011)

Most cells producing MMP-13 also produce hepatocyte growth factors (HGF). MMP-13 is involved with converting pro- HGF into active HGF (HGF-α). HGF is involved in the reversal of hepatic fibrosis and works anti-fibrogenesis. HGF-α is found, together with its phosphorylated receptor, c-Met, in the cirrhotic liver, especially around the fibrous septa. (Endo et al., 2011)

HGF-α is responsible for enhancing both the expression of MMP-2 and MMP-9. The first cleavage of collagen in the initial phase results from MMP-13. This cleaved collagen then also activates MMP-2 and MMP-9 to help degrade collagen even more and enhance the effect. This process is shown in **Figure 2**. When MMP-13 mRNA expression is induced, the enzymatic activity of MMP-2 and MMP-9 increases. These MMPs are mainly found around the fibrous septa. This means that not only MMP-13 is responsible for the recovery of cirrhosis, but MMP-2 and MMP-9 also contribute to this process. After activation of these MMPs, they will secrete cytokines and trigger the immune system even more (Uchinami et al., 2006). Recovery of liver cirrhosis is thus achieved by the MMP-13-mediated activation of HGF-α, MMP-2, and MMP-9 to degrade collagen.

HEPATIC FIBROSIS MODELS

Most studies on hepatic fibrosis are done *in vivo* with either mice or rats. Acute hepatic fibrosis can be induced by using chemical toxins, such as carbon tetrachloride (CCl_4), or thioacetamide (TAA). The toxins will be injected into the femoral vein of the model (Endo et al., 2011). Out of these different toxins, CCl_4 is used the most. Another way to introduce an acute injury is by bile-duct ligation (BDL) resulting is cholestasis-induced fibrosis. Chronic liver injuries, or cirrhosis, can be induced by giving the animal models CCl_4 for a longer period, weeks or even months (Giannandrea & Parks, 2014). CCl_4 alters the permeability of the plasma-, lysosomal, and mitochondrial membranes. Together with this alteration, free radical metabolites are formed, causing severe cirrhosis (Fujii et al., 2010).

MMP-13 PROMOTES RECOVERY OF LIVER FIBROSIS

As mentioned before, in the first few weeks after liver injury, expression of MMP-13 mRNA is observed in non-activated HSC and in a few other cells around the fibrous septa. However, after 12 weeks of treatment, cirrhotic livers have a relatively weak MMP-13 mRNA expression (Okazaki et al., 2000). When the initial immune reactions begin, macrophages, under which Kupffer cells, transport to the location of this injury, where they release MMP-13. During the recovery of hepatic fibrosis, MMP-13 mRNA expression is limited, because the Kupffer cells and other macrophages secreting MMP-13 have moved away from the injury. When TGF-β is switched off, a fall in MMP-13 mRNA expression is observed (Endo et al., 2011; Hemmann et al., 2007). After the initial response, fewer MMP-13 will be available to degrade the ECM components. This should mean that when MMP-13 mRNA expression is upregulated, remodeled fibrotic tissue can continue to be degraded.

Research of Endo et al. (2011) has shown that treatment with adenovirus-delivered MMP-13 could improve the liver cirrhosis rapid and effective (**Figure 3**). CCl_4 rats treated with this virus-delivered MMP-13 immediately resulted in a significant decrease in fibrous tissue compared to the control group. This control-group were treated with a control adenovirus and showed almost no improvement in hepatic cirrhosis. The tissues were stained with an Azan-Mallory staining on different time periods.

HEPATIC STELLATE CELLS

HSCs are closely related to ECM degradation by MMPs. In a healthy liver, HSCs are located in the space of Disse. Here they are responsible for the storage of Vitamin A. As a reaction to the liver injury, the DNA of the apoptotic hepatocytes will undergo fragmentation and form apoptotic bodies. Either KCs, HSCs or healthy hepatocytes will get rid of these apoptotic bodies through phagocytosis (Kisseleva & Brenner, 2007). Cytokines, such as TGF-β and platelet-derived growth factor

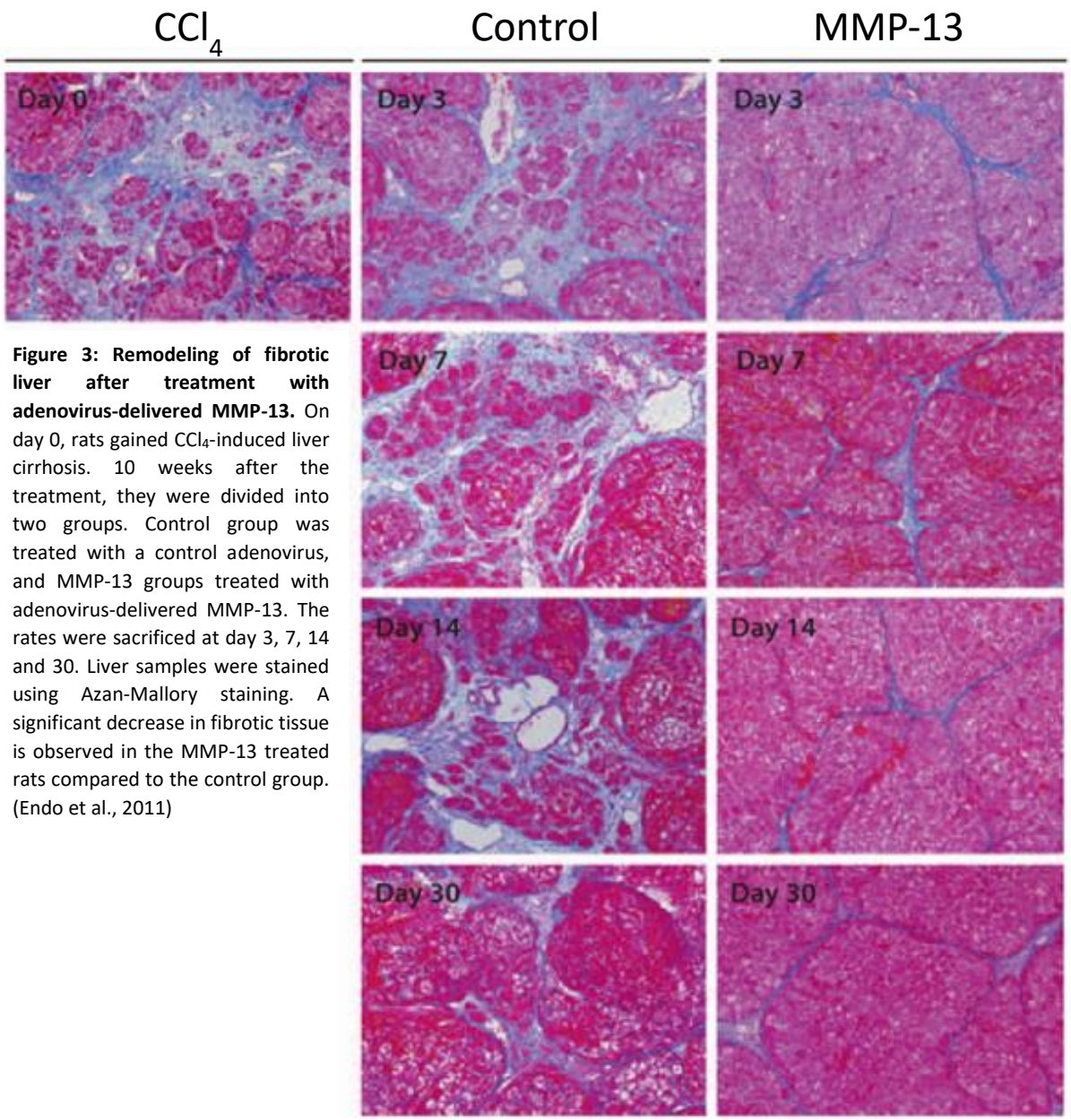

Figure 3: Remodeling of fibrotic liver after treatment with adenovirus-delivered MMP-13. On day 0, rats gained CCl_4-induced liver cirrhosis. 10 weeks after the treatment, they were divided into two groups. Control group was treated with a control adenovirus, and MMP-13 groups treated with adenovirus-delivered MMP-13. The rates were sacrificed at day 3, 7, 14 and 30. Liver samples were stained using Azan-Mallory staining. A significant decrease in fibrotic tissue is observed in the MMP-13 treated rats compared to the control group. (Endo et al., 2011)

(PDGF) (Jiao et al., 2009), will be released which will activate the cells into αSMA positive myofibroblast-like cells, and they will transfer to the location of the injury. Activated HSCs are the key producers of the fibrillar collagens, achieving this by changing the gene expression (Tsukada et al., 2006). These activated HSCs are exclusively found in the fibrotic tissue, where they rapidly proliferate. They will secrete, among other things, αSMA, fibrillar collagens type I and III, cytokines and other matrix proteins, under which TIMPs (Delire et al., 2016; Elsharkawy et al., 2005; Giannandrea & Parks, 2014; Tsukada et al., 2006). Furthermore, they have an enhanced expression of $\alpha_v\beta_3$ integrin, mediating cell-matrix (collagen type I) interactions and thus providing survival signals to the cells (Hemmann et al., 2007). This integrin is thought to play a crucial role in controlling macrophage-related inflammation (Antonov et al., 2011).

Issa et al. (2004) stated that the disbalance in ECM production and degradation and reverse hepatic fibrosis is to induce apoptosis in the activated HSCs. They observed advanced liver cirrhosis in rat models with CCl_4 induced hepatic fibrosis. Loss of the activated HSCs in less mature fibrotic areas shifted the balance to ECM degradation. This remodeling was due to a decrease in TIMPs and collagen type I. Furthermore, they also stated that

collagen type I may indirectly be able to indirectly provide a survival signal for the activated HSCs. Data suggested that MMP-2 and MMP-13 played a major role in the degradation. However, there was no significant change in MMP-13 expression, but MMP-2 gets activated as a reaction to HSC apoptosis.

Later studies by Giannandrea et al. (2014) had the same vision on the remodeling of the fibrotic liver. In addition, they suggested that de-differentiation of HSC would also shift the balance to ECM degradation.

CROSS-LINKS

As mentioned before, in fibrotic tissue, hydroxyallysine cross-links are the dominant type. Research from Slot-Verhoeven et al. (2005) has demonstrated that in absence of these increased hydroxyallysine cross-links, hepatic fibrosis turned out to be completely reversible. This means that not only the presence of the cross-links is important, but also that the type of cross-links plays a major role in regulating ECM degradation.

Furthermore, HSCs also seem to play a major role in the expression of cross-links. Activated HSCs also express the enzyme transglutaminase (tTg), which is a cross-linking enzyme. Even if the MMPs are active, the ECM degradation is limited. Collagens cross-linked by this enzyme gain a resistance to MMP-mediated degradation. In most liver injuries in which the fibrosis is irreversible, these cross-links obtained through tTg are present. A possible way to prevent tTg to create MMP-resistant cross-links is through the apoptosis of HSCs. (Issa et al., 2004)

AGE-RELATED MMP-13

Elderly people are more likely to develop hepatic diseases. For this reason, the connection between aging and liver fibrosis is of major interest. Same results concerning hepatic fibrosis and age have been obtained from animal models. It has been shown that older mice, 15 weeks old, have more severe fibrosis than younger mice, in this case, 7 weeks old. Confirming that susceptibility to hepatic diseases increases with age. (Delire et al., 2016)

Study of Delire et al. (2016) has shown that older mice have significantly less MMP-13 expression at the peak of fibrosis. Furthermore, no significant difference in TIMP expression was noticed, meaning that the balance between the MMPs and the TIMPs was shifted towards ECM production compared to the younger mice. Furthermore, 4 days after CCl_4 treatment, the fibrotic tissue was completely cleared in the young mice and the liver architecture was returned to normal, while in the old mice, almost no remodeling had happened. It is thought that this inability to degrade the ECM is due to a change in fibers. Old mice have more thick and dense fibers, as well as a higher expression of enzymes involved in collaged maturation, such as LOX. So, the inability for old mice to clear fibrotic tissue is due to a decrease in MMP and an increase in collagen cross-links. Same results were observed for myocardial MMP-13 levels (Lindsey et al., 2005).

Besides fibrosis, MMPs are also associated with multiple age-related diseases, including chronological skin aging and photoaging, atherosclerosis, osteo- and rheumatoid arthritis and renal diseases. MMP expression and activity can be regulated through ROS. These ROS also play an important role in the aging process. ROS production increases with age, resulting in metabolic defects or a decrease in antioxidants are responsible for oxidation (Dasgupta et al., 2009). Since MMPs can be activated by ROS, ROS is what links age and MMPs together. Dasgupta et al. (2009) have found that when they used mice that were superoxide dismutase-deficient, MMP-13 levels would increase. This MMP-13 is then able to clear the thicker and denser collagen fibers in older mice. In summary, increasing MMP-13 levels in older people could be a good solution for clearing the tougher fibrosis.

MMP-13 EXPRESSION IN OTHER ORGANS

The liver is the most researched organ when it comes to reversal of fibrosis through MMP-13. This is because it has shown the most promising results, even clinically. But what about remodeling in other organs?

Besides the liver, MMP-13 also plays a role in fibrogenesis in other organs, such as the lung, kidneys and skin. However, almost no research is found stating that MMP-13 might be involved in the reversal of fibrosis in these organs.

Sen et al. (2010) have done research in MMP-13 deficiency after lung injury. They did this by examining three indicators of acute lung injury, namely protein leak, fibrosis, and inflammation. MMP-13 knock-out mice were exposed to hyperoxia to induce the injury. The mice have shown no significant difference is both protein leak and fibrosis, but they did have significantly more inflammation in the bronchoalveolar lavages (BAL) compared to the control group.

Higher levels of monocyte chemoattractant protein (MCP)-1 were observed in the MMP-13 knock-out mice. This cytokine is important for the regulation of the inflammation after the injury. It was demonstrated that MMP-13 is able to cleave MCP-1, which causes it to be inactive. Despite this significant increase in inflammation, there was no difference in mortality, morbidity, or pathology between the MMP-13 knock-out and control group. Because of this, we can conclude that MMP-13 is not as important in the lungs as in the liver. (Sen et al., 2010)

Discussion

MMP-13 may be a promising treatment for hepatic fibrosis, due to its ability to cleave collagen more effectively than the other collagenases. The human body only produces MMP-13 during the early stages of hepatic fibrosis. During the activation of the HSC, most of the MMP-13 is secreted (Han, 2006). For MMP-13 to serve as a treatment, a way must be found to shift the balance between the MMPs and the TIMPs towards ECM degradation. This can be accomplished through two different methods.

The first method is to overexpress the MMP-13 levels through adenoviruses. When MMP-13 levels are upregulated, the ECM still gets degraded. The other method includes HSC apoptosis. These HSC are the key producers of the fibrillar collagens and the TIMPs. Furthermore, they are responsible for the cross-links. Meaning that if these cells would go in apoptosis upon activation, fewer ECM remodeling would take place, and fewer cross-links would form, making it easier for the MMPs to clear the fibrotic tissue. In my opinion, these methods should be used together. Since HSC are also major producers of MMP-13, apoptosis would result in lower MMP-13 expression. To compensate for this, the patient should also get a dose of MMP-13, or in this case, human MMP-1 injected.

However, a lot is not yet known, more research has to be done for this enzyme to come even close to an actual treatment. First of all, there are a lot of factors to take into account, under which age. Elderly people have more severe fibrosis (Delire et al., 2016) and would need a different amount of MMP. Further research has to be done to see if more factors could limit the effect of MMP-13. Furthermore, this is not even the biggest problem. Two of the biggest problems come from the use of animal models. First of all, it is not known if MMP-13 would have the same effect in humans as in rodents. Secondly, MMP-13 is a homolog of human MMP-1, which have some differences between the two.

Altogether, MMP-13 has shown promising results in treating hepatic cirrhosis through overexpression or HSC apoptosis. However, more research is needed for it to be able to be used as an actual treatment.

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