enzymes. Finally, normal and cirrhotic liver samples were studied by means of HPLC in order to determine tissue fluid concentrations of angiotensin II and angiotensin-(1-7). In cirrhotic liver samples we found out a marked over-expression of chymase and ACE (all P<0.01) and, to a lesser extent, of ACE2 (P<0.05). In normal liver, concentrations of angiotensin II and angiotensin-(1-7) were similar (both below 50 pg/ml); conversely, cirrhotic liver tissue showed increased concentrations of angiotensin II (1400 ± 380 pg/ml) and of angiotensin-(1-7) (260 ± 110 pg/ml). In other words, in the cirrhotic liver parenchyma the ratio between angiotensin II and angiotensin-(1-7) undergoes a fivefold increase with respect to control livers, which contributes to fibrogenesis. The reason for a preferential production of tissue angiotensin II inside the cirrhotic liver is the concurrent increase in ACE and chymase content, with respect to a smaller over-expression of the sole ACE2. These data indicate that pharmacological modulation of the chymase/ACE2 system may be promising in order to alter the process of fibrogenesis in chronic liver diseases. 1) Eur J Pharmacol 501, 1-8, 2004. 2) Hepatology 50:929-38, 2009.

Disclosures:

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2031
THERAPEUTIC POTENTIAL OF BONE MARROW TRANSPLANTATION IN LONG TERM MODELS OF *ABCB4*$^{-/-}$ MICE: CONTRIBUTION OF MMPS

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Introduction: Reports about the effects of bone-marrow derived cells on liver fibrosis and regeneration are contradictory. The medullar origin of hepatic CD34^{+} fibrocytes was verified by bone marrow transplantation (BM-Tx) in *Abcb4*$^{-/-}$-mice. Shortly after BM-Tx hepatic staging improved but grading impaired. The aim of the present study was to analyze hepatic long term changes after BM-Tx to elucidate any therapeutic potential and underlying immunomodulatory processes associated with hepatic regeneration. Methods: After lethal irradiation of recipient mice, BM-cells from GFP^{+}-donor mice (allogeneic Tx) or *Abcb4*$^{-/-}$-mice (syngeneic Tx) were applicated via tail-vein injection. Liver integrity was assessed serologically and histologically. Surrogate markers for fibrogenesis, inflammation, graft-versus-host disease (GVHD) and fibrolysis were analyzed by quantitative real-time-PCR, zymography, and immunohistology. Results: 20 weeks after syngenic and allogenic BM-Tx both, hepatic grading and staging, improved considerably. Gene expression of inflammatory cell markers (myeloperoxidase neutrophils, F4/80 macrophages, CD45 leukocytes) but also stem-cell markers (CD34 fibrocytes, CD133 stem cells) was induced two weeks after BM-Tx and declined to normal levels thereafter. Neutrophils and macrophages associated cytokines, chemokines, and their receptors fitted to the regulation of cellular markers (TNF-α, CXCL2, CCL3, CXCR2, CCR1, and CCR2). MMP-2, -7, -9, and -13 as well as TIMP-1 and -2 were regulated similarly. Neutrophil granulocytes but also CD34^{+} fibrocytes were identified as major sources of MMP-9. GFP^{+}/CD3^{+} donor T-cells infiltrated the liver two weeks after allo-BM-Tx. Conclusion: Transient inflammatory effects after BM-Tx are responsible for the enhancement of chemokines similar to GvHD. Subsequent upregulation of MMPs might be responsible for long term amelioration of hepatic fibrosis.

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MMP-13 DELETION ATTENUATES N-NITROSODIMETHYLAMINE INDUCED HEPATIC FIBROSIS IN MICE

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The pathogenesis of hepatic fibrosis is a dynamic process involving several cell types and molecular events. Connective tissue growth factor (CTGF) is a major profibrogenic molecule and plays a significant role in the pathogenesis of hepatic fibrosis. Since matrix metalloproteinase-1 (MMP-1) is absent in mice, MMP-13 is responsible for cleavage and activation of CTGF. Here, we elucidated the role of MMP-13 and CTGF in the pathogenesis of hepatic fibrosis using MMP-13 knockout mouse. Hepatic fibrosis was induced in wild-type and MMP-13 knockout mice through intraperitoneal injections of N-nitrosodimethylamine (NDMA) in doses of 1 mg/100 g body weight on 3 consecutive days of every week over a period of 4 weeks. NDMA administrations resulted in marked elevation of serum AST, ALT, hyaluronic acid (HA), TGF-β1 and procollagen-III peptide in wild-type mice. There was marked activation of hepatic stellate cells, deposition of collagen and HA in the liver. However, all these changes were attenuated in NDMA administered MMP-13 knockout mice. Immunohistochemical staining demonstrated marked upregulation of CTGF in the necrotic and fibrotic areas of NDMA-treated wild-type mice but not in the knockout. Semiquantitative and qRT-PCR for collagen I, α-smooth muscle actin (α-SMA), CTGF and TGF-β1 mRNA demonstrated marked upregulation in NDMA treated wild-type mice, but not in similarly treated MMP-13 knockout mice. Western blotting showed increased levels of collagen I, α-SMA, CTGF, and TGF-β1 in wild-type fibrotic mice, but not in knockout. Our results demonstrated that MMP-13 plays a significant role in the pathogenesis of hepatic fibrosis through cleavage and activation of CTGF. Furthermore, our study indicates that blocking of CTGF using effective molecules has potential therapeutic application to prevent hepatic fibrosis.

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ESTABLISHMENT OF A REPRODUCIBLE LIVER FIBROSIS MODEL IN NUDE MICE THROUGH THE ADMINISTRATION OF THIOACETAMIDE IN DRINKING WATER

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Introduction: Liver fibrosis, the early step leading to cirrhosis, has been studied in many different animal models. The importance of the immune system in the fribrogenesis process remains unclear. The use of a nude model could help clarify this complex interaction. Existing thioacetamide (TAA)-induced fibrosis models in nude mice have shown high rates of mortality (Cell Transplant, 2005:14; pp.270-90). We suggest that the use of a drinking water model instead of the use of intraperitoneal (IP) injections with step-wize increases in the doses of TAA will lead to lower rates of mortality and reproduce all the characteristics of the fibrotic process. Methods: Thioacetamide was administered to nude mice in drinking water [100mg/L] for 4 days followed by continuous administration at 200 mg/L thereafter. Mice were sacrified after 4, 8, 12, 16 weeks of treatments and, 2 weeks after the cessation of TAA exposure (i.e.16 weeks in order to assess the reversibility of the fibrotic process). Livers were harvested for histology (Masson Trichrome) and hydroxyproline content. Immunohistology was performed in order to