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The Role of Mesenchymal Stem Cells and Imatinib in the Process of Liver Fibrosis Healing Through *CCL2-CCR2* and *CX3CL1-CX3CR1* Axes

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Abstract

Background: Persistent liver damage contributes to the development of liver fibrosis, marked by an accumulation of extracellular matrix. Macrophages play a pivotal role in this process, with the CCL2-CCR2 and CX3CR1-CX3CL1 axes serving as key regulators of macrophage recruitment, liver infiltration, and differentiation. In this study, utilizing a rat model of carbon tetrachloride (CCL4)-induced liver fibrosis, we aimed to investigate the impact of imatinib and bone marrow-derived mesenchymal stem cells (BM-MSCs) on the expression of these axis.

Methods: Sixteen Sprague-Dawley rats were divided into four groups: healthy, liver fibrosis, imatinib-recipient, and BM-MSC-recipient. Treatment effects were evaluated using histopathology and Sirus-red staining. Quantitative real-time PCR was employed to analyze changes in the expression of the genes CCL2, CCR2, CX3CL1, and CX3CR1.

Results: Histopathological assessments revealed the efficacy of imatinib and BM-MSCs in mitigating liver fibrosis. Our findings demonstrated a significant reduction in CCL2 and CCR2 expression in both imatinib and BM-MSCs treatment groups compared to the liver fibrosis group. Conversely, the gene expression of CX3CL1 and CX3CR1 increased in both therapeutic groups compared to the liver fibrosis groups.

Conclusion: Conclusion: The notable decrease in CCL2-CCR2 genes in both therapeutic groups suggests that BM-MSCs and imatinib may contribute to a decline in inflammatory macrophages within the liver. The lower CCL2-CCR2 expression in imatinib-recipient rats indicates better efficacy in modulating the recruitment of inflammatory macrophages. The elevated expression of CX3CL1 in BM-MSC-recipient rats suggests a greater impact on the polarization of LY6Chigh (inflammatory) to LY6Clow (anti-inflammatory) macrophages, warranting further investigation.

Keywords: CCL2, CCR2, CX3CL1, CX3CR1, Liver fibrosis.

Introduction

Hepatic fibrosis is a concerning health problem worldwide, observed in the patients with chronic liver diseases (CLDs) (1–3). The biological mechanism underlying the activation of hepatic stellate cells (HSCs), disruption of liver function, and accumulation of extracellular matrix proteins (ECM) and collagen type III and I, which further results in cirrhosis and hepatocellular carcinoma (HCC), as a result of the perpetual wound healing process caused by CLDs (4,5).

The inflammatory pathways and immune cells play a crucial role in the initiation and maintenance phases of hepatic fibrosis. Kupffer cells and macrophages derived from monocytes are the two primary liver immune cells that promote liver inflammation. Kupffer cells (KCs), which are liver-dwelling macrophages, are activated upon inflammatory stimuli, and produce various pro-inflammatory cytokines and chemokines (6-8). For instance, KCs release chemokine monocyte chemotactic protein 1 (*CCL2*) (GENE ID: 24770), known as Monocyte chemoattractant protein-1 (MCP-1), which attracts $LY6C^{high}$ monocytes through CCR2 (GENE ID: 60463) receptors on

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LY6C^{high} monocytes surface (9-11). The well-known master regulator of hepatic fibrosis, LY6Chigh monocytes differentiate into LY6Chigh macrophages upon recruitment to the liver, which then cause the activation of HSCs and their trans-differentiation to myofibroblasts by secreting TGF-beta (TGF-) and platelet-derived growth factor (PDGF) (7,10,11).

CX3C chemokine ligand 1 (*CX3CL1*) (GENE ID: 89808), known as fractalkine, is an anti-inflammatory chemokine that serves as a protector against hepatic fibrosis by regulating macrophage infiltration, survival, and limits the differentiation of LY6C^{high} monocytes to LY6C^{high} macrophages as inflammatory macrophages in the liver (12). Additionally, *CX3CL1* encourages the development of LY6Chigh to LY6Clow macrophages, which help to resolve liver fibrosis by causing apoptosis in activated HSCs and degrading ECM via the release of matrix metalloproteinases 12 (MMP-12) and 13 (MMP-13). *CX3CL1* receptor (*CX3CR1*)-deficient mice (GENE ID: 171056) showed decreased numbers of monocyte-derived macrophages and increased level of fibrosis in carbon tetrachloride (CCl4)-induced liver inflammation mice (13). Moreover, a correlation between serum *CX3CL1*, and quantitative serum fibrosis markers was observed in patients with liver fibrosis, indicating that serum level of *CX3CL1* was increased consistent with the progression of hepatic fibrosis (12).

Thus, *CX3CL1*- CX3CR1 axes could be considered a great target for fabricating novel drug approaches as modulators of liver fibrosis.

Since their anti-fibrotic effect has already been discussed (15,16), imatinib and bone marrow-derived mesenchymal stem cells (BM-MSCs) are two prospective treatment modalities for treating liver fibrosis. Imatinib is a selective tyrosine kinase inhibitor (TKI) with the great potential of inhibiting both PDGF, and TGF-β pathways, which play a major role in fibrosis progression (14). Moreover, several studies indicated that BM-MSCs could provide anti-fibrotic effects on the damaged liver by induction of apoptosis, and limiting the activation of HSCs, attenuating the fibrogenesis process, and elevated degradation of ECM (15,16). The goal of the present investigation was to examine the possible effects of imatinib and BM-MSCs on the *CCL2-CCR2* and *CX3CR1-CX3CL1* axis as prospective therapeutic strategies for liver fibrosis.

Materials and Methods

Experimental Animals

16 Male Sprague-Dawley rats, weighing 200±60 g and 8-10 weeks old, in groups of four, were placed in cages covered with woodchip. Rats were housed one week in defined standard living conditions (room temperature with access to adequate pellet food, water, and light illumination cycles of 12 h/day) before the commencement of experiments. After induction of liver fibrosis, the groups were defined as the phosphate-buffered saline (PBS)-treated group (healthy group), BM-MSCs-recipient group, imatinib-recipient group, and CCL4-treated group (fibrotic experimental group).

Liver fibrosis induction

To provoke liver damage in rats, CCL4 (1 ml/kg, 99% purified, Sigma, UK) was solved in olive oil with the ratio of (1:1). The CCL4 solution was injected intraperitoneally (IP) twice weekly for six weeks. At the same time, an equal volume of PBS was administrated to the healthy group. After the 6th week, all the rats were received once-weekly administration of CCL4 or PBS as an experimental reminder. Following the last PBS or CCL4 injection, rats were euthanized after 24 h by carbon dioxide (CO2) narcosis.

Treatment with imatinib and MSCs

BM-MSCs isolation and characterization were described completely in our previously reported articles (17,18). Rats in the BM-MSCs-recipient group received approximately 1.5×10^6 BM-MSCs via intravenous (iv) injection only once at the beginning of the

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treatment. The imatinib-recipient group was administered imatinib (Osve Pharmaceutical Co, Iran) (20 mg/kg) orally by gavage daily during the 6 weeks treatment period.

Histopathological assessment

Liver tissues were immediately sectioned after euthanization and were divided into two serial sections. One part of the divided sections was stained with hematoxylin and eosin (H&E) to indicate the alternate hepatic histological features. Masson's Trichrome and Sirius-red were applied in order to demonstrate collagen depositioning.

RNA extraction and complementary DNA synthesis

Total RNA was collected from liver tissue using the RNA extraction kit (Favorgen, Taiwan) according to the manufacturer's protocol. The concentration and purity of RNA were evaluated using a NanoDrop spectrophotometer (Biotek Instruments, Winooski, VT, USA). Subsequently, Extracted RNA was reverse-transcribed using random hexamer and oligo (dT) through high-capacity cDNA reverse transcription kit (Thermo Fisher Scientific).

Gene expression analysis

Quantitative real-time PCR was carried out on the Rotor-Gene 6000 instrument ® (Qiagen AG Hilden, Germany) using an SYBR Green-based PCR Kit. Specific primers for *CCL2*, *CCR2*, *CX3CL1*, and *CX3CR1* were designed for each gene are listed in Table 1. Samples were amplified under the following conditions: 95 °C for 10 m, followed by 40 cycles of 95 °C for 20 s, 58-61 °C (*CX3CR1*: 58 °C, *CCL2*: 58 °C, *CCR2*: 60 °C, *CX3CL1*: 61 °C) for 40 s. The experiments were applied in duplicate independently. The expression level of each gene was normalized by *HPRT* as an internal control. The relative quantity of gene expressions was analyzed using REST 2009 software version 2.0.13.

Table 1. Specific primer used for expression analysis.

Gene		Sequence 5'→ 3'	Product length
CCR2	Forward	AAAAGAGGCATAGGGCTGTGA	143 bp
	Reverse	TAAGTGCATGTCAACCACACA	
CCL2	Forward	AGTTAATGCCCCACTCACCT	128 bp
	Reverse	GCTTGGTGACAAATACTACAGCT	
CX3CR2	Forward	TGCTCAGGACCTCACCAT	102 bp
	Reverse	GCCACGATGTCACCCAAAT	
CX3CL2	Forward	CATCATCCTGGAGACGAGAC	145 bp
	Reverse	CACATTGTCCACACGCTTCT	
HPRT	Forward	GACCGGTTCTGTCATGTCG	132 bp
	Reverse	ACCTGGTTCATCATCACTAATCAC	

Statistical analysis

Prism software, a statistical package, version 5 (GraphPad Software, USA) was utilized for data analyzing and visualization. Statistical analysis was performed using the student's t-test. Data were presented as the mean and standard error of the mean (S.E.M) and the significance level was considered as ($P< 0.05$).

Results

Histopathological assessment verified the anti-fibrotic potential of imatinib and BM-MSCs

The livers were removed at the conclusion of the therapy period for histological analysis. Through H&E staining, it was possible to see that the CCL4-treated group had liver fibrosis due to distorted lobular architecture, binuclear

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hepatocytes and fatty alterations, portal inflammation, and a dilated central vein. The healthy groups (PBS recipients) exhibited the usual cellular architecture, including spherical single vesicular nuclei hepatocytes inside the central vein, absence of portal inflammation, and the usual lobular pattern. Imatinib and BM-MSC recipients showed considerable improvements in the structural pattern of the lobules compared to the CCL4-induced liver fibrosis group in terms of both portal inflammation and lobular pattern. Furthermore, the CCL4 group displayed prolonged fibrous septa whereas Masson's trichrome staining of the negative (PBS) control group did not show any fibers surrounding the portal region. In compared to the CCL4 group, fibrous growth surrounding the portal region was less in the treatment groups. Sirius-red staining successfully confirmed the findings from Masson's Trichrome staining by detecting collagen deposition as histologic indicators of liver fibrogenesis (Fig. 1).

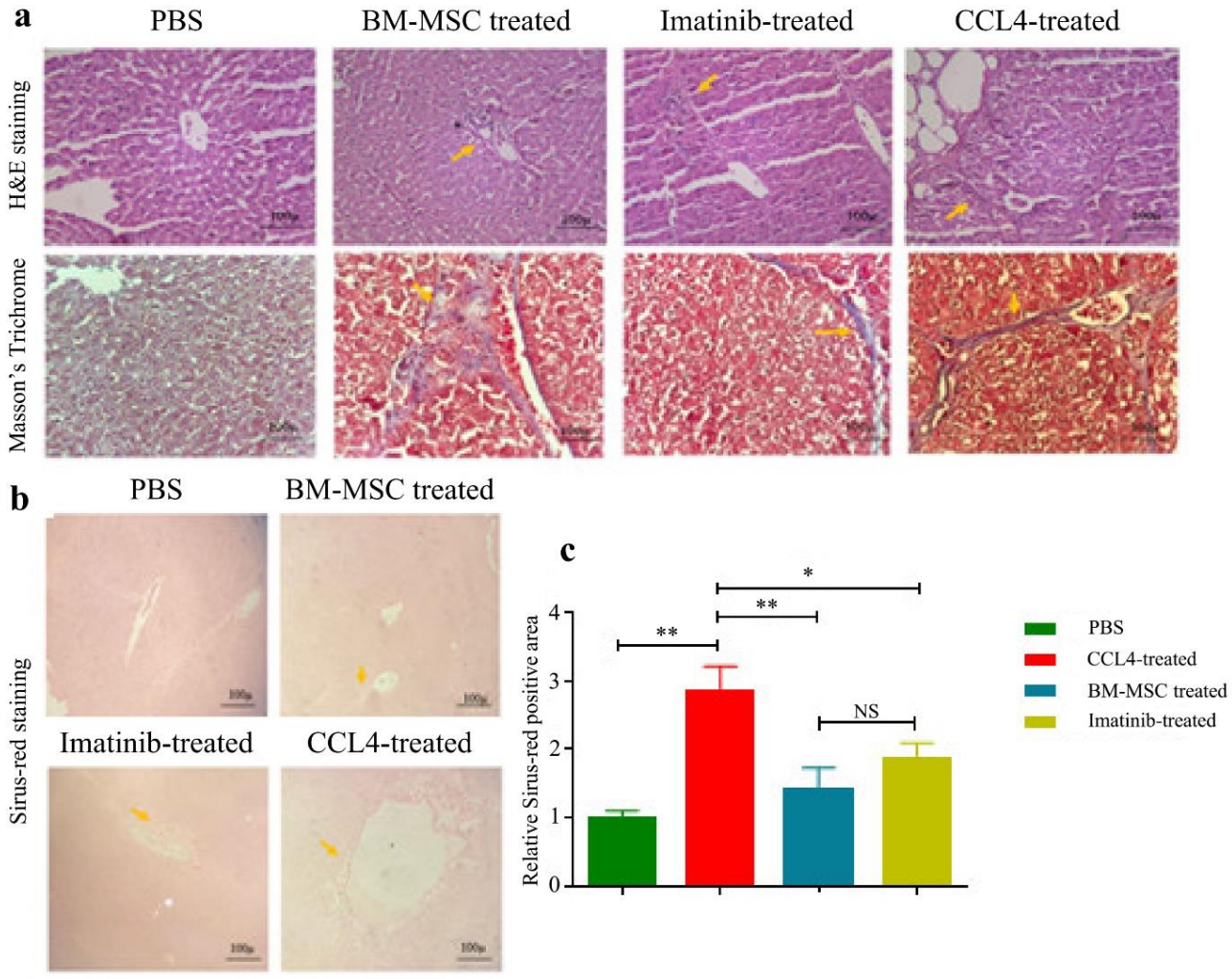

Fig. 1. Histopathological examination of fibrosis progression. a) Histopathological assessment of liver structure with H&E staining and Masson's trichrome (Magnification 200x). **b)** The collagen repositioning was demonstrated according to the Sirius-red staining. (Magnification 200x). Yellow arrows indicate collagen fibers. **c)** Sirus-red positive area quantified by ImageJ software compared to the PBS group. Student t-test was used for statistical analysis (*P< 0.01, **P< 0.001, and NS; not significant). (PBS, CCL4, BM-MSCs, imatinib are demonstrating of the experimental groups).

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Alternate expression of CCL2-CCR2 axes in both imatinib and BM-MSCs treatment group

The expressions candidate genes (*CCL2* and *CCR2*) were evaluated in rat liver samples after treatment with imatinib and BM-MSCs. The results were compared to CCL4-induced liver fibrosis group. The expression of the *CCL2* and *CCR2* genes was elevated in CCL4-induced rats, as shown in Figures 2a and 2b. The results of qRT-PCR demonstrated that the expressions of both genes were significantly decreased in imatinib (*CCL2*: P< 0.0001 and *CCR2*: P< 0.00001), and BM-MSCs (CCL2: P< 0.01 and CCR2: P< 0.0001) treated groups than CCL4-induced liver fibrosis rats. However, the expression levels in the imatinib-treated group were slightly lower than in BM-MSCs-treated group.

Increased expression of CX3CL1-CX3CR1 axes in both imatinib and BM-MSCs treatment group

The expression level of *CX3CL1* and *CX3CR1* genes as anti - fibrotic genes showed that treatment with BM-MSCs and imatinib results in upregulation of both genes (BM-MSC: P< 0.0001 and imatinib: P< 0.01) compared to CCL4-induced liver fibrosis rats (Fig. 3a). Imatinib-treated rats showed higher expression of *CX3CR1*, but the upregulation was not statistically significant for *CX3CL1 gene* (Fig. 3b).

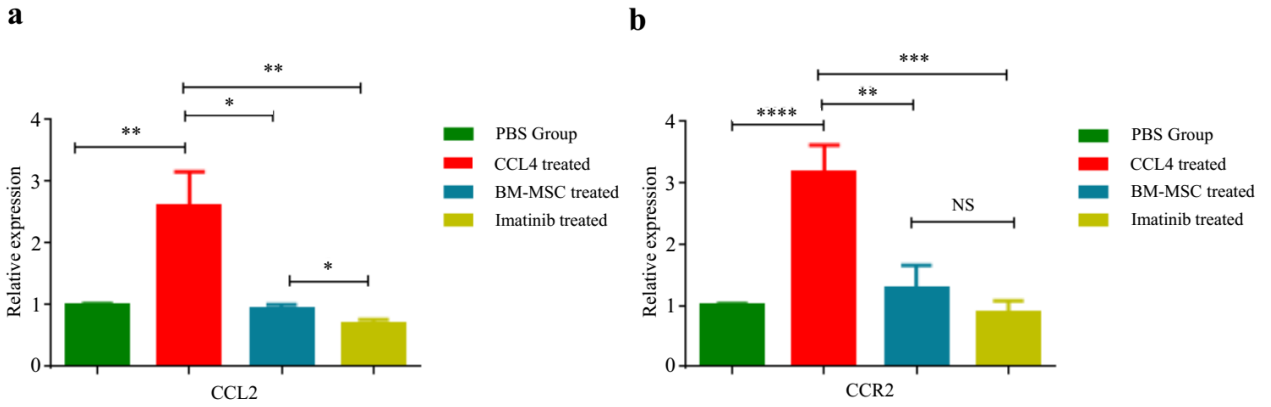

Fig. 2. Expression analysis of CCL2-CCR2 axis genes. (a) CCL2 expression was dramatically upregulated after provoking the liver fibrosis using carbon tetrachloride. Treatment separately with BM-MSC and imatinib resulted in decreased expression of CCL2. (b) Similar to CCL2, CCR2 showed Signiant decline in expression after treatment with BM-MSC and imatinib. Bars are indicating the mean + S.E.M of three independent experiments (n = 4 in each group). Student t-test was used for statistical analysis (* P< 0.01, *** P< 0.0001, and **** P< 0.00001, ns; not significant). (PBS, CCL4, BM-MSCs, imatinib are demonstrating of the experimental groups).

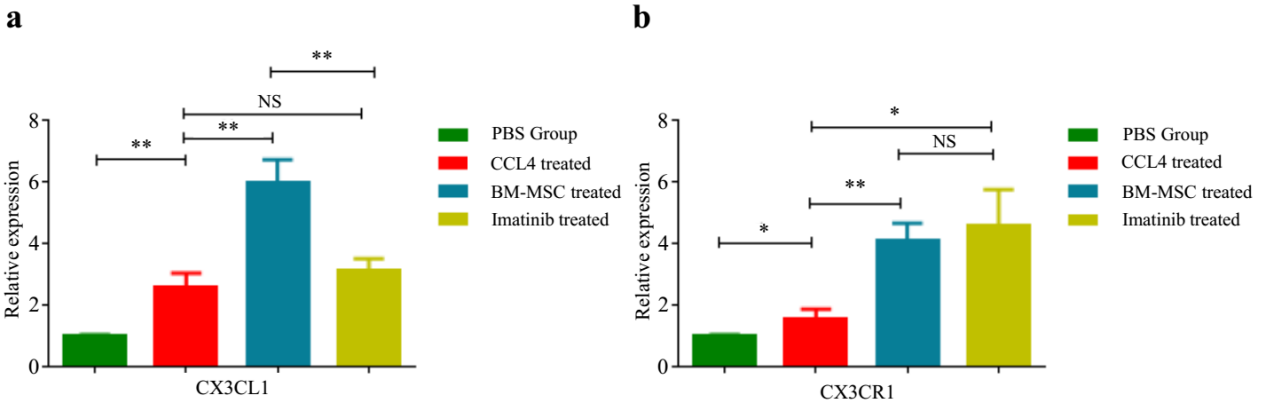

Fig. 3. Expression analysis of CX3CL1-CX3CR1 axis genes. (A) *CX3CL1* expression was notably increased upon treatment with BM-MSCs but moderately increased in imatinib treated samples. (B) *CX3CR1* expression was significantly increased in both therapeutic groups comparing to CCL4 only treated group. Bars are indicating the mean + S.E.M of three independent experiments (n = 4 in each group). Student t-test was used for statistical analysis (* P< 0.01, *** P< 0.0001, and **** P< 0.00001, ns; not significant). PBS, CCL4, BM-MSCs, imatinib are demonstrating of the experimental groups.

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Discussion

Liver inflammation triggered by sustained liver damage is the main cause of liver fibrosis and ultimately cirrhosis and HCC (19). The reversible intrinsic of liver fibrogenesis treads a path towards developing therapeutic approaches leading to amelioration, and further resolution of hepatic fibrosis (20).

To date, extensive efforts were made to develop an efficient therapeutic strategy to circumvent the global health problem caused by liver fibrosis. Among these strategies, MSCs, especially BM-MSCs and imatinib have shown encouraging results (17,21–25). The histopathological investigations, as the golden test of prognosis hepatic fibrosis showed a decrease in the progression of liver fibrosis in imatinib and BM-MSCs-recipient groups. These results were in line with previous studies, that showed the effects of imatinib (14) and BM-MSCs on the treatment of liver fibrosis. The great anti-fibrotic potential of imatinib is via the inhibition of platelet-derived growth factor (PDGF) receptors (26). BM-MSCs demonstrated anti-fibrotic effects via modulating HSC activation and suppressing collagen depositioning in the damaged live (27).

Understanding the comprehensive biological consequences of desired therapies on the reduction of liver fibrosis requires further studies. This understanding not only provides insights into the pathways, which are affected by BM-MSCs and imatinib treatment, but also lays the foundation for designing a better strategy for improving anti-fibrotic effects of therapeutical approaches.

By releasing different chemokines, liver immune cells, in particular macrophages, play a crucial role in the formation and progression of liver fibrosis. The *CCL2-CCR2* and *CX3CL1-CX3CR1* axes are among the most efficient regulators of liver fibrosis, according to an increasing body of research (7,10,12). Several attempts were made to pharmacologically inhibit *CCL2-CCR2* axis indicating that its inhibition decreases the level of liver inflammation and fibrosis (28,29). We examined the expression level of the *CCL2* and *CCR2* genes in both imatinib, and BM-MSCs-recipient groups to see if the desired therapies affect *CCL2-CCR2* axes.

Our results were the indicative of suitable regression of *CCL2* and *CCR2* expression, upregulated after CCL4 provocation of liver fibrosis, down to approximately their normal levels following treatment by imatinib and BM-MSCs. This data is representing that imatinib and BM-MSCs may possess the capacity to decrease the level of liver inflammation and decrease the monocyte infiltration to the liver. It The imatinib had a better performance in significantly decreasing the expression level of *CCL2* and *CCR2* genes compared to BM-MSCs.

The *CX3CL1-CX3CR1* axis is a notable regulator of liver fibrosis as well. This axis plays a crucial function in preventing both the influx of monocytes into the liver and the polarization of $LY6C^{high}$ macrophages into restorative $LY6C^{low}$macrophages (14), acting as a negative regulator of liver fibrosis. After receiving either imatinib or BM-MSCs, *CX3CL1* and *CX3CR1* expression was found to be upregulated, suggesting that the fibrotic phenotype has been improved. A recent study showed that there is a positive correlation between increased *CX3CL1* plasma level of newly diagnosed chronic myelogenous leukemia (CML) patients after 12 months of treatment with imatinib (30). These data suggest that imatinib actively has a great potential in activating immune responses.

Moreover, BM-MSCs increased the expression of *CX3CL1* statistically much higher than imatinib which could imply the fact that BM-MSCs trigger the activity and polarization of $LY6C^{low}$ macrophages more than imatinib. Moreover, it brings about the idea that the effect of BM-MSCs on this axis should be more studied in the future to unravel its mechanism of action for further use in the clinical section.

Similar to our findings, a recent study showed that the administration of the Fuzheng

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Huayu recipe, a locally developed medicine, improved liver fibrosis by implementing the biological function of *CX3CL1* and *CCL2* chemotaxis (31). Thus, developing therapeutic options, which can efficiently and selectively target these axes, should be considered as a great approach for tackling the treatment of liver fibrosis. Our results clearly indicated that imatinib and BM-MSCs have a notable effect on modulating inflammatory pathways of hepatic fibrosis via suppression of *CCL2-CCR2* axis and activation of the *CX3CL1-CX3CR1* axis.

In conclusion, we showed that oral imatinib treatment and intravenous delivery of BM-MSCs result in decreased expression levels of *CCL2* and *CCR2*, which are critical regulators of the migration of inflammatory macrophages to the liver in rats with CCL4-induced liver fibrosis. In parallel, the expression of *CX3CL1* and *CX3CR1* notably increased indicating that the therapeutic approaches effect on upregulation of this axis to promote the polarization of $LY6C^{low}$ leading to the resolution of hepatic fibrosis. In general, although both mesenchymal stem cells, and imatinib appear to be effective in ameliorating fibrosis, the TKI-receiving group has been better able to activate non-inflammatory pathways.

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Conflicts of interest

The authors have no conflicts of interest to declare.

Ethics approval

Ethics Committee of Shahid Beheshti University of Medical Sciences (Tehran, Iran) approved all experimental procedures. (Code of Ethics: IR.SBMU.MSP.REC.1396.269).

References

1. Marcellin P, Kutala BK. Liver diseases: A major, neglected global public health problem requiring urgent actions and large-scale screening. Liver Int. 2018;38:2–6.

2. Schuppan D, Ashfaq-Khan M, Yang AT, Kim YO. Liver fibrosis: Direct antifibrotic agents and targeted therapies. Matrix Biol. 2018;68:435–51.

3. Sacchi P, Cima S, Corbella M, Comolli G, Chiesa A, Baldanti F, et al. Liver fibrosis, microbial translocation and immune activation markers in HIV and HCV infections and in HIV/HCV co-infection. Dig Liver Dis. 2015;47(3):218–25.

4. Khomich O, Ivanov A V, Bartosch B. Metabolic hallmarks of hepatic stellate cells in liver fibrosis. Cells. 2019;9(1):24.

5. Poulsen KL, Ross CKC-D, Chaney JK, Nagy LE. Role of the chemokine system in liver fibrosis: a narrative review. Dig Med Res. 2022;5:30–30.

6. Karlmark KR, Weiskirchen R, Zimmermann HW, Gassler N, Ginhoux F, Weber C, et al. Hepatic recruitment of the inflammatory Gr1+ monocyte subset upon liver injury promotes hepatic fibrosis. Hepatology. 2009;50(1):261–74.

7. Tacke F. Targeting hepatic macrophages to treat liver diseases. J Hepatol. 2017;66(6):1300–12.

8. Papadopoulos C, Mimidis K, Papazoglou D, Kolios G, Tentes I, Anagnostopoulos K. Red blood cell-conditioned media from non-alcoholic fatty liver disease patients contain

[DOI: 10.61186/rbmb.12.2.350]

increased MCP1 and induce TNF-α release. Reports Biochem Mol Biol. 2022;11(1):54.
9. Triantafyllou E, Woollard KJ, McPhail MJW, Antoniades CG, Possamai LA. The role of monocytes and macrophages in acute and acute-on-chronic liver failure. Front Immunol. 2018; 9: 2948. Epub 2019/01/09. doi: 10.3389/fimmu. 2018.02948 30619308; 2018.
10. Baghaei K, Mazhari S, Tokhanbigli S, Parsamanesh G, Alavifard H, Schaafsma D, et al. Therapeutic potential of targeting regulatory mechanisms of hepatic stellate cell activation in liver fibrosis. Drug Discov Today. 2022;27(4):1044–61.
11. Hayatbakhsh MM, Shabgah AG, Pishgouyi S, Afshari JT, Zeidabadi H, Mohammadi M. The serum levels of CCL2 and CCL16 expression in patients with irritable bowel syndrome. Reports Biochem Mol Biol. 2019;8(1):9.
12. Karlmark KR, Zimmermann HW, Roderburg C, Gassler N, Wasmuth HE, Luedde T, et al. The fractalkine receptor CX3CR1 protects against liver fibrosis by controlling differentiation and survival of infiltrating hepatic monocytes. Hepatology. 2010;52(5):1769–82.
13. Aoyama T, Inokuchi S, Brenner DA, Seki E. CX3CL1-CX3CR1 interaction prevents carbon tetrachloride-induced liver inflammation and fibrosis in mice. Hepatology. 2010;52(4):1390–400.
14. El-Mezayen NS, El-Hadidy WF, El-Refaie WM, Shalaby TI, Khattab MM, El-Khatib AS. Hepatic stellate cell-targeted imatinib nanomedicine versus conventional imatinib: a novel strategy with potent efficacy in experimental liver fibrosis. J Control release. 2017;266:226–37.
15. Khalil MR, El-Demerdash RS, Elminshawy HH, Mehanna ET, Mesbah NM, Abo-Elmatty DM. Therapeutic effect of bone marrow mesenchymal stem cells in a rat model of carbon tetrachloride induced liver fibrosis. Biomed J. 2021;44(5):598–610.
16. Zhao D-C, Lei J-X, Chen R, Yu W-H, Zhang X-M, Li S-N, et al. Bone marrow-derived mesenchymal stem cells protect against experimental liver fibrosis in rats. World J Gastroenterol WJG. 2005;11(22):3431.
17. Mazhari S, Gitiara A, Baghaei K, Hatami B, Rad RE, Asadirad A, et al. Therapeutic potential of bone marrow-derived mesenchymal stem cells and imatinib in a rat model of liver fibrosis. Eur J Pharmacol. 2020;882:173263.
18. Baghaei K, Hashemi SM, Tokhanbigli S, Rad AA, Assadzadeh-Aghdaei H, Sharifian A, et al. Isolation, differentiation, and characterization of mesenchymal stem cells from human bone marrow. Gastroenterol Hepatol from bed to bench. 2017;10(3):208.
19. Tacke F. Functional role of intrahepatic monocyte subsets for the progression of liver inflammation and liver fibrosis in vivo. In: Fibrogenesis & tissue repair. Springer; 2012. p. 1–8.
20. Weiskirchen R, Tacke F. Liver fibrosis: from pathogenesis to novel therapies. Dig Dis. 2016;34(4):410–22.
21. Mansour MF, Greish SM, El-Serafi AT, Abdelall H, El-Wazir YM. Therapeutic potential of human umbilical cord derived mesenchymal stem cells on rat model of liver fibrosis. Am J Stem Cells. 2019;8(1):7.
22. Yoshiji H, Noguchi R, Kuriyama S, Ikenaka Y, Yoshii J, Yanase K, et al. Imatinib mesylate (STI-571) attenuates liver fibrosis development in rats. Am J Physiol Liver Physiol. 2005;288(5):G907–13.
23. Sakaida I, Terai S, Yamamoto N, Aoyama K, Ishikawa T, Nishina H, et al. Transplantation of bone marrow cells reduces CCl4-induced liver fibrosis in mice. Hepatology. 2004;40(6):1304–11.
24. Gorji SM, Malekshah AAK, Hashemi-Soteh MB, Rafiei A, Parivar K, Aghdami N. Effect of mesenchymal stem cells on doxorubicin-induced fibrosis. Cell J. 2012;14(2):142.

[DOI: 10.61186/rbmb.12.2.350]

25. Akhmetshina A, Venalis P, Dees C, Busch N, Zwerina J, Schett G, et al. Treatment with imatinib prevents fibrosis in different preclinical models of systemic sclerosis and induces regression of established fibrosis. Arthritis Rheum. 2009;60(1):219–24.
26. Kuo W-L, Yu M-C, Lee J-F, Tsai C-N, Chen T-C, Chen M-F. Imatinib mesylate improves liver regeneration and attenuates liver fibrogenesis in CCL4-treated mice. J Gastrointest Surg. 2012;16(2):361–9.
27. Scott CL, Zheng F, De Baetselier P, Martens L, Saeys Y, De Prijck S, et al. Bone marrow-derived monocytes give rise to self-renewing and fully differentiated Kupffer cells. Nat Commun. 2016;7(1):1–10.
28. Baeck C, Wehr A, Karlmark KR, Heymann F, Vucur M, Gassler N, et al. Pharmacological inhibition of the chemokine CCL2 (MCP-1) diminishes liver macrophage infiltration and steatohepatitis in chronic hepatic injury. Gut. 2012;61(3):416–26.
29. Puengel T, Krenkel O, Kohlhepp M, Lefebvre E, Luedde T, Trautwein C, et al. Differential impact of the dual CCR2/CCR5 inhibitor cenicriviroc on migration of monocyte and lymphocyte subsets in acute liver injury. PLoS One. 2017;12(9):e0184694.
30. Kreutzman A, Yadav B, Brummendorf TH, Gjertsen BT, Hee Lee M, Janssen J, et al. Immunological monitoring of newly diagnosed CML patients treated with bosutinib or imatinib first-line. Oncoimmunology. 2019;8(9):e1638210.
31. Zhang M, Liu H, Huang K, Peng Y, Tao Y, Zhao C, et al. Fuzheng Huayu recipe prevented and treated CCl4-induced mice liver fibrosis through regulating polarization and chemotaxis of intrahepatic macrophages via CCL2 and CX3CL1. Evidence-Based Complement Altern Med. 2020;2020 :8591892.

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