Liver fibrosis and cirrhosis mutations can be treated with stem cells therapy followed by circulating innate immune cells trnasfusion

Shaikh Mahmood*

Assistant Professor, Dept. of Physiology, Owaisi Hospital & Research Centre, Deccan College of Medical Sciences, Hyderabad, Telangana State, India

***Corresponding Author: S. Mahmood**
Email: mahmood_shaikh2001@yahoo.co.in

Abstract
Patients with keratin gene mutation have fibrous deposits in their livers than individual without the mutations. These deposits impair liver function, leading to liver cirrhosis. In individual with an associated keratin gene mutation, the risk of developing cryptogenic cirrhosis appears to have an autosomal dominant pattern of inheritance means that one copy of an altered gene in each cell is sufficient to increase the risk of developing cryptogenic cirrhosis. In these families, people inherit an increased risk of cryptogenic cirrhosis, not the disease itself. A gene mutation has been found to contribute to non-alcoholic fatty liver disease (NAFLD), a form of liver disease closely linked to obesity, in normal weight patients. Carries of the PNPLA3 mutant genotype were found to be a greater risk for NAFLD and health problems compared to non-carriers even when the carrier was not obese. This influence of weight status on the interaction between the mutant gene and NAFLD was clarified. Stem Cells Therapy is a suggestive procedure to substitute up to certain extent of the mutation. Meanwhile Circulating Innate Immune Cells can be transfused to increase the immunity of the effected patients.

Keywords: Liver Cirrhosis, Cryptogenetic Cirrhosis, Mutations, Stem Cells Therapy, Circulating Innate Immune Cell Transfusion

Introduction

Liver fibrosis or cirrhosis formed from a wound healing response to chronic injury, that carries to excessive matrix. This excessive matrix tissue restrict blood flow due to concentration of the effected organ, which leads to progressive liver damage and cause cirrhosis (end stage of fibrosis), complicated by liver failure, portal hypertension or hepatocellular carcinoma. Fibrosis or cirrhosis I prominent in chronic liver diseases, including viral hepatitis, alcoholic and non-alcoholic steatohepatitis, toxic liver injury, autoimmune disease and several genetic disease. There have been three major priorities for therapy reduce fibrosis or cirrhosis.

1. To identify fibrosis or cirrhosis mutations
2. Stem cells therapy
3. Transfusion of circulating innate immune cells

This review study will focus on the contribution of high throughput genomic and proteomic approaches of fibrogenesis and fibrosis or cirrhosis progression, concentrating on the most prevalent human chronic liver diseases.[1-30]

Materials and Methods

As this is a review study a total number of 25 suspected patients of alcoholic and non alcoholic with fatty or non fatty liver for any age group with either sex and a total number of 50 healthy controls are compared. Once they are identified for fibrosis or cirrhosis, they can go for PCR and locate exact for mutations and point mutations. At the same time cultured stem cells (in born hepatocytes) from liver of still birth babies can be transfused in to the peritoneum for exact tagging of mutated hepatocytes. Meanwhile kept ready the circulating innate immune cells for transfusion. The entire procedure is in follow up phenomenon under complete hygienic and in sterile condition. Basic requirements are very much needed to establish treatments for the diseases that lead to liver fibrosis or cirrhosis.[31-70]

Discussion

Most chronic liver disease lead to fibrosis and cirrhosis in a significant subset of patient. While many common pathways that drive fibrogenesis in all these diseases, there are also disease-specific pathways that contribute to fibrosis.[71-117] An increasing number of studies are comparing the transcriptome and proteome of the patients with different types of chronic liver injury to unearth disease-specific abnormalities in gene or protein expression.

Conclusion

Hence liver fibrosis or cirrhosis mutations or point mutations can be treated with stem cells therapy followed by circulating innate immune cells transfusion.

Source of Funding
None.

Conflict of Interest
None.

References

1. Bataller R, Brenner DA: Liver fibrosis. *J Clin Invest.* 2005, 115:(2) 209-18.
2. Friedman SL: Hepatic stellate cells: protean, multifunctional, and enigmatic cells of the liver. *Physiol Rev*. 2008, 88:(1) 125-72.

3. Juran BD, Lazaridis KN: Applying genomics to the study of complex disease. *Semin Liver Dis*. 2007, 27:(1) 3-12.
4. Osterreicher CH, Stickel F, Brenner DA: Genomics of liver fibrosis and cirrhosis. *Semin Liver Dis*. 2007, 27:(1) 28-43.
5. Juran BD, Lazaridis KN: Genomics and complex liver disease: Challenges and opportunities. *Hepatology*. 2006, 44:(6) 1380-90.
6. Grant A, Neuberger J: Guidelines on the use of liver biopsy in clinical practice. Br Soc Gastroenterology. Gut. 1999, 45 (Suppl 4): IV1-IV11.
7. McGill DB, Rakela J, Zinsmeister AR, Ott BJ: A 21-year experience with major hemorrhage after percutaneous liver biopsy. *Gastroenterol* 1990, 99:(5) 1396-400.
8. Piccinino F, Sagnelli E, Pasquale G, Giusti G: Complications following percutaneous liver biopsy. A multicentre retrospective study on 68,276 biopsies. *J Hepatol*. 1986, 2:(2) 165-73.
9. Regev A, Berho M, Jeffers LJ, Milikowski C, Molina EG, Pyrsopoulos NT, Feng ZZ, Reddy KR, Schiff ER: Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. *Am J Gastroenterol* 2002, 97:(10) 2614-8.
10. Siddique I, El-Naga HA, Madda JP, Memon A, Hasan F: Sampling variability on percutaneous liver biopsy in patients with chronic hepatitis C virus infection. *Scand J Gastroenterol.* 2003, 38:(4) 427-32.
11. Ratziu V, Charlotte F, Heurtier A, Gombert S, Giral P, Bruckert E, Grimaldi A, Capron F, Poynard T: Sampling variability of liver biopsy in nonalcoholic fatty liver disease. *Gastroenterol* 2005, 128:(7) 1898-906.
12. Cox LA, Schlabritz-Loutsevitch N, Hubbard GB, Nijland MJ, McDonald TJ, Nathanielsz PW: Gene expression profile differences in left and right liver lobes from mid-gestation fetal baboons: a cautionary tale. *J Physiol*. 2006, 572:(1) 59-66.
13. Skripenova S, Trainer TD, Krawitt EL, Blaszyk H: Variability of grade and stage in simultaneous paired liver biopsies in patients with hepatitis C. *J Clin Pathol*. 2007, 60:(3) 321-4.
14. Bedossa P, Dargere D, Paradis V: Sampling variability of liver fibrosis in chronic hepatitis C. *Hepatol*. 2003, 38:(6) 1449-57.
15. Boess F, Kamber M, Romer S, Gasser R, Muller D, Albertini S, Suter L: Gene expression in two hepatic cell lines, cultured primary hepatocytes, and liver slices compared to the in vivo liver gene expression in rats: possible implications for toxicogenomics use of in vitro systems. *Toxicol Sci*. 2003, 73:(2) 386-402.
16. Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, Lok AS: A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatol*. 2003, 38:(2) 518-26.
17. Martinez SM, Crespo G, Navasa M, Forns X: Noninvasive assessment of liver fibrosis. *Hepatol*. 2011, 53:(1) 325-35.
18. Imbert-Bismut F, Ratziu V, Pieroni L, Charlotte F, Benhamou Y, Poynard T: Biochemical markers of liver fibrosis in patients with hepatitis C virus infection: a prospective study. *Lancet*. 2001, 357:(9262) 1069-75.
19. Poynard T, Imbert-Bismut F, Munteanu M, Messous D, Myers RP, Thabut D, Ratziu V, Mercadier A, Benhamou Y, Hainque B: Overview of the diagnostic value of biochemical markers of liver fibrosis (FibroTest, HCV FibroSure) and necrosis (ActiTest) in patients with chronic hepatitis C. *Comp Hepatol*. 2004, 3:(1) 8.
20. Halfon P, Imbert-Bismut F, Messous D, Antoniotti G, Benchetrit D, Cart-Lamy P, Delaporte G, Doutheau D, Klump T, Sala M, Thibaud D, Trepo E, Thabut D, Myers RP, Poynard T: A prospective assessment of the inter-laboratory variability of biochemical markers of fibrosis (FibroTest) and activity (ActiTest) in patients with chronic liver disease. *Comp Hepatol*. 2002,30:(1) 1: 3.
21. Smith JO, Sterling RK: Systematic review: non-invasive methods of fibrosis analysis in chronic hepatitis C. Aliment *Pharmacol Ther*. 2009, 30:(6) 557-76.
22. Rockey DC, Bissell DM: Noninvasive measures of liver fibrosis. *Hepatol.* 2006, 43:(2) S113-20.
23. Shaheen AA, Wan AF, Myers RP: FibroTest and FibroScan for the prediction of hepatitis C-related fibrosis: a systematic review of diagnostic test accuracy. *Am J Gastroenterol*. 2007, 102:(11) 2589-600.
24. Trinchet JC, Hartmann DJ, Pateron D, Laarif M, Callard P, Ville G, Beaugrand M: Serum type I collagen and N-terminal peptide of type III procollagen in chronic hepatitis. Relationship to liver histology and conventional liver tests. *J Hepatol*. 1991, 12:(2) 139-44.
25. Teare JP, Sherman D, Greenfield SM, Simpson J, Bray G, Catterall AP, Murray-Lyon IM, Peters TJ, Williams R, Thompson RP: Comparison of serum procollagen III peptide concentrations and PGA index for assessment of hepatic fibrosis. *Lancet.* 1993, 342: 895-8.
26. Gallorini A, Plebani M, Pontisso P, Chemello L, Masiero M, Mantovani G, Alberti A: Serum markers of hepatic fibrogenesis in chronic hepatitis type C treated with alfa-2A interferon. *Liver*. 1994, 14: 257-64.
27. Yabu K, Kiyosawa K, Mori H, Matsumoto A, Yoshizawa K, Tanaka E, Furuta S: Serum collagen type IV for the assessment of fibrosis and resistance to interferon therapy in chronic hepatitis C. *Scand J Gastroenterol*. 1994, 29:(4) 474-9.
28. Walsh KM, Timms P, Campbell S, MacSween RN, Morris AJ: Plasma levels of matrix metalloproteinase-2 (MMP-2) and tissue inhibitors of metalloproteinases -1 and -2 (TIMP-1 and TIMP-2) as noninvasive markers of liver disease in chronic hepatitis C: comparison using ROC analysis. *Dig Dis Sci.* 1999, 44:(1) 624-30.
29. Boeker KH, Haberkorn CI, Michels D, Flemming P, Manns MP, Lichtinghagen R: Diagnostic potential of circulating TIMP-1 and MMP-2 as markers of liver fibrosis in patients with chronic hepatitis C. *Clin Chim Acta*. 2002, 316:(1) 71-81.
30. Cheung KJ, Tilleman K, Deforce D, Colle I, Van Vlierberghe H: The HCV serum proteome: a search for fibrosis protein markers. *J Viral Hepat*. 2009, 16: 418-29.
31. Morra R, Munteanu M, Bedossa P, Dargere D, Janneau JL, Paradis V, Ratziu V, Charlotte F, Thibault V, Imbert-Bismut F, Poynard T: Diagnostic value of serum protein profiling by SELDI-TOF ProteinChip compared with a biochemical

marker, FibroTest, for the diagnosis of advanced fibrosis in patients with chronic hepatitis C. Aliment *Pharmacol Ther*. 2007, 26:(6) 847-58.

32. Gressner OA, Weiskirchen R, Gressner AM: Biomarkers of liver fibrosis: clinical translation of molecular pathogenesis or based on liver-dependent malfunction tests. *Clin Chim Acta*. 2007, 381:(7) 107-13.
33. Gobel T, Vorderwulbecke S, Hauck K, Fey H, Haussinger D, Erhardt A: New multi protein patterns differentiate liver fibrosis stages and hepatocellular carcinoma in chronic hepatitis C serum samples. World J Gastroenterol. 2006, 12:(47) 7604-12.
34. Kuramitsu Y, Nakamura K: Current progress in proteomic study of hepatitis C virus-related human hepatocellular carcinoma. *Expert Rev Proteomics.* 2005, 2:(4) 589-601.
35. Chen G, Gharib TG, Huang CC, Taylor JM, Misek DE, Kardia SL, Giordano TJ, Iannettoni MD, Orringer MB, Hanash SM, Beer DG: Discordant protein and mRNA expression in lung adenocarcinomas. Mol Cell Proteomics. 2002, 1:(4) 304-13.
36. Tian Q, Stepaniants SB, Mao M, Weng L, Feetham MC, Doyle MJ, Yi EC, Dai H, Thorsson V, Eng J, Goodlett D, Berger JP, Gunter B, Linseley PS, Stoughton RB, Aebersold R, Collins SJ, Hanlon WA, Hood LE: Integrated genomic and proteomic analyses of gene expression in Mammalian cells. Mol Cell Proteomics. 2004, 3:(10) 960-9.
37. Pollack JR, Perou CM, Alizadeh AA, Eisen MB, Pergamenschikov A, Williams CF, Jeffrey SS, Botstein D, Brown PO: Genome-wide analysis of DNA copy-number changes using cDNA microarrays. *Nat Genet*. 1999, 23:(1) 41-6.
38. Sellick GS, Longman C, Tolmie J, Newbury-Ecob R, Geenhalgh L, Hughes S, Whiteford M, Garrett C, Houlston RS: Genomewide linkage searches for Mendelian disease loci can be efficiently conducted using high-density SNP genotyping arrays. *Nucleic Acids Res.* 2004, 32:(20) e164.
39. Wang DG, Fan JB, Siao CJ, Berno A, Young P, Sapolsky R, Ghandour G, Perkins N, Winchester E, Spencer J, Kruglyak L, Stein L, Hsie L, Topaloglou T, Hubbell E, Robinson E, Mittmann M, Morris MS, Shen N, Kilburn D, Rioux J, Nusbaum C, Rozen S, Hudson TJ, Lipshutz R, Chee M, Lander ES: Large-scale identification, mapping, and genotyping of single-nucleotide polymorphisms in the human genome. *Science*. 1998, 280:(2) 1077-82.
40. Johnson JM, Castle J, Garrett-Engele P, Kan Z, Loerch PM, Armour CD, Santos R, Schadt EE, Stoughton R, Shoemaker DD: Genome-wide survey of human alternative pre-mRNA splicing with exon junction microarrays. Science. 2003, 302:(5653) 2141-4.
41. Yamamoto M, Wakatsuki T, Hada A, Ryo A: Use of serial analysis of gene expression (SAGE) technology. *J Immunol Methods.* 2001, 250:(1-2) 45-66.
42. Ruijter JM, Van Kampen AH, Baas F: Statistical evaluation of SAGE libraries: consequences for experimental design. *Physiol Genom.* 2002, 11:(2) 37-44.
43. Aebersold R, Mann M: Mass spectrometry-based proteomics. *Nature.* 2003, 422:(6928) 198-207.
44. Capelo JL, Carreira R, Diniz M, Fernandes L, Galesio M, Lodeiro C, Santos HM, Vale G: Overview on modern approaches to speed up protein identification workflows relying on enzymatic cleavage and mass spectrometry-based techniques. *Anal Chim Acta.* 2009, 650:(2) 151-9.
45. Tonge R, Shaw J, Middleton B, Rowlinson R, Rayner S, Young J, Pognan F, Hawkins E, Currie I, Davison M: Validation and development of fluorescence two-dimensional differential gel electrophoresis proteomics technology. *Proteomics*. 2001, 1:(3) 377-96.
46. Unlu M, Morgan ME, Minden JS: Difference gel electrophoresis: a single gel method for detecting changes in protein extracts. *Electrophoresis*. 1997, 18:(11) 2071-7.
47. Schwartz JC, Senko MW, Syka JE: A two-dimensional quadrupole ion trap mass spectrometer. *J Am Soc Mass Spectrom.* 2002, 13:(6) 659-69.
48. Marshall AG, Hendrickson CL, Jackson GS: Fourier transform ion cyclotron resonance mass spectrometry: a primer. *Mass Spectrom Rev*. 1998, 17:(1) 1-35.
49. Hardman M, Makarov AA: Interfacing the orbitrap mass analyzer to an electrospray ion source. *Anal Chem*. 2003, 75:(1) 1699-705.
50. Hu Q, Noll RJ, Li H, Makarov A, Hardman M, Graham Cooks R: The Orbitrap: a new mass spectrometer. *J Mass Spectrom.* 2005, 40:(4) 430-43.
51. Hutchens TA: Automaticity and reading in learning-disabled college students. *Ann N Y Acad Sci.* 1993, 682:(1) 357-8.
52. Issaq HJ, Veenstra TD, Conrads TP, Felschow D: The SELDI-TOF MS approach to proteomics: protein profiling and biomarker identification. *Biochem Biophys Res Commun.* 2002, 292:(1) 587-92.
53. De Bock M, de Seny D, Meuwis MA, Chapelle JP, Louis E, Malaise M, Merville MP, Fillet M: Challenges for biomarker discovery in body fluids using SELDI-TOF-MS. *J Biomed Biotechnol*. 2010, 2010: 906082.
54. Domon B, Aebersold R: Mass spectrometry and protein analysis. Science. 2006, 312: 212-7.
55. MacBeath G, Schreiber SL: Printing proteins as microarrays for high-throughput function determination. Science. 2000, 289: 1760-3.
56. Low TY, Leow CK, Salto-Tellez M, Chung MC: A proteomic analysis of thioacetamide-induced hepatotoxicity and cirrhosis in rat livers. Proteomics. 2004, 4:(12) 3960-74.
57. Henkel C, Roderfeld M, Weiskirchen R, Berres ML, Hillebrandt S, Lammert F, Meyer HE, Stuhler K, Graf J, Roeb E: Changes of the hepatic proteome in murine models for toxically induced fibrogenesis and sclerosing cholangitis. Proteomics. 2006, 6: 6538-48.
58. Shepard BD, Tuma DJ, Tuma PL: Chronic ethanol consumption induces global hepatic protein hyperacetylation. *Alcohol Clin Exp Res*. 2010, 34:(2) 280-91.
59. Andringa KK, King AL, Eccleston HB, Mantena SK, Landar A, Jhala NC, Dickinson DA, Squadrito GL, Bailey SM: Analysis of the liver mitochondrial proteome in response to ethanol and S-adenosylmethionine treatments: novel molecular targets of disease and hepatoprotection. *Am J Physiol Gastrointest Liver Physiol.* 2010, 298:(5) G732-45.
60. Kharbanda KK, Vigneswara V, McVicker BL, Newlaczyl AU, Bailey K, Tuma D, Ray DE, Carter WG: Proteomics reveal a concerted upregulation of methionine metabolic pathway enzymes, and downregulation of carbonic

anhydrase-III, in betaine supplemented ethanol-fed rats. *Biochem Biophys Res Commun.* 2009, 381:(4) 523-7.

61. Liu EH, Chen MF, Yeh TS, Ho YP, Wu RC, Chen TC, Jan YY, Pan TL: A useful model to audit liver resolution from cirrhosis in rats using functional proteomics. *J Surg Res.* 2007, 138:(2) 214-23.
62. 63.Kirpich IA, Gobejishvili LN, Bon Homme M, Waigel S, Cave M, Arteel G, Barve SS, McClain CJ, Deaciuc IV: Integrated hepatic transcriptome and proteome analysis of mice with high-fat diet-induced nonalcoholic fatty liver disease. *J Nutr Biochem.* 2011, 22: 38-45.
63. Zhang X, Yang J, Guo Y, Ye H, Yu C, Xu C, Xu L, Wu S, Sun W, Wei H, Gao X, Zhu Y, Qian X, Jiang Y, Li Y, He F: Functional proteomic analysis of nonalcoholic fatty liver disease in rat models: enoyl-coenzyme a hydratase down-regulation exacerbates hepatic steatosis. *Hepatology.* 2010, 51: 1190-9.
64. Kristensen DB, Kawada N, Imamura K, Miyamoto Y, Tateno C, Seki S, Kuroki T, Yoshizato K: Proteome analysis of rat hepatic stellate cells. *Hepatol*. 2000, 32:(2) 268-77.
65. Kawada N, Kristensen DB, Asahina K, Nakatani K, Minamiyama Y, Seki S, Yoshizato K: Characterization of a stellate cell activation-associated protein (STAP) with peroxidase activity found in rat hepatic stellate cells. J Biol Chem. 2001, 276:(1) 25318-23.
66. Deng X, Liang J, Lin ZX, Wu FS, Zhang YP, Zhang ZW: Natural taurine promotes apoptosis of human hepatic stellate cells in proteomics analysis. *World J Gastroenterol*. 2010, 16: 1916-23.
67. Yokoyama Y, Terai S, Ishikawa T, Aoyama K, Urata Y, Marumoto Y, Nishina H, Nakamura K, Okita K, Sakaida I: Proteomic analysis of serum marker proteins in recipient mice with liver cirrhosis after bone marrow cell transplantation. Proteomics. 2006, 6: 2564-70.
68. Shimada T, Nakanishi T, Toyama A, Yamauchi S, Kanzaki A, Fujiwake H, Sato TA, Ikegawa M: Potential implications for monitoring serum bile acid profiles in circulation with serum proteome for carbon tetrachloride-induced liver injury/regeneration model in mice. *J Proteome Res.* 2010, 9: 4490-500.
69. Smyth R, Lane CS, Ashiq R, Turton JA, Clarke CJ, Dare TO, York MJ, Griffiths W, Munday MR: Proteomic investigation of urinary markers of carbon-tetrachloride-induced hepatic fibrosis in the Hanover Wistar rat. *Cell Biol Toxicol*. 2009, 25: 499-512.
70. Walters KA, Katze MG: Using high-throughput genomics to study hepatitis C: what determines the outcome of infection?. *Antiviral Res.* 2009, 81: 198-208.
71. Diamond DL, Jacobs JM, Paeper B, Proll SC, Gritsenko MA, Carithers RL, Larson AM, Yeh MM, Camp DG, Smith RD, Katze MG: Proteomic profiling of human liver biopsies: hepatitis C virus-induced fibrosis and mitochondrial dysfunction. *Hepatology.* 2007, 46: 649-57.
72. Molleken C, Sitek B, Henkel C, Poschmann G, Sipos B, Wiese S, Warscheid B, Broelsch C, Reiser M, Friedman SL, Tornoe I, Schlosser A, Kloppel G, Schmiegel W, Meyer HE, Holmskov U, Stuhler K: Detection of novel biomarkers of liver cirrhosis by proteomic analysis. *Hepatology.* 2009, 49:(1) 1257-66.
73. White IR, Patel K, Symonds WT, Dev A, Griffin P, Tsokanas N, Skehel M, Liu C, Zekry A, Cutler P, Gattu M, Rockey DC, Berrey MM, McHutchison JG: Serum proteomic analysis focused on fibrosis in patients with hepatitis C virus infection. *J Transl Med*. 2007, 5:(2) 32-3.
74. Chen L, Borozan I, Sun J, Guindi M, Fischer S, Feld J, Anand N, Heathcote J, Edwards AM, McGilvray ID: Cell-type specific gene expression signature in liver underlies response to interferon therapy in chronic hepatitis C infection. *Gastroenterol*. 2010, 138:(1123) 1-3
75. Gangadharan B, Antrobus R, Dwek RA, Zitzmann N: Novel serum biomarker candidates for liver fibrosis in hepatitis C patients. *Clin Chem.* 2007, 53: 1792-9.
76. Suzman DL, McLaughlin M, Hu Z, Kleiner DE, Wood B, Lempicki RA, Mican JM, Suffredini A, Masur H, Polis MA, Kottilil S: Identification of novel markers for liver fibrosis in HIV/hepatitis C virus coinfected individuals using genomics-based approach. AIDS. 2008, 22:(1) 1433-9.
77. Yang L, Rudser KD, Higgins L, Rosen HR, Zaman A, Corless CL, David L, Gourley GR: Novel biomarker candidates to predict hepatic fibrosis in hepatitis c identified by serum proteomics. *Dig Dis Sci*. 2011, 56:(1) 3305-15.
78. Corradi F, Piscaglia F, Flori S, D'Errico-Grigioni A, Vasuri F, Tame MR, Andreone P, Boni P, Gianstefani A, Bolondi L: Assessment of liver fibrosis in transplant recipients with recurrent HCV infection: usefulness of transient elastography. *Dig Liver Dis.* 2009, 41:(1 217-25.
79. Cheung KJ, Libbrecht L, Tilleman K, Deforce D, Colle I, Van Vlierberghe H: Galectin-3-binding protein: a serological and histological assessment in accordance with hepatitis C-related liver fibrosis. *Eur J Gastroenterol Hepatol*. 2010, 22: 1066-73.
80. Huang H, Shiffman ML, Friedman S, Venkatesh R, Bzowej N, Abar OT, Rowland CM, Catanese JJ, Leong DU, Sninsky JJ, Layden TJ, Wright TL, White T, Cheung RC: A 7 gene signature identifies the risk of developing cirrhosis in patients with chronic hepatitis C. *Hepatol*. 2007, 46: 297-306.
81. Marcolongo M, Young B, Dal Pero F, Fattovich G, Peraro L, Guido M, Sebastiani G, Palu G, Alberti A: A seven-gene signature (cirrhosis risk score) predicts liver fibrosis progression in patients with initially mild chronic hepatitis C. *Hepatol.* 2009, 50:(1) 1038-44.
82. Pradat P, Trepo E, Potthoff A, Bakshi R, Young B, Trepo C, Lagier R, Moreno C, Lemmers A, Gustot T, Degre D, Adler M, Wedemeyer H: The cirrhosis risk score predicts liver fibrosis progression in patients with initially mild chronic hepatitis C. *Hepatol*. 2010, 51:(1) 356-7.
83. Narayan R, Gangadharan B, Hantz O, Antrobus R, Garcia A, Dwek RA, Zitzmann N: Proteomic analysis of HepaRG cells: a novel cell line that supports hepatitis B virus infection. *J Proteome Res.* 2009, 8:(1) 118-22.
84. Dienstag JL, McHutchison JG: American Gastroenterological Association medical position statement on the management of hepatitis C. *Gastroenterol* 2006, 130:(6) 225-30.
85. Asselah T, Bieche I, Narguet S, Sabbagh A, Laurendeau I, Ripault MP, Boyer N, Martinot-Peignoux M, Valla D, Vidaud M, Marcellin P: Liver gene expression signature to predict response to pegylated interferon plus ribavirin

combination therapy in patients with chronic hepatitis C. *Gut*. 2008, 57:(4) 516-24.

86. Hayashida K, Daiba A, Sakai A, Tanaka T, Kaji K, Inaba N, Ando S, Kajiyama N, Terasaki H, Abe A, Ogasawara M, Kohara M, Harada M, Okanoue T, Ito S, Kaneko S: Pretreatment prediction of interferon-alfa efficacy in chronic hepatitis C patients. *Clin Gastroenterol Hepatol*. 2005, 3:(1) 1253-9.
87. Feld JJ, Nanda S, Huang Y, Chen W, Cam M, Pusek SN, Schweigler LM, Theodore D, Zacks SL, Liang TJ, Fried MW: Hepatic gene expression during treatment with peginterferon and ribavirin: Identifying molecular pathways for treatment response. *Hepatology*. 2007, 46:(5) 1548-63.
88. Suppiah V, Moldovan M, Ahlenstiel G, Berg T, Weltman M, Abate ML, Bassendine M, Spengler U, Dore GJ, Powell E, Riordan S, Sheridan D, Smedile A, Fragomeli V, Muller T, Bahlo M, Stewart GJ, Booth DR, George J: IL28B is associated with response to chronic hepatitis C interferon-alpha and ribavirin therapy. *Nat Genet.* 2009, 41: 1100-4.
89. Tanaka Y, Nishida N, Sugiyama M, Kurosaki M, Matsuura K, Sakamoto N, Nakagawa M, Korenaga M, Hino K, Hige S, Ito Y, Mita E, Tanaka E, Mochida S, Murawaki Y, Honda M, Sakai A, Hiasa Y, Nishiguchi S, Koike A, Sakaida I, Imamura M, Ito K, Yano K, Masaki N, Sugauchi F, Izumi N, Tokunaga K, Mizokami M: Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. Nat Genet. 2009, 41: 1105-9.
90. Thompson AJ, Fellay J, Patel K, Tillmann HL, Naggie S, Ge D, Urban TJ, Shianna KV, Muir AJ, Fried MW, Afdhal NH, Goldstein DB, McHutchison JG: Variants in the ITPA gene protect against ribavirin-induced hemolytic anemia and decrease the need for ribavirin dose reduction. *Gastroenterol*. 2010, 139:(1) 1181-9.
91. Sarasin-Filipowicz M, Oakeley EJ, Duong FH, Christen V, Terracciano L, Filipowicz W, Heim MH: Interferon signaling and treatment outcome in chronic hepatitis C. *Proc Natl Acad Sci*. 2008, 105:(19) 7034-9.
92. Devitt EJ, Power KA, Lawless MW, Browne JA, Gaora PO, Gallagher WM, Crowe J: Early proteomic analysis may allow noninvasive identification of hepatitis C response to treatment with pegylated interferon alpha-2b and ribavirin. *Eur J Gastroent Hepatol*. 2011, 23:(2) 177-83.
93. Sun W, Zhong F, Zhi L, Zhou G, He F: Systematic -omics analysis of HBV-associated liver diseases. *Cancer Lett*. 2009, 286:(4) 89-95.
94. Zhang L, Peng X, Zhang Z, Feng Y, Jia X, Shi Y, Yang H, Zhang X, Liu L, Yin L, Yuan Z: Subcellular proteome analysis unraveled annexin A2 related to immune liver fibrosis. *J Cell Biochem.* 2010, 110:(1) 219-28.
95. Lu Y, Liu J, Lin C, Wang H, Jiang Y, Wang J, Yang P, He F: Peroxiredoxin 2: a potential biomarker for early diagnosis of hepatitis B virus-related liver fibrosis identified by proteomic analysis of the plasma. *BMC Gastroenterol*. 2010, 10:(1) 115.
96. Marrocco C, Rinalducci S, Mohamadkhani A, D'Amici GM, Zolla L: Plasma gelsolin protein: a candidate biomarker for hepatitis B-associated liver cirrhosis identified by a proteomic approach. *Blood Transfus.* 2010, 8: (3) s105-12.
97. Mohamadkhani A, Jazii FR, Sayehmiri K, Jafari-Nejad S, Montaser-Kouhsari L, Poustchi H, Montazeri G: Plasma myeloperoxidase activity and apolipoprotein A-1 expression in chronic hepatitis B patients. *Arch Iran Med*. 2011, 14:(4) 254-8.
98. Poon TC, Hui AY, Chan HL, Ang IL, Chow SM, Wong N, Sung JJ: Prediction of liver fibrosis and cirrhosis in chronic hepatitis B infection by serum proteomic fingerprinting: a pilot study. *Clin Chem.* 2005, 51:(2) 328-35.
99. Myers RP, Tainturier MH, Ratziu V, Piton A, Thibault V, Imbert-Bismut F, Messous D, Charlotte F, Di Martino V, Benhamou Y, Poynard T: Prediction of liver histological lesions with biochemical markers in patients with chronic hepatitis *B. J Hepatol*. 2003, 39:(2) 222-30.
100. Wang J, Jiang D, Zhang H, Lv S, Rao H, Fei R, Wei L: Proteome responses to stable hepatitis B virus transfection and following interferon alpha treatment in human liver cell line HepG2. *Proteomics*. 2009, 9: 1672-82.
101. Seth D, Gorrell MD, Cordoba S, McCaughan GW, Haber PS: Intrahepatic gene expression in human alcoholic hepatitis. *J Hepatol.* 2006, 45:(2) 306-20.
102. Younossi ZM, Baranova A, Ziegler K, Del Giacco L, Schlauch K, Born TL, Elariny H, Gorreta F, VanMeter A, Younoszai A, Ong JP, Goodman Z, Chandhoke V: A genomic and proteomic study of the spectrum of nonalcoholic fatty liver disease. *Hepatology*. 2005, 42:(3) 665-74.
103. Bell LN, Theodorakis JL, Vuppalanchi R, Saxena R, Bemis KG, Wang M, Chalasani N: Serum proteomics and biomarker discovery across the spectrum of nonalcoholic fatty liver disease. *Hepatology*. 2010, 51:(1) 111-20.
104. Ulukaya E, Yilmaz Y, Moshkovskii S, Karpova M, Pyatnitskiy M, Atug O, Dolar E: Proteomic analysis of serum in patients with non-alcoholic steatohepatitis using matrix-assisted laser desorption ionization time-of-flight mass spectrometry. *Scand J Gastroenterol.* 2009, 44:(1) 1471-6.
105. Calvert VS, Collantes R, Elariny H, Afendy A, Baranova A, Mendoza M, Goodman Z, Liotta LA, Petricoin EF, Younossi ZM: A systems biology approach to the pathogenesis of obesity-related nonalcoholic fatty liver disease using reverse phase protein microarrays for multiplexed cell signaling analysis. *Hepatology*. 2007, 46:(1) 166-72.
106. Wilfred de Alwis NM, Day CP: Genes and nonalcoholic fatty liver disease. Curr Diab Rep. 2008, 8: 156-63.
107. Gray J, Chattopadhyay D, Beale GS, Patman GL, Miele L, King BP, Stewart S, Hudson M, Day CP, Manas DM, Reeves HL: A proteomic strategy to identify novel serum biomarkers for liver cirrhosis and hepatocellular cancer in individuals with fatty liver disease. *BMC Cancer*. 2009, 9: 271.
108. Charlton M: Noninvasive indices of fibrosis in NAFLD: starting to think about a three-hit (at least) phenomenon. Am J Gastroenterol. 2007, 102:(2) 409-11.
109. Juran BD, Lazaridis KN: Genetics and genomics of primary biliary cirrhosis. *Clin Liver Dis*. 2008, 12:(2) 349-65. ix
110. Shackel NA, McGuinness PH, Abbott CA, Gorrell MD, McCaughan GW: Identification of novel molecules and pathogenic pathways in primary biliary cirrhosis: cDNA

array analysis of intrahepatic differential gene expression. *Gut*. 2001, 49:(4) 565-76.

111. 112 .Li YZ, Hu CJ, Leng XM, Zhao GF, Li N, Xu Y: Promising diagnostic biomarkers for primary biliary cirrhosis identified with magnetic beads and MALDI-TOF-MS. *Anat Rec (Hoboken)*. 2009, 292:(2) 455-60.
112. Tahiri F, Le Naour F, Huguet S, Lai-Kuen R, Samuel D, Johanet C, Saubamea B, Tricottet V, Duclos-Vallee JC, Ballot E: Identification of plasma membrane autoantigens in autoimmune hepatitis type 1 using a proteomics tool. Hepatology. 2008, 47:(3) 937-48.
113. Song H, Sokolov M: Analysis of protein expression and compartmentalization in retinal neurons using serial tangential sectioning of the retina. *J Proteome Res.* 2009, 8:(1) 346-51.
114. 115.Bowlus CL, Seeley EH, Roder J, Grigorieva J, Roder H, Caprioli RM, Gershwin M: In situ mass spectrometry of autoimmune liver diseases. *Cell Mol Immunol*. 2011, 8: 237-42.
115. Villanueva A, Newell P, Chiang DY, Friedman SL, Llovet JM: Genomics and signaling pathways in hepatocellular carcinoma. *Semin Liver Dis*. 2007, 27:(1) 55-76.
116. Makridakis M, Vlahou A: Secretome proteomics for discovery of cancer biomarkers. *J Proteomics*. 2010, 73:(12) 2291-305.
117. Peng ZG, Fan B, Du NN, Wang YP, Gao LM, Li YH, Liu F, You XF, Han YX, Zhao ZY, Cen S, Li JR, Song DQ, Jiang JD: Small molecular compounds that inhibit hepatitis C virus replication through destabilizing heat shock cognate 70 messenger RNA. *Hepatology.* 2010, 52: 845-53.

How to cite: Mahmood S et al. Liver fibrosis and cirrhosis mutations can be treated with stem cells therapy followed by circulating innate immune cells trnasfusion *IP Journal of Urology, Nephrology & Hepatology Science*.2021;4(4):. 95-100