

RECOMMENDATIONS

The results of the present study may have several future clinical implications:

- Further studies are needed to study the role of the oncogenic miR 17~92 cluster in the progression of chronic HCV infection to HCC.
- Clinical trials are required to assess the value of plasma levels of *MIR17HG* protein as a potential biomarker for HCV-related liver disease and as a non-invasive predictor of the severity of liver fibrosis.
- The effect of anti-viral therapy in modulating the miR 17~92 cluster in relation to the improvement in HCV-induced liver pathology needs to be evaluated.
- Future studies are required to assess the effects of the miR 17~92 cluster inhibitors on hepatic inflammation, steatosis and fibrosis in patients with chronic HCV infection.
- The use of PTEN mimics could be a promising therapeutic target for limiting inflammation, fibrosis and steatosis in HCV-related liver disease.

REFERENCES

1. Chen SL, Morgan TR. The Natural history of hepatitis C virus (HCV) infection. *Int J Med Sci* 2006; 3: 47-52.
2. Lavanchy D. The global burden of hepatitis C. *Liver Int* 2009; 29: 74-81.
3. Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. *Lancet Infect Dis* 2005; 5: 558-67.
4. El-Zanaty F, Way A. Egypt Demographic and Health Survey 2008. Egyptian Ministry of Health 2009: 431.
5. Hiroishi K, Ito T, Imawari M. Immune responses in hepatitis C virus infection and mechanisms of hepatitis C virus persistence. *J Gastroenterol Hepatol* 2008; 23: 1473-82.
6. Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology* 2009; 49: 1335-74.
7. Moore C, Levitsky J. [The current state and future prospects of chronic hepatitis C virus infection treatment](#). *Curr Infect Dis Rep* 2014; 16: 413.
8. Zeuzem S, Andreone P, Pol S, Lawitz E, Diago M, Roberts S, et al. Telaprevir for retreatment of HCV infection. *N Engl J Med* 2011; 364: 2417-28.
9. Poordad F, McCone JJr, Bacon BR, Bruno S, Manns MP, Sulkowski MS, et al. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med* 2011; 364: 1195-206.
10. Temesgen Z, Talwani R, Rizza SA. [Sofosbuvir for the treatment of chronic hepatitis C virus infection](#). *Drugs Today (Barc)* 2014; 50: 421-34.
11. Manns M, Marcellin P, Poordad F, de Araujo ES, Buti M, Horsmans Y, et al. [Simeprevir with pegylated interferon alfa 2a or 2b plus ribavirin in treatment-naïve patients with chronic hepatitis C virus genotype 1 infection \(QUEST-2\): a randomised, double-blind, placebo-controlled phase 3 trial](#). *Lancet* 2014; 14: 60538-9.
12. Suzuki T, Murakami K, Shoji I, Wakita T, Aizaki H. Molecular biology of hepatitis C virus. *J Gastroenterol* 2007; 42: 411-23.
13. Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a bloodborne non-A, non-B viral hepatitis genome. *Science* 1989; 244: 359-62.
14. Ashfaq UA, Javed T, Rehman S, Nawaz Z, Riazuddin S. An overview of HCV molecular biology, replication and immune responses. *Virol J* 2011; 8: 161.

References

15. Friebe P, Lohmann V, Krieger N, Bartenschlager R. Sequences in the 5' nontranslated region of hepatitis C virus required for RNA replication. *J Virol* 2001; 75: 12047-57.
16. Song Y, Friebe P, Tzima E, Junemann C, Bartenschlager R, Niepmann M. The hepatitis C virus RNA 3'-untranslated region strongly enhances translation directed by the internal ribosome entry site. *J Virol* 2006; 80: 11579-88.
17. Tang H, Grisé H. Cellular and molecular biology of HCV infection and hepatitis. *Clin Sci* 2009; 117: 49-65.
18. Bukh J, Purcell RH, Miller RH. Sequence analysis of the core gene of 14 hepatitis C virus genotypes. *Proc Natl Acad Sci USA* 1994; 91: 8239-43.
19. Santolini E, Migliaccio G, La Monica N. Biosynthesis and biochemical properties of the hepatitis C virus core protein. *J Virol* 1994; 68: 3631-41.
20. Suzuki R, Sakamoto S, Tsutsumi T, Rikimaru A, Tanaka K, Shimoike T, et al. Molecular determinants for subcellular localization of hepatitis C virus core protein. *J Virol* 2005; 79: 1271-81.
21. Tellinghuisen TL, Rice CM. Interaction between hepatitis C virus proteins and host cell factors. *Curr Opin Microbiol* 2002; 5: 419-27.
22. Hope RG, Murphy DJ, Mc Lauchlan J. The domains required to direct core proteins of hepatitis C virus and GB virus-B to lipid droplets share common features with plant oleosin proteins. *J Biol Chem* 2002; 277: 4261-70.
23. Fishman SL, Factor SH, Balestrieri C, Fan X, Dibisceglie AM, Desai SM, et al. Mutations in the hepatitis C virus core gene are associated with advanced liver disease and hepatocellular carcinoma. *Clin Cancer Res* 2009; 15: 3205-13.
24. Kittlesen DJ, Chianese-Bullock KA, Yao ZQ, Braciale TJ, Hahn YS. Interaction between complement receptor gC1qR and hepatitis C virus core protein inhibits T-lymphocyte proliferation. *J Clin Invest* 2000; 106: 1239-49.
25. Goffard A, Callens N, Bartosch B, Wychowski C, Cosset FL, Montpellier C, et al. Role of N-linked glycans in the functions of hepatitis C virus envelope glycoproteins. *J Virol* 2005; 79: 8400-9.
26. Drummer HE, Maerz A, Pountourios P. Cell surface expression of functional hepatitis C virus E1 and E2 glycoproteins. *FEBS Lett* 2003; 546: 385-90.
27. Owsianka AM, Timms JM, Tarr AW, Brown RJ, Hickling TP, Szwejk A, et al. Identification of conserved residues in the E2 envelope glycoprotein of the hepatitis C virus that are critical for cd81 binding. *J Virol* 2006; 80: 8695-704.
28. Bartosch B, Verney G, Dreux M, Donot P, Morice Y, Penin F, et al. An interplay between hypervariable region 1 of the hepatitis C virus E2 glycoprotein, the scavenger receptor bi, and high-density lipoprotein promotes both enhancement of infection and protection against neutralizing antibodies. *J Virol* 2005; 79: 8217-29.

References

29. Haqshenas G, Mackenzie JM, Dong X, Gowans EJ. Hepatitis C virus p7 protein is localized in the endoplasmic reticulum when it is encoded by a replication-complement genome. *J Gene Virol* 2007; 88: 134-42.
30. Luik P, Chew C, Aittoniemi J, Chang J, Wentworth PJr, Dwek RA, et al. The 3-dimensional structure of a hepatitis C virus p7 ion channel by electron microscopy. *Proc Nat Acad Sci USA* 2009; 106: 12712-6.
31. Sakai A, Claire MS, Faulk K, Govindarajan S, Emerson SU, Purcell RH, et al. The p7 polypeptide of hepatitis C virus is critical for infectivity and contains functionally important genotype-specific sequences. *Proc Nat Acad Sci USA* 2003; 100: 11646-51.
32. Jones CT, Murray CL, Eastman DK, Tassello J, Rice CM. Hepatitis C virus p7 and NS2 proteins are essential for production of infectious virus. *J Virol* 2007; 81: 8374-83.
33. Yamaga AK, Oh JH. Membrane topology of the hepatitis C virus NS2 protein. *J Biol Chem* 2002; 277: 33228-34.
34. Welbourn S, Pause A. The hepatitis C virus NS2/3 protease. *Curr Issu Mol Biol* 2007; 9: 63-9.
35. Gallinari P, Brennan D, Nardi C, Brunetti M, Tomei L, Steinkuhler C, et al. **Multiple enzymatic activities associated with recombinant NS3 protein of hepatitis C virus.** *J Virol* 1998; 72: 6758-69.
36. Bartenschlager R, Ahlborn-Laake L, Mous J, Jacobsen H. Nonstructural protein 3 of the hepatitis C virus encodes a serine-type proteinase required for cleavage at the NS3/4 and NS4/5 junctions. *J Virol* 1993; 67: 3835-44.
37. Gale MJr, Foy EM. Evasion of intracellular host defense by hepatitis C virus. *Nature* 2005; 436: 939-45.
38. Serebrov V, Pyle AM. Periodic cycles of RNA unwinding and pausing by hepatitis C virus NS3 helicase. *Nature* 2004; 430: 476-80.
39. Kim JL, Morgenstern KA, Lin C, Fox T, Dwyer MD, Landro JA, et al. Crystal structure of the hepatitis C virus NS3 protease domain complexed with a synthetic NS4A cofactor peptide. *Cell* 1996; 87: 343-55.
40. Wolk B, Sansonno D, Krausslich HG, Dammacco F, Rice CM, Blum HE, et al. Subcellular localization, stability and trans-cleavage competence of the hepatitis C virus NS3-NS4A complex expressed in tetracycline-regulated cell lines. *J Virol* 2000; 74: 2293-304.
41. Lin C, Wu Jw, Hsiao K, Su MS. The hepatitis C virus NS4A protein: interactions with the NS4B and NS5A proteins. *J Virol* 1997; 71: 6465-71.
42. Sillanpaa M, Melen K, Porkka P, Fagerlund R, Nevalainen K, Lappalainen M, et al. Hepatitis C virus core, NS3, NS4B and NS5A are the major immunogenic proteins in humoral immunity in chronic HCV infection. *Virol J* 2009; 6: 84.

References

43. Lundin M, Lindstrom H, Gronwall C, Persson MA. Dual topology of the processed hepatitis C virus protein NS4B is influenced by the NS5A protein. *J Gen Virol* 2006; 87: 3263-72.
44. Hugle T, Fehrmann F, Bieck E, Kohara M, Krausslich HG, Rice CM, et al. The hepatitis C virus nonstructural protein 4B is an integral endoplasmic reticulum membrane protein. *Virology* 2001; 284: 70-81.
45. Huang L, Hwang J, Sharma SD, Hargittai MR, Chen Y, Arnold JJ, et al. Hepatitis C virus nonstructural protein 5a (NS5A) is an RNA-binding protein. *J Bio Chem* 2005; 280: 36417-28.
46. Gale MJ Jr, Korth MJ, Tang NM, Tan SL, Hopkins DA, Dever TE, et al. Evidence that hepatitis C virus resistance to interferon is mediated through repression of the PKR protein kinase by the nonstructural 5A protein. *Virology* 1997; 230: 217-27.
47. Appel N, Zayas M, Miller S, Krijnse-locker J, Schaller T, Friebe P, et al. Essential role of domain III of nonstructural protein 5A for hepatitis C virus infectious particle assembly. *Plos Pathog* 2008; 4: e1000035.
48. Behrens SE, Tomei L, De Francesco R. **Identification and properties of the RNA-dependent RNA polymerase of hepatitis C virus.** *Embo J* 1996; 15: 12-22.
49. Lesburg CA, Cable MB, Ferrari E, Hong Z, Mannarino AF, Weber PC. Crystal structure of the RNA-dependent RNA polymerase from hepatitis C virus reveals a fully-encircled active site. *Nat Struct Biol* 1999; 6: 937-43.
50. De Francesco R, Migliaccio G. Challenges and successes in developing new therapies for hepatitis C. *Nature* 2005; 436: 953-60.
51. Helle F, Dubuisson J. Hepatitis C virus entry into host cells. *Cell Mol life Sci* 2008; 65: 100-12.
52. Barth H, Schafer C, Adah MI, Zhang F, Linhardt RJ, Toyoda H, et al. Cellular binding of hepatitis C virus envelope glycoprotein E2 requires cell surface heparan sulphate. *J Biol Chem* 2003; 278: 41003-12.
53. Wunschmann S, Medh JD, Klinzmann D, Schmidt WN, Stapleton JT. Characterization of hepatitis C virus (HCV) and HCV E2 interactions with CD81 and the low-density lipoprotein receptor. *J Virol* 2000; 74: 10055-62.
54. Molina S, Castet V, Fournier-Wirth C, Pichard-Garcia L, Avner R, Harats D, et al. The low-density lipoprotein receptor plays a role in the infection of primary human hepatocytes by hepatitis C virus. *J Hepatol* 2007; 46: 411-9.
55. Suzuki T, Ishii K, Aizaki H, Wakita T. Hepatitis C viral life cycle. *Adv Drug Deliv Rev* 2007; 59: 1200-12.
56. El-Hage N, Luo G. Replication of hepatitis C virus RNA occurs in a membrane-bound replication complex containing nonstructural viral proteins and RNA. *J Gen Virol* 2003; 84: 2761-9.

References

57. Penin F, Brass V, Appel N, Ramboarina S, Montserret R, Ficheux D, et al. Structure and function of the membrane anchor domain of hepatitis C virus nonstructural protein 5A. *J Biol Chem* 2004; 279: 40835-43.
58. Pawlotsky JM, Chevalier S, Mc Hutchison JG. The hepatitis C virus life cycle as a target for new antiviral therapies. *Gastroenterol* 2007; 132: 1979-98.
59. Irshad M, Ansari MA, Singh A, Nag P, Raghvendra L, Singh S, et al. HCV-genotypes: a review on their origin, global status, assay system, pathogenecity and response to treatment. *Hepatogastroenterology* 2010; 57: 1529-38.
60. El Sharkawi FZ, Chudy M, Hanschmann KM, Kress J, Nübling CM. Consistency of quantitation of HCV genotype 4 from Egypt across three HCV-RNA amplification assays. *J Med Virol* 2008; 80: 2086-91.
61. Simmonds P. Genetic diversity and evolution of hepatitis C virus-15 years on. *J Gen Virol* 2004; 85: 3173-88.
62. Chayama K, Hayes CN. Hepatitis C virus: How genetic variability affects pathobiology of disease. *J Gastroenterol Hepatol* 2011; 26 (Suppl 1): 83-95.
63. Martell M, Esteban JI, Quer J, Genesca J, Weiner A, Esteban R, et al. Hepatitis C virus (HCV) circulates as a population of different but closely related genomes: quasispecies nature of HCV genome distribution. *J Virol* 1992; 66: 3225-9.
64. Pawlotsky JM. Hepatitis C virus population dynamics during infection. *Curr Top Microbiol Immunol* 2006; 299: 261-84.
65. Cristina J, del Pilar Moreno M, Moratorio G. Hepatitis C virus genetic variability in patients undergoing antiviral therapy. *Virus Res* 2007; 127: 185-94.
66. Hoofnagle JH. Course and outcome of hepatitis C. *Hepatology* 2002; 36 (5 Suppl. 1): S21-S9.
67. Orland JR, Wright TL, Cooper S. Acute hepatitis C. *Hepatology* 2001; 33: 321-7.
68. Chung RT. Acute hepatitis C virus infection. *CID* 2005; 41 (Suppl 1): S14-7.
69. Santantonio T, Sinisi E, Guastadisegni A, Casalino C, Mazzola M, Gentile A, et al. Natural course of acute hepatitis C: a long term prospective study. *Dig Liver Dis* 2003; 35: 104-13.
70. Pham TN, MacParland SA, Mulrooney PM, Cooksley H, Naoumov NV. Hepatitis C virus persistence after spontaneous or treatment-induced resolution of hepatitis C. *J Virol* 2004; 78: 5867-74.
71. Muir AJ. The natural history of hepatitis C viral infection. *Semin Gastrointest Dis* 2000; 11: 54-61.
72. Shiffman ML, Diago M, Tran A, Pockros P, Reindollar R, Prati D, et al. Chronic hepatitis C in patients with persistently normal alanine transaminase levels. *Clin Gastroenterol Hepatol* 2006; 4: 645-52.

References

73. Persico M, Perrotta S, Persico E, Terracciano L, Folgori A, Ruggeri L, et al. Hepatitis C virus carriers with persistently normal ALT levels: biological peculiarities and update of the natural history of liver disease at 10 years. J Viral Hepat 2006; 13: 290-6.
74. Kleiner DE. The liver biopsy in chronic hepatitis C: a view from the other side of the microscope. *Semin Liver Dis* 2005; 25: 52-64.
75. Desmet VJ, Gerber M, Hoofnagle JH, Manns M, Scheuer PJ. Classification of chronic hepatitis: diagnosis, grading and staging. *Hepatology* 1994; 19: 1513-20.
76. The METAVIR Cooperative Group. Inter- and intra-observer variation in the assessment of liver biopsy of chronic hepatitis C. *Hepatology* 1994; 20: 15-20.
77. Ishak K, Baptista A, Bianchi L, Callea F, De Groote J, Gudat F, et al. Histological grading and staging of chronic hepatitis. *J Hepatol* 1995; 22: 696-9.
78. Petta S, Cammà C, Di Marco V, Macaluso FS, Maida M, Pizzolanti G, et al. Hepatic steatosis and insulin resistance are associated with severe fibrosis in patients with chronic hepatitis caused by HBV or HCV infection. Liver Int 2011; 31: 507-15.
79. Galossi A, Guarisco R, Bellis L, Puoti C. Extrahepatic manifestations of chronic HCV infection. *J Gastrointest Liver Dis* 2007; 16: 65-73.
80. Lauletta G, Russi S, Contedua V, Sansonno L. Hepatitis C virus infection and mixed cryoglobulinemia. *Clin Dev Immunol* 2012; 2012: 502156.
81. Mao XR, Zhang LT, Chen H, Xiao P, Zhang YC. Possible factors affecting thyroid dysfunction in hepatitis C virus-infected untreated patients. *Exp Ther Med* 2014; 8: 133-40.
82. Chehadeh W, Kurien SS, Abdella N, Ben-Nakhi A, Al-Arouj M, Almuaili T, et al. Hepatitis C virus infection in a population with high incidence of type 2 diabetes: Impact on diabetes complications. *J Infect Public Health* 2011; 4: 200-6.
83. Arase Y, Suzuki F, Suzuki Y, Akuta N, Kobayashi M, Kawamura Y, et al. Hepatitis C virus enhances incidence of idiopathic pulmonary fibrosis. *World J Gastroenterol* 2008; 14: 5880-6.
84. Khosla S, Hassoun AA, Baker BK, Liu F, Zein NN, Whyte MP, et al. Insulin-like growth factor system abnormalities in hepatitis C-associated osteosclerosis. Potential insights into increasing bone mass in adults. *J Clin Invest* 1998; 101: 2165-73.
85. Mutsumori A, Ohashi N, Hasegawa K, Sasayama S, Eto T. Hepatitis C virus infection and heart diseases: a multicentric study in Japan. *Jpn Circ J* 1998; 62: 389-91.
86. Deuffic-Burban S, Poynard T, Valleron AJ. Quantification of fibrosis progression in patients with chronic hepatitis C using a Markov model. *J Viral Hepat* 2002; 9: 114-22.

References

87. Tuma P, Medrano J, Resino S, Vispo E, Madejón A, Sánchez-Piedra C, et al. Incidence of liver cirrhosis in HIV-infected patients with chronic hepatitis B or C in the era of highly active antiretroviral therapy. *Antivir Ther* 2010; 15: 881-6.
88. Bukhtiari N, Hussain T, Iqbal M, [Malik AM](#), [Qureshi AH](#), [Hussain A](#). Hepatitis B and C single and co-infection in chronic liver disease and their effect on the disease pattern. *J Pak Med Assoc* 2003; 53: 136-40.
89. Westin J, Lagging LM, Spak F, *Quaglio GL, Lugoboni F, Pajusco B*, et al. Moderate alcohol intake increases fibrosis progression in untreated patients with hepatitis C virus infection. *J Viral Hepat* 2002; 9: 235-41.
90. Isom HC, McDevitt EI, Moon MS. Elevated hepatic iron: a confounding factor in chronic hepatitis C. *Biochim Biophys Acta* 2009; 1790: 650-62.
91. Kallwitz ER, Layden-Almer J, Dhamija M, Berkes J, Guzman G, Lepe R, et al. Ethnicity and body mass index are associated with hepatitis C presentation and progression. *Clin Gastroenterol Hepatol* 2010; 8: 72-8.
92. Fabris C, Falletti E, Cussigh A, Bitetto D, Fontanini E, Bignulin S, et al. IL-28B rs12979860 C/T allele distribution in patients with liver cirrhosis: Role in the course of chronic viral hepatitis and the development of HCC. *J Hepatol* 2011; 54: 716-22.
93. Romero-Gomez M, Eslam M, Ruiz A, Maraver M. Genes and hepatitis C: susceptibility, fibrosis progression and response to treatment. *Scand J Immunol* 2011; 74: 282-7.
94. Ksiaa Cheikhrouhou L, Sfar I, Aounallah-Skhiri H, Aouadi H, Jendoubi-Ayed S, Ben Abdallah T, et al. Cytokine and apoptosis gene polymorphisms influence the outcome of hepatitis C virus infection. *Hepatobiliary Pancreat Dis Int* 2011; 10: 280-8.
95. Post JJ, Ratnarajah S, Lloyd AR. Immunological determinants of the outcomes from primary hepatitis C infection. *Cell Mol Life Sci* 2009; 66: 733-56.
96. Freeman AJ, Dore GJ, Law MG, Thorpe M, Von Overbeck J, Lloyd AR et al. Estimating progression to cirrhosis in chronic hepatitis C virus infection. *Hepatology* 2001; 34 (Part 1): 809-16.
97. Alazawi W, Cunningham M, Dearden J, Foster GR. Systematic review: outcome of compensated cirrhosis due to chronic hepatitis C infection. *Aliment Pharmacol Ther* 2010; 32: 344-55.
98. Fattovich G, Giustina G, Degos F, Tremolada F, Diodati G, Almasio P, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. *Gastroenterology* 1997; 112: 463-72.
99. Thompson CJ, Rogers G, Hewson P, Wright D, Anderson R, Cramp M, et al. Surveillance of cirrhosis for hepatocellular carcinoma: systematic review and economic analysis. *Health Technol Assess* 2007; 11: 1-206.

References

100. Donato F, Boffetta P, Puoti M. A meta-analysis of epidemiological studies on the combined effect of hepatitis B and C virus infections in causing hepatocellular carcinoma. *Int J Cancer* 1998; 75: 347-54.
101. Hiroishi K, Ito T, Imawari M. Immune responses in hepatitis C virus infection and mechanisms of hepatitis C virus persistence. *J Gastroenterol Hepatol* 2008; 23: 1473-82.
102. Kanto T, Hayashi N. Immunopathogenesis of hepatitis C virus infection: multifaceted strategies subverting innate and adaptive immunity. *Intern Med* 2006; 45: 183-91.
103. Ishii S, Koziel MJ. Immune responses during acute and chronic infection with hepatitis C virus. *Clin Immunol* 2008; 128: 133-47.
104. Binder M, Kochs G, Bartenschlager R, Lohmann V. Hepatitis C virus escape from the interferon regulatory factor 3 pathway by a passive and active evasion strategy. *Hepatology* 2007; 46: 1365-74.
105. Li K, Foy E, Ferreon JC, Nakamura M, Ferreon AC, Ikeda M, et al. Immune evasion by hepatitis C virus NS3/4A protease-mediated cleavage of the Toll-like receptor 3 adaptor protein TRIF. *Proc Natl Acad Sci USA* 2005; 102: 2992-7.
106. Crotta S, Stilla A, Wach A, D'Andrea A, Nuti S, D'Oro U, et al. Inhibition of natural killer cells through engagement of CD81 by the major hepatitis C virus envelope protein. *J Exp Med* 2002; 195: 35-41.
107. Herzer K, Falk CS, Enche J, Eichhorst ST, Ulsenheimer A, Seliger B, et al. Upregulation of major histocompatibility complex class I on liver cells by hepatitis C virus core protein via p53 and TAP1 impairs natural killer cell cytotoxicity. *J Virol* 2003; 77: 8299-309.
108. Sarobe P, Lasarte JJ, Zabaleta A, Arribillaga L, Arina A, Melero I, et al. Hepatitis C virus structural proteins impair dendritic cell maturation and inhibit in vivo induction of cellular immune responses. *J Virol* 2003; 77: 10862-71.
109. Szabo G, Dolganiuc A. Subversion of plasmacytoid and myeloid dendritic cell functions in chronic HCV infection. *Immunobiology* 2005; 210: 237-47.
110. Jinushi M, Takehara T, Tatsumi T, Kanto T, Miyagi T, Suzuki T, et al. Negative regulation of NK cell activities by inhibitory receptor CD94/NKG2A leads to altered NK cell-induced modulation of dendritic cell functions in chronic hepatitis C virus infection. *J Immunol* 2004; 173: 6072-81.
111. Jinushi M, Takehara T, Kanto T. Critical role of MHC class I-related chain A and B expression on INF-alpha-stimulated dendritic cells in NK cell activation: impairment in chronic hepatitis C virus infection. *J Immunol* 2003; 170: 1249-56.
112. Fiore G, Angarano I, Caccetta L, Serrone M, Jirillo E, Schiraldi O, et al. In-situ immunophenotyping study of hepatic-infiltrating cytotoxic cells in chronic active hepatitis C. *Eur J Gastroenterol Hepatol* 1997; 9: 491-6.

References

113. Ulsenheimer A, Gerlach JT, Gruener NH. Detection of functionally altered hepatitis C virus-specific CD4⁺ T cells in acute and chronic hepatitis C. *Hepatology* 2003; 37: 1189-98.
114. Wedemeyer H, He XS, Nascimbeni M. Impaired effector function of hepatitis C virus-specific CD8⁺ T cells in chronic hepatitis C virus infection. *J Immunol* 2002; 169: 3447-58.
115. Meyer-Olson D, Shoukry NH, Brady KW, Kim H, Olson DP, Hartman K, et al. Limited T cell receptor diversity of HCV-specific T cell responses is associated with CTL escape. *J Exp Med* 2004; 200: 307-19.
116. Seifert U, Liermann H, Racanelli V, Halenius A, Wiese M, Wedemeyer H, et al. Hepatitis C virus mutation effects proteasomal epitope processing. *J Clin Invest* 2004; 114: 250-9.
117. Spangenberg HC, Viazov S, Kersting N, Neumann-Haefelin C, McKinney D, Roggendorf M, et al. Intrahepatic CD8⁺ T-failure during chronic hepatitis C virus infection. *Hepatology* 2005; 42: 828-37.
118. Kanto T, Inoue M, Miyatake H, Sato A, Sakakibara M, Yakushijin T, et al. Reduced numbers and impaired ability of myeloid and plasmacytoid dendritic cells to polarize T helper cells in chronic hepatitis C virus infection. *J Infect Dis* 2004; 190: 1919-26.
119. Wang JH, Layden TJ, Eckels DD. Modulation of the peripheral T-cell response by CD4 mutants of hepatitis C virus: transition from a Th1 to a Th2 response. *Hum Immunol* 2003; 64: 662-73.
120. MacDonald AJ, Duffy M, Brady MT, McKiernan S, Hall W, Hegarty J, et al. CD4 T helper type 1 and regulatory T cells induced against the same epitopes on the core protein in hepatitis C virus-infected persons. *J Infect Dis* 2002; 185: 720-7.
121. Bartel DP. MicroRNAs: target recognition and regulatory functions. *Cell* 2009; 136: 215-33.
122. Bentwich I, Avniel A, Karov Y, Aharonov R, Gilad S, Barad O, et al. Identification of hundreds of conserved and nonconserved human microRNAs. *Nat Genet* 2005; 37: 766-70.
123. Berkhout B, Jeang KT. RISCy business: MicroRNAs, pathogenesis, and viruses. *J Biol Chem* 2007; 282: 26641-5.
124. Berezikov E, Cuppen E, Plasterk RH. Approaches to microRNA discovery. *Nat Genet* 2006; 38 (Suppl): S2-7.
125. Lee RC, Feinbaum RL, Ambros V. The *C. elegans* heterochronic gene *lin-4* encodes small RNAs with antisense complementarity to *lin-14*. *Cell* 1993; 75: 843-54.
126. Ambros V, Horvitz HR. Heterochronic mutants of the nematode *Caenorhabditis elegans*. *Science* 1984; 226: 409-16.

References

127. Wightman B, Ha I, Ruvkun G. Posttranscriptional regulation of the heterochronic gene *lin-14* by *lin-4* mediates temporal pattern formation in *C. elegans*. *Cell* 1993; 75: 855-62.
128. Lee RC, Ambros V. An extensive class of small RNAs in *Caenorhabditis elegans*. *Science* 2001; 294: 862-4.
129. Reinhart BJ, Slack FJ, Basson M, Pasquinelli AE, Bettinger JC, Rougvie AE, et al. The 21-nucleotide *let-7* RNA regulates developmental timing in *Caenorhabditis elegans*. *Nature* 2000; 403: 901-6.
130. Vella MC, Choi EY, Lin SY, Reinert K, Slack FJ. The *C. elegans* microRNA *let-7* binds to imperfect *let-7* complementary sites from the *lin-41* 3'utr. *Genes Dev* 2004; 18: 132-7.
131. Lawrie CH, Gal S, Dunlop HM, Pushkaran B, Liggins AP, Pulford K, et al. Detection of elevated levels of tumour-associated microRNAs in serum of patients with diffuse large b-cell lymphoma. *Br J Haematol* 2008; 141: 672-5.
132. Weber JA, Baxter DH, Zhang S, Huang DY, Huang KH, Lee MJ, et al. The microRNA spectrum in 12 body fluids. *Clin Chem* 2010; 56: 1733-41.
133. Cortez MA, Bueso-Ramos C, Ferdin J, Lopez-Berestein G, Sood AK, Calin GA. MicroRNAs in body fluids—the mix of hormones and biomarkers. *Nat Rev Clin Oncol* 2011; 8: 467-77.
134. Chen X, Ba Y, Ma L, Cai X, Yin Y, Wang K, et al. Characterization of microRNAs in serum: a novel class of biomarkers for diagnosis of cancer and other diseases. *Cell Res* 2008; 18: 997-1006.
135. Heneghan HM, Miller N, Kerin MJ. MiRNAs as biomarkers and therapeutic targets in cancer. *Curr Opin Pharmacol* 2010; 10: 543-50.
136. Kong YW, Ferland-McCollough D, Jackson TJ, Bushell M. microRNAs in cancer management. *Lancet Oncol* 2012; 13: e249-58.
137. De Guire V, Caron M, Scott N, Menard C, Gaumont-Leclerc MF, Chartrand P, et al. Designing small multiple-target artificial RNAs. *Nucleic Acids Res* 2010; 38: e140.
138. Rodriguez A, Griffiths-Jones S, Ashurst JL, Bradley A. Identification of mammalian microRNA host genes and transcription units. *Genome Res* 2004; 14: 1902-10.
139. Lee Y, Kim M, Han J, Yeom KH, Lee S, Baek SH, et al. MicroRNA genes are transcribed by RNA polymerase II. *EMBO J* 2004; 23: 4051-60.
140. Borchert GM, Lanier W, Davidson BL. RNA polymerase III transcribes human microRNAs. *Nat Struct Mol Biol* 2006; 13: 1097-101.
141. Denli AM, Tops BB, Plasterk RH, Ketting RF, Hannon GJ. Processing of primary microRNAs by the Microprocessor complex. *Nature* 2004; 432: 231-5.

References

142. Lund E, Guttinger S, Calado A, Dahlberg JE, Kutay U. Nuclear export of microRNA precursors. *Science* 2004; 303: 95-8.
143. Yi R, Qin Y, Macara IG, Cullen BR. Exportin-5 mediates the nuclear export of pre-microRNAs and short hairpin RNAs. *Genes Dev* 2003; 17: 3011-6.
144. Ketting RF, Haverkamp TH, Van Luenen HG, Bernstein E, Sijen T, Hannon GJ, et al. Dicer functions in RNA interference and in synthesis of small RNA involved in developmental timing in *C. elegans*. *Genes Dev* 2001; 15: 2654-9.
145. Gregory RI, Chendrimada TP, Cooch N, Shiekhattar R. Human RISC couples microRNA biogenesis and posttranscriptional gene silencing. *Cell* 2005; 123: 631-40.
146. Davis-Dusenbery BN, Hata A. Mechanisms of control of microRNA biogenesis. *J Biochem* 2010; 148: 381-92.
147. Anindo MIK, Yaqinuddin A. Insights into the potential use of microRNAs as biomarker in cancer. *Int J Surgery* 2012; 10: 443-9.
148. Kozomara A, Griffiths-Jones S. MiRBase: integrating microRNA annotation and deep sequencing data. *Nucleic Acids Res* 2011; 39: D152-7.
149. Bartel DP. MicroRNAs. *Genomics, biogenesis, mechanism, and function. Cell* 2004; 116: 281-97.
150. Altuvia Y, Landgraf P, Lithwick G, Elefant N, Pfeffer S, Aravin A, et al. Clustering and conservation patterns of human microRNAs. *Nucleic Acids Res* 2005; 33: 2697-706.
151. Zhang Y, Zhang R, Su B. Diversity and evolution of MicroRNA gene clusters. *Sci China C Life Sci* 2009; 52: 261-6.
152. He L, Hannon GJ. MicroRNAs: small RNAs with a big role in gene regulation. *Nat Rev Genet* 2004; 5: 522-31.
153. Lytle JR, Yario TA, Steitz JA. Target mRNAs are repressed as efficiently by microRNA-binding sites in the 5'UTR as in the 3'UTR. *Proc Natl Acad Sci U S A* 2007; 104: 9667-72.
154. Grimson A, Farh KK, Johnston WK, Garrett-Engle P, Lim LP, Bartel DP. MicroRNA targeting specificity in mammals: determinants beyond seed pairing. *Mol Cell* 2007; 27: 91-105.
155. Vasudevan S, Tong Y, Steitz JA. Switching from repression to activation: microRNAs can up-regulate translation. *Science* 2007; 318: 1931-4.
156. Guo H, Ingolia NT, Weissman JS, Bartel DP. Mammalian microRNAs predominantly act to decrease target mRNA levels. *Nature* 2010; 466: 835-40.
157. Friedman RC, Farh KK, Burge CB, Bartel DP. Most mammalian mRNAs are conserved targets of microRNAs. *Genome Res* 2009; 19: 92-105.

References

158. Lai EC. MicroRNAs are complementary to 3'UTR sequence motifs that mediate negative post-transcriptional regulation. *Nat Genet* 2002; 30: 363-4.
159. Lewis BP, Shih IH, Jones-Rhoades MW, Bartel DP, Burge CB. Prediction of mammalian microRNA targets. *Cell* 2003; 115: 787-98.
160. Brennecke J, Stark A, Russell RB, Cohen SM. Principles of microRNA-target recognition. *PLoS Biol* 2005; 3: e85.
161. Doench JG, Sharp PA. Specificity of microRNA target selection in translational repression. *Genes Dev* 2004; 18: 504-11.
162. Lai EC. Predicting and validating microRNA targets. *Genome Biol* 2004; 5: 115.
163. Bushati N, Cohen SM. MicroRNA functions. *Annu Rev Cell Dev Biol* 2007; 23: 175-205.
164. Soifer HS, Rossi JJ, Sætrom P. MicroRNAs in disease and potential therapeutic applications. *Mol Ther* 2007; 15: 2070-9.
165. Wyman EL, Mitchell PS, Allen DW, Lin N, Gentleman RL, Nelson DB, et al. Circulating microRNAs as stable blood-based markers for cancer detection. *Proc Natl Acad Sci U S A* 2008; 105: 10513-8.
166. Bratkovič T, Glavan G, Štrukelj B, Živin M, Rogelj B. Exploiting microRNAs for cell engineering and therapy. *Biotechnology Advances* 2012; 30: 753-65.
167. Lovat F, Valeri N, Croce CM. MicroRNAs in the pathogenesis of cancer. *Semin Oncol* 2011; 38: 724-33.
168. Calin GA, Ferracin M, Cimmino A, Di Leva G, Shimizu M, Wojcik SE, et al. MicroRNA signature associated with prognosis and progression in chronic lymphocytic leukemia. *N Engl J Med* 2005; 353: 1793-801.
169. Cheng CJ, Slack FJ. [The duality of oncomiR addiction in the maintenance and treatment of cancer.](#) *Cancer J* 2012; 18: 232-7.
170. Mencía A, Modamio-Høybjør S, Redshaw N, Morín M, Mayo-Merino F, Olavarrieta L, et al. Mutations in the seed region of human miR-96 are responsible for non syndromic progressive hearing loss. *Nat Genet* 2009; 41: 609-13.
171. Hughes AE, Bradley DT, Campbell M, Lechner J, Dash DP, Simpson DA, et al. [Mutation altering the mir-184 seed region causes familial keratoconus with cataract.](#) *Am J Human Genet* 2011; 89: 628-33.
172. Yao E, Callier P, Faivre L, Drouin V, Cariou S, Van Haeringen A, et al. Germline deletion of the miR-17~92 cluster causes skeletal and growth defects in humans. *Nat Genet* 2011; 43: 1026-30.
173. Stanczyk J, Pedrioli DM, Brentano F, Sanchez-Pernaute O, Kolling C, Gay RE, et al. Altered expression of MicroRNA in synovial fibroblasts and synovial tissue in rheumatoid arthritis. *Arthritis Rheum* 2008; 58: 1001-9.

References

174. [Aghabozorg Afjeh SS, Ghaderian SM. The role of microRNAs in cardiovascular disease. Int J Mol Cell Med 2013; 2: 50-7.](#)
175. Frost RJ, Olson EN. Control of glucose homeostasis and insulin sensitivity by the Let-7 family of microRNAs. *Proc Natl Acad Sci U S A* 2011; 108: 21075-80.
176. Nelson PT, Wang WX, Rajeev BW. MicroRNAs (miRNAs) in neurodegenerative diseases. *Brain Pathol* 2008; 18: 130-8.
177. Wang B, Koh P, Winbanks C, Coughlan MT, McClelland A, Watson A, et al. MiR-200a prevents renal fibrogenesis through repression of TGF-beta2 expression. *Diabetes* 2011; 60: 280-7.
178. Duisters RF, Tijssen AJ, Schroen B, Leenders JJ, Lentink V, van der Made I, et al. MiR-133 and miR-30 regulate connective tissue growth factor: implications for a role of microRNAs in myocardial matrix remodeling. *Circ Res* 2009; 104: 170-8.
179. Gottwein E, Cullen BR. Viral and cellular microRNAs as determinants of viral pathogenesis and immunity. *Cell Host Microbe* 2008; 3: 375-87.
180. Shimakami T, Yamane D, Jangra RK, Kempf BJ, Spaniel C, Barton DJ, et al. Stabilization of hepatitis C virus RNA by an Ago2-miR-122 complex. *Proc Natl Acad Sci USA* 2012; 109: 941-6.
181. Cortez MA, Calin GA. MicroRNA identification in plasma and serum: a new tool to diagnose and monitor diseases. *Expert Opin Biol Therapy* 2009; 9: 703-11.
182. Ratajczak J, Wysoczynski M, Hayek F, Janowska-Wieczorek A, Ratajczak MZ. Membrane-derived microvesicles: important and underappreciated mediators of cell-to-cell communication. *Leukemia* 2006; 20: 1487-95.
183. Camussi G, Deregibus MC, Bruno S, Cantaluppi V, Biancone L. Exosomes/microvesicles as a mechanism of cell-to-cell communication. *Kidney Int* 2011; 78: 838-48.
184. Tsui NB, Ng EK, Lo YM. Stability of endogenous and added RNA in blood specimens, serum, and plasma. *Clin Chem* 2002; 48: 1647-53.
185. Di Stefano V, Zaccagnini G, Capogrossi MC, Martelli F. microRNAs as peripheral blood biomarkers of cardiovascular disease. *Vascul Pharmacol* 2011; 55: 111-8.
186. Wittmann J, Jäck HM. Serum microRNAs as powerful cancer biomarkers. *Biochim Biochim Biophys Acta* 2010; 1806: 200-7.
187. [van Rooij E, Kauppinen S. Development of microRNA therapeutics is coming of age. EMBO Mol Med 2014; 6: 851-64.](#)
188. Rossbach M. Small non-coding RNAs as novel therapeutics. *Curr Mol Med* 2010; 10: 361-8.
189. Van Rooij E, Marshall WS, Olson EN. Toward microRNA-based therapeutics for heart disease: the sense in antisense. *Circ Res* 2008; 103: 919-28.

References

190. Gandellini P, Profumo V, Folini M, Zaffaroni N. MicroRNAs as new therapeutic targets and tools in cancer. *Expert Opin Ther Targets* 2011; 15: 265-79.
191. Olive V, Jiang I, He L. Mir-17-92, a cluster of miRNAs in the midst of the cancer network. *Int J Biochem Cell Biol* 2010; 42: 1348-54.
192. He L, Thomson JM, Hemann MT, Hernando-Monge E, Mu D, Goodson S, et al. A microRNA polycistron as a potential human oncogene. *Nature* 2005; 435: 828-33.
193. Tanzer A, Stadler PF. Molecular evolution of a microRNA cluster. *J Mol Biol* 2004; 339: 327-35.
194. Ventura A, Young AG, Winslow MM, Lintault L, Meissner A, Erkland SJ, et al. Targeted deletion reveals essential and overlapping functions of the mir-17 through 92 family of miRNA clusters. *Cell* 2008; 132: 875-86.
195. Ota A, Tagawa H, Karnan S, Tsuzuki S, Karpas A, Kira S, et al. Identification and characterization of a novel gene, c13orf25, as a target for 13q31-q32 amplification in malignant lymphoma. *Cancer Res* 2004; 64: 3087-95.
196. Bonauer A, Dimmeler S. The microRNA-17~92 cluster. Still a miRacle? *Cell Cycle* 2009; 8: 3866-73.
197. O'Donnell KA, Wentzel EA, Zeller KI, Dang CV, Mendell JT. C-Myc-regulated microRNAs modulate E2F1 expression. *Nature* 2005; 435: 839-43.
198. Schulte JH, Horn S, Otto T, Samans B, Heukamp LC, Eilers UC, et al. MYCN regulates oncogenic MicroRNAs in neuroblastoma. *Int J Cancer* 2008; 122: 699-704.
199. Dews M, Homayouni A, Yu D, Murphy D, Sevignani C, Wentzel E, et al. Augmentation of tumor angiogenesis by a Myc-activated microRNA cluster. *Nat Genet* 2006; 38: 1060-5.
200. Woods K, Thomson JM, Hammond SM. Direct regulation of an oncogenic microRNA cluster by e2f transcription factors. *J Bio Chem* 2007; 282: 2130-4.
201. Muller H, Helin K. The e2f transcription factors: Key regulators of cell proliferation. *Biochim Biophys Acta* 2000; 1470: M1-12.
202. Brock M, Trenkmann M, Gay RE, Michel BA, Gay S, Fischler M, et al. Interleukin-6 modulates the expression of the bone morphogenic protein receptor type II through a novel STAT3-microRNA cluster 17/92 pathway. *Circ Res* 2009; 104: 1184-91.
203. Yan HL, Xue G, Mei Q, Wang YZ, Ding FX, Liu MF, et al. Repression of the mir-17-92 cluster by p53 has an important function in hypoxia-induced apoptosis. *EMBO J* 2009; 28: 2719-32.
204. Brosh R, Shalgi R, Liran A, Landan G, Korotayev K, Nguyen GH, et al. p53-Repressed miRNAs are involved with E2F in a feed-forward loop promoting proliferation. *Mol Syst Biol* 2008; 4: 229.

References

205. Ou YH, Chung PH, Hsu FF, Sun TP, Chang WY, Shieh SY. The candidate tumor suppressor BTG3 is a transcriptional target of p53 that inhibits E2F1. *EMBO J* 2007; 26: 3968-80.
206. Grillari, J., Hackl, M., Grillari-Voglauer, R., miR-17-92 cluster: ups and down in cancer and aging. *Biogerontology* 2010; 11: 501-6.
207. Liu SQ, Jiang S, Li C, Zhang B, Li QJ. miR-17-92 cluster targets phosphatase and tensin homology and Ikaros Family Zinc Finger 4 to promote TH17-mediated inflammation. *J Biol Chem* 2014; 289: 12446-56.
208. Wang F, Li T, Zhang B, Li H, Wua Q, Yang L, et al. MicroRNA-19a/b regulates multidrug resistance in human gastric cancer cells by targeting PTEN. *Biochem Biophys Res Commun* 2013; 434: 688-94.
209. Pickering MT, Stadler BM, Kowalik TF. miR-17 and miR-20a temper an E2F1-induced G1 checkpoint to regulate cell cycle progression. *Oncogene* 2009; 28: 140-5.
210. Fontana L, Fiori ME, Albin S, Cifaldi L, Giovinnazzi S, Forloni M, et al. Antagomir-17-5p abolishes the growth of therapy-resistant neuroblastoma through p21 and BIM. *PLoS One* 2008; 3: e2236.
211. Dews M, Fox JL, Hultine S, Sundaram P, Wang W, Liu YY, et al. The myc-mir-17~92 axis blunts TGF β signaling and production of multiple TGF β -dependent antiangiogenic factors. *Cancer Res* 2010; 70: 8233-46.
212. Manni I, Artuso S, Careccia S, Rizzo MG, [Baserga R](#), [Piaggio G](#), et al. The microRNA miR-92 increases proliferation of myeloid cells and by targeting p63 modulates the abundance of its isoforms. *FASEB J* 2009; 23: 3957-66.
213. Dews M, Homayouni A, Yu D, Murphy D, Sevignani C, Wentzel E, et al. Augmentation of tumor angiogenesis by a myc-activated microrna cluster. *Nat Genet* 2006; 38: 1060-5.
214. Taguchi A, Yanagisawa K, Tanaka M, Cao K, Matsuyama Y, Goto H, et al. Identification of hypoxia-inducible factor-1 α as a novel target for *miR-17-92* microRNA cluster. *Cancer Res* 2008; 68: 5540-5.
215. Wang J, Greene SB, Bonilla-Claudio M, Tao Y, Zhang J, Bai Y, et al. Bmp signaling regulates myocardial differentiation from cardiac progenitors through a microrna mediated mechanism. *Dev Cell* 2010; 19: 903-12.
216. Trenkmann M, Brock M, Gay RE, Michel BA, Gay S, Huber LC. Tumor necrosis factor α -induced microRNA-18a activates rheumatoid arthritis synovial fibroblasts through a feedback loop in NF- κ B signaling. *Arthritis Rheum* 2013; 65: 916-27.
217. Gantier MP, Stunden HJ, McCoy CE, Behlke MA, Wang D, Kaparakis-Liaskos M, et al. A miR-19 regulon that controls NF- κ B signaling. *Nucleic Acids Res* 2012; 40: 8048-58.

References

218. Pichiorri F, Suh SS, Ladetto M, Kuehl M, Palumbo T, Drandi D, et al. [MicroRNAs regulate critical genes associated with multiple myeloma pathogenesis](#). Proc Natl Acad Sci U S A 2008; 105: 12885-90.
219. Olive V, Li Q, He L. *mir-17-92*, a polycistronic oncomir with pleiotropic functions. Immunol Rev 2013; 253: 158-66.
220. Mogilyansky E, Rigoutsos I. The miR-17/92 cluster: a comprehensive update on its genomics, genetics, functions and increasingly important and numerous roles in health and disease. Cell Death Differ 2013; 20: 1603-14.
221. Concepcion CP, Bonetti C, Ventura A. The microrna-17-92 family of microrna clusters in development and disease. Cancer J 2012; 18: 262-7.
222. Mendell JT. MiRiad roles for the miR-17-92 cluster in development and disease. Cell 2008; 133: 217-22.
223. Marcelis CL, Hol FA, Graham GE, Rieu PN, Kellermayer R, Meijer RP, et al. Genotype phenotype correlations in mycn-related feingold syndrome. Hum Mut 2008; 29: 1125-32.
224. de Pontual L, Yao E, Callier P, Faivre L, Drouin V, Cariou S, et al. Germline deletion of the mir-17 approximately 92 cluster causes skeletal and growth defects in humans. Nature Genet 2011; 43: 1026-30.
225. Carraro G, El-Hashash A, Guidolin D, Tiozzo C, Turcatel G, Young BM, et al. Mir-17 family of microRNAs controls fgf10-mediated embryonic lung epithelial branching morphogenesis through mapk14 and stat3 regulation of e-cadherin distribution. Dev Biol 2009; 333: 238-50.
226. [Danielson LS](#), [Park DS](#), [Rotllan N](#), [Chamorro-Jorganes A](#), [Guijarro MV](#), [Fernandez-Hernando C](#), et al. [Cardiovascular dysregulation of miR-17-92 causes a lethal hypertrophic cardiomyopathy and arrhythmogenesis](#). FASEB J 2013; 27: 1460-7.
227. [Qin DN](#), [Qian L](#), [Hu DL](#), [Yu ZB](#), [Han SP](#), [Zhu C](#), et al. [Effects of miR-19b overexpression on proliferation, differentiation, apoptosis and Wnt/ \$\beta\$ -catenin signaling pathway in P19 cell model of cardiac differentiation in vitro](#). Cell Biochem Biophys 2013; 66: 709-22.
228. Ranji N, Sadeghizadeh M, Shokrgozar MA, Bakhshandeh B, Karimipour M, Amanzadeh A, et al. miR-17-92 cluster: an apoptosis inducer or proliferation enhancer. Mol Cell Biochem 2013; 380: 229-38.
229. Tsitsiou E, Lindsay MA. microRNAs and the immune response. Curr Opin Pharmacol 2009; 9: 514-20.
230. Fontana L, Pelosi E, Greco P, Racanicchi S, Testa U, Liuzzi F, et al. MicroRNAs 17-5p-20a-106a control monocytopenia through AML1 targeting and M-CSF receptor upregulation. Nat Cell Biol 2007; 9: 775-87.

References

231. Chen CZ, Li L, Lodish HF, Bartel DP. MicroRNAs modulate hematopoietic lineage differentiation. *Science* 2004; 303: 83-6.
232. Xiao C, Srinivasan L, Calado DP, Patterson HC, Zhang B, Wang J, et al. Lymphoproliferative disease and autoimmunity in mice with increased miR-17-92 expression in lymphocytes. *Nat Immunol* 2008; 9: 405-14.
233. Jiang S, Li C, Olive V, Lykken E, Feng F, Sevilla J, et al. Molecular dissection of the miR-17-92 cluster's critical dual roles in promoting Th1 responses and preventing inducible Treg differentiation. *Blood* 2011; 118: 5487-97.
234. Simpson LJ, Patel S, Bhakta NR, Choy DF, Brightbill HD, Ren X, et al. A microRNA upregulated in asthma airway T cells promotes TH2 cytokine production. *Nat Immunol* 2014; 15: 1162-70.
235. Wu T, Wieland A, Araki K, Davis CW, Ye L, Hale JS, et al. Temporal expression of microRNA cluster miR-17-92 regulates effector and memory CD8⁺ T-cell differentiation. *Proc Nat Acad Sci U S A* 2012; 109: 9965-70.
236. Inomata M, Tagawa H, Guo YM, Kameoka Y, Takahashi N, Sawada K. MicroRNA-17-92 down-regulates expression of distinct targets in different B-cell lymphoma subtypes. *Blood* 2009; 113: 396-402.
237. Philippe L, Alsaleh G, Bahram S, Pfeffer S, Georgel P. The miR-17~92 cluster: a key player in the control of inflammation during rheumatoid arthritis. *Front Immunol* 2013; 4: 70.
238. Brock M, Trenkmann M, Gay RE, Gay S, Speich R, Huber LC. MicroRNA-18a enhances the interleukin-6-mediated production of the acute-phase proteins fibrinogen and haptoglobin in human hepatocytes. *J Biol Chem* 2011; 286: 40142-50.
239. Zhou R, Hu G, Liu J, Gong AY, Drescher KM, Chen XM. NF-kappaB p65-dependent transactivation of miRNA genes following cryptosporidium parvum infection stimulates epithelial cell immune responses. *PLoS Pathog* 2009; 5: e1000681.
240. Zhou R, Hu G, Gong AY, Chen XM. Binding of NF-kappaB p65 subunit to the promoter elements is involved in LPS-induced transactivation of miRNA genes in human biliary epithelial cells. *Nucleic Acids Res* 2010; 38: 3222-32.
241. [Zhu D, Pan C, Li L, Bian Z, Lv Z, Shi L, et al. MicroRNA-17/20a/106a modulate macrophage inflammatory responses through targeting signal-regulatory protein \$\alpha\$. *J Allergy Clin Immunol* 2013; 132: 426-36.](#)
242. [Rao R, Nagarkatti PS, Nagarkatti M. \$\Delta^9\$ Tetrahydrocannabinol attenuates Staphylococcal enterotoxin B-induced inflammatory lung injury and prevents mortality in mice by modulation of miR-17-92 cluster and induction of T-regulatory cells. *Br J Pharmacol* 2015; 172: 1792-806.](#)

References

243. Ye H, Liu X, Lv M, Wu Y, Kuang S, Gong J, et al. MicroRNA and transcription factor co-regulatory network analysis reveals miR-19 inhibits CYLD in T-cell acute lymphoblastic leukemia. *Nucleic Acids Res* 2012; 40: 5201-14.
244. Philippe L, Alsaleh G, Suffert G, Meyer A, Georgel P, Sibilia J, et al. TLR2 expression is regulated by microRNA miR-19 in rheumatoid fibroblast-like synoviocytes. *J Immunol* 2012; 188: 454-61.
245. Philippe L, Alsaleh G, Pichot A, Ostermann E, Zuber G, Frisch B, et al. MiR-20a regulates ASK1 expression and TLR4-dependent cytokine release in rheumatoid fibroblast-like synoviocytes. *Ann Rheum Dis* 2013; 72: 1071-9.
246. White ES, Atrasz RG, Hu B, Phan SH, Stambolic V, Mak TW, et al. Negative regulation of myofibroblast differentiation by PTEN (phosphatase and tensin homolog deleted on chromosome 10). *Am J Respir Crit Care Med* 2006; 173: 112-21.
247. Hong L, Lai M, Chen M, Xie C, Liao R, Kang YJ, et al. The miR-17-92 cluster of microRNAs confers tumorigenicity by inhibiting oncogene-induced senescence. *Cancer Res* 2010; 70: 8547-57.
248. Dakhllallah D, Batte K, Wang Y, Cantemir-Stone CZ, Yan P, Nuovo G, et al. Epigenetic regulation of miR-17~92 contributes to the pathogenesis of pulmonary fibrosis. *Am J Respir Crit Care Med* 2013; 187: 397-405.
249. van Almen GC, Verhesen W, van Leeuwen RE, van de Vrie M, Eurlings C, Schellings MW, et al. MicroRNA-18 and microRNA-19 regulate CTGF and TSP-1 expression in age-related heart failure. *Aging Cell* 2011; 10: 769-79.
250. Kodama T, Takehara T, Hikita H, [Shimizu S](#), [Shigekawa M](#), [Tsunematsu H](#), et al. Increases in p53 expression induce CTGF synthesis by mouse and human hepatocytes and result in liver fibrosis in mice. *J Clin Invest* 2011; 121: 3343-56.
251. Lakner AM, Steuerwald NM, Walling TL, Ghosh S, Li T, McKillop IH, et al. Inhibitory effects of microRNA 19b in hepatic stellate cell mediated fibrogenesis. *Hepatology* 2012; 56: 300-10.
252. Li L, Shi JY, Zhu GQ, Shi B. Mir-17~92 cluster regulates cell proliferation and collagen synthesis by targeting TGFb pathway in mouse palatal mesenchymal cells. *J Cell Biochem* 2012; 113: 1235-44.
253. Moussay E, Wang K, Cho JH, van Moer K, Pierson S, Paggetti J, et al. MicroRNA as biomarkers and regulators in B-cell chronic lymphocytic leukemia. *Proc Natl Acad Sci USA* 2011; 108: 6573-8.
254. Reichek JL, Duan F, Smith LM, Gustafson DM, O'Connor RS, Zhang C, et al. Genomic and clinical analysis of amplification of the 13q31 chromosomal region in alveolar rhabdomyosarcoma: A report from the Children's Oncology Group. *Clin Cancer Res* 2011; 17: 1464-723.

References

255. Szafranska AE, Davison TS, John J, Cannon T, Sipos B, Maghnouj A, et al. MicroRNA expression alterations are linked to tumorigenesis and non-neoplastic processes in pancreatic ductal adenocarcinoma. *Oncogene* 2007; 26: 4442-52.
256. Morimura R, Komatsu S, Ichikawa D, Takeshita H, Tsujiura M, Nagata H, et al. Novel diagnostic value of circulating mir-18a in plasma of patients with pancreatic cancer. *Br J Cancer* 2011; 105: 1733-40.
257. Osada H, Takahashi T. Let-7 and mir-17-92: Small-sized major players in lung cancer development. *Cancer Sci* 2011; 102: 9-17.
258. Yu Z, Willmarth NE, Zhou J, Katiyar S, Wang M, Liu Y, et al. MicroRNA 17/20 inhibits cellular invasion and tumor metastasis in breast cancer by heterotypic signaling. *Proc Natl Acad Sci USA* 2010; 107: 8231-6.
259. Chow TF, Mankaruos M, Scorilas A, Youssef Y, Girgis A, Mossad S, et al. The mir-17-92 cluster is over expressed in and has an oncogenic effect on renal cell carcinoma. *J Urol* 2010; 183: 743-51.
260. Connolly E, Melegari M, Landgraf P, Tchaikovskaya T, Tennant BC, Slagle BL, et al. Elevated expression of the mir-17-92 polycistron and mir-21 in hepatitis virus-associated hepatocellular carcinoma contributes to the malignant phenotype. *Am J Pathol* 2008; 173: 856-64.
261. Li J, Yen C, Liaw D, Podsypanina K, Bose S, Wang SI, et al. PTEN, a putative protein tyrosine phosphatase gene mutated in human brain, breast, and prostate cancer. *Science* 1997; 275: 1943-7.
262. Steck PA, Pershouse MA, Jasser SA, Yung WK, Lin H, Ligon AH, et al. Identification of a candidate tumour suppressor gene, MMAC1, at chromosome 10q23.3 that is mutated in multiple advanced cancers. *Nat Genet* 1997; 15: 356-62.
263. Li DM, Sun H. TEP1, encoded by a candidate tumor suppressor locus, is a novel protein tyrosine phosphatase regulated by transforming growth factor beta. *Cancer Res* 1997; 57: 2124-9.
264. Denu JM, Stuckey JA, Saper MA, Dixon JE. Form and function in protein dephosphorylation. *Cell* 1996; 87: 361-4.
265. Lee JO, Yang H, Georgescu MM, Di Cristofano A, Maehama T, Shi Y, et al. Crystal structure of the PTEN tumor suppressor: implications for its phosphoinositide phosphatase activity and membrane association. *Cell* 1999; 99: 323-34.
266. Redfern RE, Redfern D, Furgason ML, Munson M, Ross AH, Gericke A. PTEN phosphatase selectively binds phosphoinositides and undergoes structural changes. *Biochemistry* 2008; 47: 2162-71.
267. Liaw D, Marsh DJ, Li J, Dahia PL, Wang SI, Zheng Z, et al. Germline mutations of the PTEN gene in Cowden disease, an inherited breast and thyroid cancer syndrome. *Nat Genet* 1997; 16: 64-7.

References

268. Maehama T, Dixon JE. The tumor suppressor, PTEN/MMAC1, dephosphorylates the lipid second messenger, phosphatidylinositol 3,4,5-trisphosphate. *J Biol Chem* 1998; 273: 13375-8.
269. Waite KA, Eng C. Protean PTEN: form and function. *Am J Hum Genet* 2002; 70: 829-44.
270. Georgescu MM, Kirsch KH, Kaloudis P, Yang H, Pavletich NP, Hanafusa H. Stabilization and productive positioning roles of the C2 domain of PTEN tumor suppressor. *Cancer Res* 2000; 60: 7033-8.
271. Song MS, Salmena L, Pandolfi PP. The functions and regulation of the PTEN tumor suppressor. *Nat Rev Mol Cell Biol* 2012; 13: 283-96.
272. Shi Y, Paluch BE, Wang X, Jiang X. PTEN at a glance. *J Cell Sci* 2012; 125: 4687-92.
273. Sumitomo M, Iwase A, Zheng R, Navarro D, Kaminetzky D, Shen R, et al. Synergy in tumor suppression by direct interaction of neutral endopeptidase with PTEN. *Cancer Cell* 2004; 5: 67-78.
274. Sanchez T, Thangada S, Wu MT, Kontos CD, Wu D, Wu H, et al. PTEN as an effector in the signaling of antimigratory G protein-coupled receptor. *Proc Natl Acad Sci USA* 2005; 102: 4312-7.
275. Wu H, Feng W, Chen J, Chan LN, Huang S, Zhang M. PDZ domains of Par-3 as potential phosphoinositide signaling integrators. *Mol Cell* 2007; 28: 886-98.
276. Vazquez F, Devreotes P. Regulation of PTEN function as a PIP3 gatekeeper through membrane interaction. *Cell Cycle* 2006; 5: 1523-7.
277. Gericke A, Munson M, Ross AH. Regulation of the PTEN phosphatase. *Gene* 2006; 374: 1-9.
278. Patel L, Pass I, Coxon P, Downes CP, Smith SA, Macphée CH. Tumor suppressor and anti-inflammatory actions of PPAR gamma agonists are mediated via upregulation of PTEN. *Curr Biol* 2001; 11: 764-8.
279. Stambolic V, MacPherson D, Sas D, Lin Y, Snow B, Jang Y, et al. Regulation of PTEN transcription by p53. *Mol Cell* 2001; 8: 317-25.
280. Virolle T, Adamson ED, Baron V, Birlle D, Mercola D, Mustelin T, et al. The Egr-1 transcription factor directly activates PTEN during irradiation-induced signalling. *Nat Cell Biol* 2001; 3: 1124-8.
281. Lau MT, Klausen C, Leung PC. E-cadherin inhibits tumor cell growth by suppressing PI3K/Akt signaling via b-catenin- Egr1-mediated PTEN expression. *Oncogene* 2011; 30: 2753-66.
282. Meng X, Wang Y, Zheng X, [Liu C](#), [Su B](#), [Nie H](#), et al. ShRNA-mediated knockdown of Bmi-1 inhibit lung adenocarcinoma cell migration and metastasis. *Lung Cancer* 2012; 77: 24-30.
283. Tian L, Fang YX, Xue JL, Chen JZ. Four microRNAs promote prostate cell proliferation with regulation of PTEN and its downstream signals in vitro. *PLoS One* 2013; 8: e75885.
284. Tamguney T, Stokoe D. New insights into PTEN. *J Cell Sci* 2007; 120: 4071-9.

References

285. Seo JH, Ahn Y, Lee SR, Yeol Yeo C, Chung Hur K. The major target of the endogenously generated reactive oxygen species in response to insulin stimulation is phosphatase and tensin homolog and not phosphoinositide-3 kinase (PI-3 kinase) in the PI-3 kinase/Akt pathway. *Mol Biol Cell* 2005; 16: 348–57.
286. Maehama T, Dixon JE. The tumor suppressor, PTEN/MMAC1, dephosphorylates the lipid second messenger, phosphatidylinositol 3,4,5-trisphosphate. *J Biol Chem* 1998; 273: 13375-8.
287. Stambolic V, Suzuki A, de la Pompa JL, Brothers GM, Mirtsos C, Sasaki T, et al. Negative regulation of PKB/Akt-dependent cell survival by the tumor suppressor PTEN. *Cell* 1998; 95: 29-39.
288. Sun H, Lesche R, Li DM, Liliental J, Zhang H, Gao J, et al. PTEN modulates cell cycle progression and cell survival by regulating phosphatidylinositol 3,4,5,-trisphosphate and Akt/protein kinase B signaling pathway. *Proc Natl Acad Sci USA* 1999; 96: 6199-204.
289. Vivanco I, Sawyers CL. The phosphatidylinositol 3-kinase AKT pathway in human cancer. *Nat Rev Cancer* 2002; 2: 489-501.
290. Tamguney T, Stokoe D. New insights into PTEN. *J Cell Sci* 2007; 120: 4071-9.
291. Trotman LC, Wang X, Alimonti A, Chen Z, Teruya-Feldstein J, Yang H, et al. Ubiquitination regulates PTEN nuclear import and tumor suppression. *Cell* 2007; 128: 141-56.
292. Yang Z, Yuan XG, Chen J, Lu NH. Is NEDD4-1 a negative regulator of phosphatase and tensin homolog in gastric carcinogenesis? *World J Gastroenterol* 2012; 18: 6345-8.
293. Vasudevan KM, Gurumurthy S, Rangnekar VM. Suppression of PTEN expression by NF-kappa B prevents apoptosis. *Mol Cell Biol* 2004; 24: 1007-21.
294. Gu J, Tamura M, Yamada KM. Tumor Suppressor PTEN inhibits integrin and growth factor-mediated mitogen-activated protein (MAP) kinase signaling pathways. *J Cell Biol* 1998; 143: 1375-83.
295. Tamura M, Gu J, Takino T, Yamada KM. Tumor suppressor PTEN inhibition of cell invasion, migration, and growth: differential involvement of focal adhesion kinase and p130Cas. *Cancer Res* 1999; 59: 442-9.
296. Song MS, Carracedo A, Salmena L, [Song SJ](#), [Egia A](#), [Malumbres M](#), et al. Nuclear PTEN regulates the APC-CDH1 tumor-suppressive complex in a phosphatase-independent manner. *Cell* 2011; 144: 187-99.
297. Haier J, Nicolson GL. PTEN regulates tumor cell adhesion of colon carcinoma cells under dynamic conditions of fluid flow. *Oncogene* 2002; 21: 1450-60.
298. Buckler JL, Liu X, Turka LA. Regulation of T-cell responses by PTEN. *Immunol Rev* 2008; 224: 239-48.
299. Okkenhaug K, Patton DT, Bilancio A, Garcon F, Rowan WC, Vanhaesebroeck B. The p110delta isoform of phosphoinositide 3-kinase controls clonal expansion and differentiation of Th cells. *J Immunol* 2006; 177: 5122-8.
300. Soond DR, Bjorgo E, Moltu K, Dale VQ, Patton DT, Torgersen KM, et al. PI3K p110delta regulates T-cell cytokine production during primary and secondary immune responses in mice and humans. *Blood* 2010; 115: 2203-13.

References

301. Suzuki A, Matsuda S, Terauchi Y, Fujiwara M, Ohteki T, Asano T, et al. Critical roles of Pten in B cell homeostasis and immunoglobulin class switch recombination. *J Exp Med* 2003; 197: 657-67.
302. Stephens L, Ellson C, Hawkins P. Roles of PI3Ks in leukocyte chemotaxis and phagocytosis. *Curr Opin Cell Biol* 2002; 14: 203-13.
303. Kuwano K. PTEN as a new agent in the fight against fibrogenesis. *Am J Respir Crit Care Med* 2006; 173: 5-6.
304. [Xia H, Khalil W, Kahm J, Jessurun J, Kleidon J, Henke CA. Pathologic caveolin-1 regulation of PTEN in idiopathic pulmonary fibrosis. *Am J Pathol* 2010; 176: 2626-37.](#)
305. Hao LS, Zhang XL, An JY, Karlin J, Tian XP, Dun ZN, et al. PTEN expression is down-regulated in liver tissues of rats with hepatic fibrosis induced by biliary stenosis. *APMIS* 2009; 117: 681-91.
306. Crackower MA, Oudit GY, Kozieradzki I, Sarao R, Sun H, Sasaki T, et al. Regulation of myocardial contractility and cell size by distinct PI3K-PTEN signaling pathways. *Cell* 2002; 110: 737-49.
307. [Parapuram SK, Shi-wen X, Elliott C, Welch ID, Jones H, Baron M, et al. Loss of PTEN expression by dermal fibroblasts causes skin fibrosis. *J Invest Dermatol* 2011; 131: 1996-2003.](#)
308. [Guo L, Chen L, Bi S, Chai L, Wang Z, Cao C, et al. PTEN inhibits proliferation and functions of hypertrophic scar fibroblasts. *Mol Cell Biochem* 2012; 361: 161-8.](#)
309. [He Z, Deng Y, Li W, Chen Y, Xing S, Zhao X, et al. Overexpression of PTEN suppresses lipopolysaccharide-induced lung fibroblast proliferation, differentiation and collagen secretion through inhibition of the PI3-K-Akt-GSK3beta pathway. *Cell Biosci* 2014; 4: 2.](#)
310. [Liu S, Parapuram SK, Leask A. Fibrosis caused by loss of PTEN expression in mouse fibroblasts is crucially dependent on CCN2. *Arthritis Rheum* 2013; 65: 2940-4.](#)
311. Tamura M, Gu J, Matsumoto K, Aota S, Parsons R, Yamada KM. [Inhibition of cell migration, spreading, and focal adhesions by tumor suppressor PTEN. *Science* 1998; 280: 1614-7.](#)
312. [Nho RS, Xia H, Diebold D, Kahm J, Kleidon J, White E, et al. PTEN regulates fibroblast elimination during collagen matrix contraction. *J Biol Chem* 2006; 281: 33291-301.](#)
313. Koul D, Parthasarathy R, Shen R, Davies MA, Jasser SA, Chintala SK, et al. Suppression of matrix metalloproteinase-2 gene expression and invasion in human glioma cells by MMAC/PTEN. *Oncogene* 2001; 20: 6669-78.

References

314. Koul D, Yao Y, Abbruzzese JL, Yung WK, Reddy SA. Tumor suppressor MMAC/PTEN inhibits cytokine-induced NFkappaB activation without interfering with the IkappaB degradation pathway. *J Biol Chem* 2001; 276: 11402-8.
315. Waris G, Felmlee DJ, Negro F, Siddiqui A. Hepatitis C virus induces proteolytic cleavage of sterol regulatory element binding proteins and stimulates their phosphorylation via oxidative stress. *J Virol* 2007; 81: 8122-30.
316. Porstmann T, Griffiths B, Chung YL, Delpuech O, Griffiths JR, Downward J, et al. PKB/Akt induces transcription of enzymes involved in cholesterol and fatty acid biosynthesis via activation of SREBP. *Oncogene* 2005; 24: 6465-81.
317. Mirandola S, Bowman D, Hussain MM, Alberti A. Hepatic steatosis in hepatitis C is a storage disease due to HCV interaction with microsomal triglyceride transfer protein (MTP). *Nutr Metab (Lond)* 2010; 7: 13.
318. Nakamuta M, Yada R, Fujino T, Yada M, Higuchi N, Tanaka M, et al. Changes in the expression of cholesterol metabolism-associated genes in HCV infected liver: a novel target for therapy? *Int J Mol Med* 2009; 24: 825-8.
319. Yu S, Matsusue K, Kashireddy P, Cao WQ, Yeldandi V, Yeldandi AV, et al. Adipocyte-specific gene expression and adipogenic steatosis in the mouse liver due to peroxisome proliferator-activated receptor gamma1 (PPARgamma1) overexpression. *J Biol Chem* 2003; 278: 498-505.
320. Marcus SL, Miyata KS, Zhang B, Subramani S, Rachubinski RA, Capone JP. Diverse peroxisome proliferator-activated receptors bind to the peroxisome proliferator-responsive elements of the rat hydratase/dehydrogenase and fatty acyl-CoA oxidase genes but differentially induce expression. *Proc Natl Acad Sci USA* 1993; 90: 5723-7.
321. Vinciguerra M, Veyrat-Durebex C, Moukil MA, Rubbia-Brandt L, Rohner-Jeanrenaud F, Foti M. PTEN Down-regulation by unsaturated fatty acids triggers hepatic steatosis via an NF-kBp65/mTOR-dependent mechanism. *Gastroenterology* 2008; 134: 268-80.
322. Matsumoto M, Han S, Kitamura T, Accili D. Dual role of transcription factor FoxO1 in controlling hepatic insulin sensitivity and lipid metabolism. *J Clin Invest* 2006; 116: 2464-72.
323. Stiles B, Wang Y, Stahl A, [Bassilian S](#), [Lee WP](#), [Kim YJ](#), et al. Liver-specific deletion of negative regulator Pten results in fatty liver and insulin hypersensitivity [corrected]. *Proc Natl Acad Sci U S A* 2004; 101: 2082-7.
324. Clément S, Peyrou M, Sanchez-Pareja A, Bourgoïn L, Ramadori P, Suter D, et al. Down-regulation of phosphatase and tensin homolog by hepatitis C virus core 3a in hepatocytes triggers the formation of large lipid droplets. *Hepatology* 2011; 54: 38-49.
325. Macías Rodríguez MA, Rendón Unceta P, Navas Relinque C, Tejada Cabrera M, Infantes Hernández JM, [Martín Herrera L](#). Ultrasonography in patients with chronic

References

- liver disease: its usefulness in the diagnosis of cirrhosis. *Rev Esp Enferm Dig* 2003; 95: 258-64.
326. Hoffbrand AV, Pettit J, Moss P. *Essential Hematology*, 4th ed. Oxford: Blackwell Science. 2001.
327. Friedman LS, Martin P, Munoz SJ. Laboratory methods for evaluation of the patient with liver disease. In: Zakim D, Boyer TD, eds. *Hepatology: A Textbook of Liver Disease*, 4th ed. Philadelphia: Saunders. 2002: 661-708.
328. Pawlostky JM. Use of interpretation of virological tests for hepatitis C. *Hepatology* 2002; 36: 65-73.
329. Fanning L, Kenny-Walsh E, Levis J, Choudhury KR, Cannon B, Sheehan M, et al. Natural fluctuations of hepatitis C viral load in a homogeneous patient population: A prospective study. *Hepatology* 2000; 31: 225-9.
330. [Jordan W](#). Antigen measurement using ELISA. In: Walker JM, ed. [The Protein protocols handbook](#), 3rd ed. New York: Humana Press. 2009: 1827-33.
331. Brunt EM, Janney CG, Di Bisceglie AM, Neuschwander-Tetri BA, Bacon BR. Nonalcoholic steatohepatitis: A proposal for the grading and staging of histological lesions. *Am J Gastroenterol* 1999; 94: 2467-74.
332. Sophie C, Marion P, Lucie B, Pierluigi R, David S, Manlio V, et al. Down-Regulation of Phosphatase and Tensin Homolog by hepatitis C virus core 3a in hepatocytes triggers the formation of large lipid droplets. *Hepatology* 2011; 54: 38-49.
333. Li W, Tan D, Zenali MJ, Brown RE. Constitutive activation of nuclear factor-kappa B (NF-κB) signaling pathway in fibrolamellar hepatocellular carcinoma. *Int J Clin Exp Pathol* 2010; 3: 238-43.
334. Zimmer V, Lammert F. Genetics in liver disease: new concepts. *Curr Opin Gastroenterol* 2011; 27: 231-9.
335. Oksuz Z, Serin MS, Kaplan E, Dogen A, Tezcan S, Aslan G, et al. Serum microRNAs; miR-30c-5p, miR-223-3p, miR-302c-3p and miR-17-5p could be used as novel non-invasive biomarkers for HCV-positive cirrhosis and hepatocellular carcinoma. *Mol Biol Rep* 2015; 42: 713-20.
336. El Tayebi HM, Omar K, Hegy S, El Maghrabi M, El Brolosy M, Hosny KA, et al. Repression of miR-17-5p with elevated expression of E2F-1 and c-MYC in non-metastatic hepatocellular carcinoma and enhancement of cell growth upon reversing this expression pattern. *Biochem Biophys Res Commun* 2013; 434: 421-7.
337. Shrivastava S, Petrone J, Steele R, Lauer GM, Di Bisceglie AM, Ray RB. Up-regulation of circulating miR-20a is correlated with hepatitis C virus-mediated liver disease progression. *Hepatology* 2013; 58: 863-71.

References

338. Li LM, Hu ZB, Zhou ZX, Chen X, Liu FY, Zhang JF, et al. Serum microRNA profiles serve as novel biomarkers for HBV infection and diagnosis of HBV-positive hepatocarcinoma. *Cancer Res* 2010; 70: 9798-807.
339. Liu X, Wang T, Wakita T, Yang W. Systematic identification of microRNA and messenger RNA profiles in hepatitis C virus-infected human hepatoma cells. *Virology* 2010; 398: 57-67.
340. Tsubota A, Mogushi K, Aizaki H, Miyaguchi K, Nagatsuma K, Matsudaira H, et al. Involvement of MAP3K8 and miR-17-5p in poor virologic response to interferon-based combination therapy for chronic hepatitis C. *PLoS One* 2014; 9: e97078.
341. Murakami Y, Tanaka M, Toyoda H, Hayashi K, Kuroda M, Tajima A, et al. Hepatic microRNA expression is associated with the response to interferon treatment of chronic hepatitis C. *BMC Med Genomics* 2010; 3: 48.
342. Higgs MR, Lerat H, Pawlotsky JM. Hepatitis C virus-induced activation of β -catenin promotes c-Myc expression and a cascade of pro-carcinogenic events. *Oncogene* 2013; 32: 4683-93.
343. Idrees S, Ashfaq UA, Masoud MS, Qasim M, Javed T, Ali A. Gene expression profiling of immune responsive and fibrosis genes in hepatitis C virus infected patients. *Viral Immunol* 2014; 27: 250-4.
344. [Farinati F](#), [Cardin R](#), [Bortolami M](#), [Guido M](#), [Rugge M](#). [Oxidative damage, pro-inflammatory cytokines, TGF-alpha and c-myc in chronic HCV-related hepatitis and cirrhosis.](#) *World J Gastroenterol* 2006; 12: 2065-9.
345. Cho J, Baek W, Yang S, Chang J, Sung YC, Suh M. HCV core protein modulates Rb pathway through pRb down-regulation and E2F-1 up-regulation. *Biochim Biophys Acta* 2001; 1538: 59-66.
346. Hassan M, Ghozlan H, Abdel-Kader O. Activation of RB/E2F signaling pathway is required for the modulation of hepatitis C virus core protein-induced cell growth in liver and non-liver cells. *Cell Signal* 2004; 16: 1375-85.
347. Jung YJ, Kim JW, Park SJ, Min BY, Jang ES, Kim NY, et al. c-Myc-mediated overexpression of miR-17-92 suppresses replication of hepatitis B virus in human hepatoma cells. *J Med Virol* 2013; 85: 969-78.
348. Ura S, Honda M, Yamashita T, Ueda T, Takatori H, Nishino R, et al. Differential MicroRNA expression between hepatitis B and hepatitis C leading disease progression to hepatocellular carcinoma. *Hepatology* 2009; 49: 1098-112.
349. Zheng ZM, Wang X. Regulation of cellular miRNA expression by human papillomaviruses. *Biochim Biophys Acta* 2011; 1809: 668-77.
350. Wang CL, Wang BB, Bartha G, Li L, Channa N, Klinger M, et al. Activation of an oncogenic microRNA cistron by provirus integration. *PNAS* 2006; 103: 18680-4.

References

351. Riley KJ, Rabinowitz GS, Yario TA, Luna JM, Darnell RB, Steitz JA. EBV and human microRNAs co-target oncogenic and apoptotic viral and human genes during latency. *EMBO J* 2012; 31: 2207-21.
352. Song L, Liu H, Gao S, Jiang W, Huang W. Cellular microRNAs inhibit replication of the H1N1 influenza A virus in infected cells. *J Virol* 2010; 84: 8849-60.
353. Klase Z, Houzet L, Jeang KT. MicroRNAs and HIV-1: complex interactions. *J Biol Chem* 2012; 287: 40884-90.
354. Carl JW Jr, Trgovcich J, Hannonhalli S. Widespread evidence of viral miRNAs targeting host pathways. *BMC Bioinf* 2013; 14 (Suppl 2): S3.
355. Kincaid RP, Sullivan CS. Virus-encoded microRNAs: an overview and a look to the future. *PLoS Pathog* 2012; 8: e1003018.
356. Li C, Hu J, Hao J, Zhao B, Wu B, Sun L, et al. Competitive virus and host RNAs: the interplay of a hidden virus and host interaction. *Protein Cell* 2014; 5: 348-56.
357. Ala U, Karreth FA, Bosia C, Pagnani A, Taulli R, Léopold V, et al. Integrated transcriptional and competitive endogenous RNA networks are crossregulated in permissive molecular environments. *Proc Natl Acad Sci USA* 2013; 110: 7154-9.
358. Wang Y, Jiang L, Ji X, Yang B, Zhang Y, Fu XD. Hepatitis B viral RNA directly mediates down-regulation of the tumor suppressor microRNA miR-15a/miR-16-1 in hepatocytes. *J Biol Chem* 2013; 288: 18484-93.
359. Shimakami T, Yamane D, Jangra RK, Kempf BJ, Spaniel C, Barton DJ, et al. Stabilization of hepatitis C virus RNA by an Ago2-miR-122 complex. *Proc Natl Acad Sci USA* 2012; 109: 941-6.
360. Danielson LS, Park DS, Rotllan N, Chamorro-Jorganes A, Guijarro MV, Fernandez-Hernando C, et al. Cardiovascular dysregulation of miR-17-92 causes a lethal hypertrophic cardiomyopathy and arrhythmogenesis. *FASEB J* 2013; 27: 1460-7.
361. [Miele E](#), [Buttarelli FR](#), [Arcella A](#), [Begalli F](#), [Garg N](#), [Silvano M](#), et al. [High-throughput microRNA profiling of pediatric high-grade gliomas](#). *Neuro Oncol* 2014; 16: 228-40.
362. Ernst A, Campos B, Meier J, Devens F, Liesenberg F, Wolter M, et al. De-repression of CTGF via the miR-17-92 cluster upon differentiation of human glioblastoma spheroid cultures. *Oncogene* 2010; 29: 3411-22.
363. Humphreys KJ, Cobiac L, Le Leu RK, Van der Hoek MB, Michael MZ. Histone deacetylase inhibition in colorectal cancer cells reveals competing roles for members of the oncogenic miR-17-92 cluster. *Mol Carcinog* 2013; 52: 459-74.
364. Kim S, Domon-Dell C, Kang J, Chung DH, Freund JN, Evers BM. Down-regulation of the tumor suppressor PTEN by the tumor necrosis factor-alpha/nuclear factor-kappaB (NF-kappaB)-inducing kinase/NF-kappaB pathway is linked to a default IkappaB-alpha autoregulatory loop. *J Biol Chem* 2004; 279: 4285-91.

References

365. Zhang Y, Li RQ, Feng XD, Zhang YH, Wang L. Down-regulation of PTEN by HCV core protein through activating nuclear factor- κ B. *Int J Clin Exp Pathol* 2014; 7: 7351-9.
366. Cheng D, Zhang L, Yang G, Zhao L, Peng F, Tian Y, et al. Hepatitis C virus NS5A drives a PTEN-PI3K/Akt feedback loop to support cell survival. *Liver Int* 2014; Nov 11 [Ahead of publication].
367. Bao W, Florea L, Wu N, Wang Z, Banaudha K, Qian J, et al. Loss of nuclear PTEN in HCV-infected human hepatocytes. *Infect Agent Cancer* 2014; 9: 23.
368. Peyrou M, Clément S, Maier C, Bourgoïn L, Branche E, Conzelmann S, et al. PTEN protein phosphatase activity regulates hepatitis C virus secretion through modulation of cholesterol metabolism. *J Hepatol* 2013; 59: 420-6.
369. Gericke A, Munson M, Ross AH. Regulation of the PTEN phosphatases. *Gene* 2006; 374: 1-9.
370. Peng X, Li Y, Walters KA, Rosenzweig ER, Lederer SL, Aicher LD, et al. Computational identification of hepatitis C virus associated microRNA-mRNA regulatory modules in human livers. *BMC Genomics* 2009; 10: 373.
371. Xie YF, Shu R, Jiang SY, Liu DL, Zhang XL. Comparison of microRNA profiles of human periodontal diseased and healthy gingival tissues. *Int J Oral Sci* 2011; 3: 125-34.
372. Napetschnig J, Wu H. Molecular basis of NF- κ B signaling. *Annu Rev Biophys* 2013; 42: 443-68.
373. Lawrence T. The nuclear factor NF- κ B pathway in inflammation. *Cold Spring Harb Perspect Biol* 2009; 1: a001651.
374. [Tai DI, Tsai SL, Chen YM, Chuang YL, Peng CY, Sheen IS, et al. Activation of nuclear factor kappaB in hepatitis C virus infection: implications for pathogenesis and hepatocarcinogenesis. *Hepatology* 2000; 31: 656-64.](#)
375. [Boya P, Larrea E, Sola I, Majano PL, Jiménez C, Civeira MP, et al. Nuclear factor-kappaB in the liver of patients with chronic hepatitis C: decreased RelA expression is associated with enhanced fibrosis progression. *Hepatology* 2001; 34: 1041-8.](#)
376. [Li ZH, Tang QB, Wang J, Zhou L, Huang WL, Liu RY, et al. Hepatitis C virus core protein induces malignant transformation of biliary epithelial cells by activating nuclear factor-kappaB pathway. *J Gastroenterol Hepatol* 2010; 25: 1315-20.](#)
377. [Gaweco AS, Wiesner RH, Porayko M, Rustgi VK, Yong S, Hamdani R, et al. Intra-graft localization of activated nuclear factor kappaB in recurrent hepatitis C virus disease following liver transplantation. *Hepatology* 2000; 31: 1183-91.](#)
378. [Li K, Li NL, Wei D, Pfeffer SR, Fan M, Pfeffer LM. Activation of chemokine and inflammatory cytokine response in hepatitis C virus-infected hepatocytes depends](#)

- [on Toll-like receptor 3 sensing of hepatitis C virus double-stranded RNA intermediates. *Hepatology* 2012; 55: 666-75.](#)
379. [Girard S, Vossman E, Misek DE, Podevin P, Hanash S, Bréchet C, et al. Hepatitis C virus NS5A-regulated gene expression and signaling revealed via microarray and comparative promoter analyses. *Hepatology* 2004; 40: 708-18.](#)
380. [Li S, Ye L, Yu X, Xu B, Li K, Zhu X, et al. Hepatitis C virus NS4B induces unfolded protein response and endoplasmic reticulum overload response-dependent NF-kappa B activation. *Virology* 2009; 391: 257-64.](#)
381. Mayo MW, Madrid LV, Westerheide SD, Jones DR, Yuan XJ, Baldwin AS, et al. PTEN blocks tumor necrosis factor-induced NF- κ B-dependent transcription by inhibiting the transactivation potential of the p65 subunit. *J Biol Chem* 2002; 277: 11116-25.
382. Asano T, Yao Y, Zhu J, Li D, Abbruzzese JL, Reddy SA. The PI3-kinase/Akt signaling pathway is activated due to aberrant Pten expression and targets transcription factors NF-kappa B and c-Myc in pancreatic cancer cells. *Oncogene* 2004; 23: 8571-80.
383. Gui J, Tian Y, Wen X, Zhang W, Zhang P, Gao J, et al. Serum microRNA characterization identifies miR-885-5p as a potential marker for detecting liver pathologies. *Clin Sci (Lond)* 2011; 120: 183-93.
384. [Zheng J, Wu C, Lin Z, Guo Y, Shi L, Dong P, et al. Curcumin up-regulates phosphatase and tensin homologue deleted on chromosome 10 through microRNA-mediated control of DNA methylation--a novel mechanism suppressing liver fibrosis. *FEBS J* 2014; 281: 88-103.](#)
385. [Zheng L, Chen X, Guo J, Sun H, Liu L, Shih DQ, et al. Differential expression of PTEN in hepatic tissue and hepatic stellate cells during rat liver fibrosis and its reversal. *Int J Mol Med* 2012; 30: 1424-30.](#)
386. [Takashima M, Parsons CJ, Ikejima K, Watanabe S, White ES, Rippe RA. The tumor suppressor protein PTEN inhibits rat hepatic stellate cell activation. *J Gastroenterol* 2009; 44: 847-55.](#)

References

387. Watanabe S, Horie Y, Kataoka E, Sato W, Dohmen T, Ohshima S, et al. Non-alcoholic steatohepatitis and hepatocellular carcinoma: lessons from hepatocyte-specific phosphatase and tensin homolog (PTEN)-deficient mice. *J Gastroenterol Hepatol* 2007; 22 Suppl 1: S96-S100.
388. [Bian EB, Huang C, Ma TT, Tao H, Zhang H, Cheng C, et al. DNMT1-mediated PTEN hypermethylation confers hepatic stellate cell activation and liver fibrogenesis in rats. *Toxicol Appl Pharmacol* 2012; 264: 13-22.](#)
389. [Zheng J, Wu C, Xu Z, Xia P, Dong P, Chen B, et al. Hepatic stellate cell is activated by microRNA-181b via PTEN/Akt pathway. *Mol Cell Biochem* 2015; 398: 1-9.](#)
390. [Shen W, Chen G, Dong R, Zhao R, Zheng S. MicroRNA-21/PTEN/Akt axis in the fibrogenesis of biliary atresia. *J Pediatr Surg* 2014; 49: 1738-41.](#)
391. Gabele E, Reif S, Tsukada S, Bataller R, Yata Y, Morris T, et al. The role of p70S6K in hepatic stellate cell collagen gene expression and cell proliferation. *J Biol Chem* 2005; 280: 13374-82.
392. White ES, Thannickal VJ, Carskadon SL, Dickie EG, Livant DL, Markwart S, et al. Integrin alpha4beta1 regulates migration across basement membranes by lung fibroblasts: a role for phosphatase and tensin homologue deleted on chromosome 10. *Am J Respir Crit Care Med* 2003; 168: 436-42.
393. Peyrou M, Bourgoin L, Foti M. PTEN in non-alcoholic fatty liver disease/non-alcoholic steatohepatitis and cancer. *Dig Dis* 2010; 28: 236-46.
394. Horie Y, Suzuki A, Kataoka E, Sasaki T, Hamada K, Sasaki J, et al. Hepatocyte specific Pten deficiency results in steatohepatitis and hepatocellular carcinomas. *J Clin Invest* 2004; 113: 1774-83.
395. [Watanabe S, Horie Y, Suzuki A. Hepatocyte-specific Pten-deficient mice as a novel model for nonalcoholic steatohepatitis and hepatocellular carcinoma. *Hepatol Res* 2005; 33: 161-6.](#)
396. Moon BC, Hernandez-Ono A, Stiles B, Wu H, Ginsberg HN. Apolipoprotein B secretion is regulated by hepatic triglyceride, and not insulin, in a model of increased hepatic insulin signaling. *Arterioscler Thromb Vasc Biol* 2012; 32: 236-46.
397. Sheikh MY, Choi J, Qadri I, Friedman JE, Sanyal AJ. Hepatitis C virus infection: Molecular pathways to metabolic syndrome. *Hepatology* 2008; 47: 2127-33.
398. Adinolfi LE, Gambardella M, Andreana A, Tripodi MF, Utili R, Ruggiero G. Steatosis accelerates the progression of liver damage of chronic hepatitis C patients and correlates with specific HCV genotype and visceral obesity. *Hepatology* 2001; 33: 1358-64.
399. Del Campo JA, Romero-Gómez M. Steatosis and insulin resistance in hepatitis C: A way out for the virus? *World J Gastroenterol* 2009; 15: 5014-9.

References

400. Syed GH, Amako Y, Siddiqui A. Hepatitis C virus hijacks host lipid metabolism. *Trends Endocrinol Metab* 2010; 21:33-40.
401. Lerat H, Honda M, Beard MR, Loesch K, Sun J, Yang Y, et al. Steatosis and liver cancer in transgenic mice expressing the structural and nonstructural proteins of hepatitis C virus. *Gastroenterology* 2002; 122: 352-65.
402. Shi ST, Polyak SJ, Tu H, Taylor DR, Gretch DR, Lai MM. Hepatitis C virus NS5A colocalizes with the core protein on lipid droplets and interacts with apolipoprotein. *Virology* 2002; 292: 198-210.

المخلص العربي

كتلة الحمض النووي الريبوزي الصغير ١٧~٩٢ وهدفه مماثل فوسفاتيز وتنسين (بيتين) في العدوى المزمنة بفيروس الإلتهاب الكبدي سي

مقدمة البحث:

تعتبر الإصابة بفيروس الإلتهاب الكبدي "سي" من أهم أسباب حدوث الإلتهاب الكبدي المزمن والتليف الكبدي وسرطان الكبد. وعلى الرغم من أن العوامل التي تسهم في استمرار الفيروس وتقدم مراحل الإصابة لم يتم بعد تحديدها فقد وجد أن الإصابة بالفيروس تؤدي إلى حدوث تغيرات في عدة مئات من الجينات، وهذا يؤثر على قدرة الجسم على التخلص من الفيروس وتقدم المرض.

الأحماض النووية الريبوزية "أ ن ر" الصغيرة هي عائلة من الأحماض النووية الريبوزية التي لا تكون بروتينات وتتراوح بين حوالي ٢٤-٢١ نيوكليوتيدات في الطول، وتلعب دوراً رئيسياً في تنظيم التعبير الجيني في مرحلة ما بعد النسخ مما يؤدي إلى تثبيط الجينات، وقد تبين أن "أ ن ر" الصغيرة موجودة ليس فقط في الأنسجة ولكن أيضاً تفرز من الخلايا ويمكنها الوصول إلى الدم، وبالتالي يمكن استخدامها كمؤشرات حيوية للكشف عن المرض. وعادة تتكون "أ ن ر" الصغيرة بشكل فردي وفي بعض الأحيان تتكون كتلة مكونة من مجموعة من "أ ن ر" الصغيرة الفردية التي تنشئ من نفس النسخة الجينية.

تتكون كتلة "أ ن ر" الصغير ١٧~٩٢ من ستة من "أ ن ر" الصغيرة الفردية. ويلقب جين هذه الكتلة باسم "الجين المضيف" "أ ن ر" الصغير-١٧. ومن المثير للاهتمام أن هذا الجين يستطيع نسخ بروتين مكون من ٧٠ حمض أميني يوصف بأنه "بروتين الجين المضيف" "أ ن ر" الصغير-١٧ ويمكنه الوصول إلى الدم مثل "أ ن ر" الصغيرة. وتعمل كتلة "أ ن ر" الصغير ١٧~٩٢ كنظم رئيسي لمجموعة واسعة من العمليات البيولوجية بما في ذلك تكاثر الخلايا والتمثيل الغذائي والاستجابة المناعية، والاستجابات الإلتهابية، وتكون الأوعية الدموية. كما وجد أن هذه الكتلة تنشط بصورة غير مباشرة العامل النووي كبا "بي" وهو أحد العوامل المسببة للإلتهابات. وتعمل كتلة "أ ن ر" الصغير ١٧~٩٢ على تثبيط العديد من الجينات منها مماثل فوسفاتيز وتنسين "بيتين". وقد وجد أن نقص "بيتين" في خلايا الكبد يؤدي إلى التدهن الكبدي وتليف الكبد.

الهدف من البحث:

الهدف من هذا البحث هو تقييم مستوي بروتين الجين المضيف "أ ن ر" الصغير-١٧ في البلازما واطهار "بيتين" في الكبد في مرضى العدوى المزمنة بفيروس الإلتهاب الكبدي "سي" وعلاقتهما بالتدهن والإلتهاب والتليف الكبدي.

حالات البحث:

اشتملت الدراسة على ٣٠ من مرضى العدوى المزمنة بفيروس الإلتهاب الكبدي "سي" الذين لم يسبق علاجهم، بعد منهم ١٨ مريضاً مصاباً بالإلتهاب الكبدي "سي" المزمن و ١٢ مريضاً لديهم تليف بالكبد. وجميع المرضى لديهم أجسام مضادة للفيروس والحمض النووي للفيروس في الدم وتغيرات بأنسجة الكبد نتيجة العدوى المزمنة بالفيروس. كما اشتملت الدراسة على ١٥ من الأشخاص الأصحاء كعينة ضابطة. وقد استثنى من البحث المرضى المصابين بفيروس الإلتهاب الكبدي "بي" ومرض الكبد الناتج عن تناول الكحوليات أو الإصابة بالبلهارسيا، أو غيرها من الأسباب المعروفة لأمراض الكبد المزمنة. كما تم استبعاد المرضى المصابين بارتفاع درجة الحرارة، أو الإلتهابات حادة، أو أورام سرطانية، أو أمراض قلبية أو صدرية أو كلوية أو أمراض مزمنة أخرى مثل مرض السكري أو أمراض النسيج الضام أو الذين تلقوا علاجاً للإلتهاب الكبدي "سي" المزمن.

خطة البحث و طرق الفحص:

- اشتملت خطة البحث و طرق الفحص علي تقييم كل المرضى و الاشخاص الاصحاء كالاتي:
- الفحص الاكلينيكي الشامل مع التركيز علي مدة الإصابة الظاهرية بفيروس الإلتهاب الكبدى "سى" والأسباب المحتملة للأصابة والأعراض والمظاهر الاكلينيكية لمرض الكبد المزمن وحجم الكبد والطحال.
- الفحص باستخدام الموجات فوق الصوتية لفحص نمط صدى الكبد و تشخيص التليف الكبدى واستسقاء البطن وتضخم الطحال.
- الفحوصات المعملية و خاصة عد الدم الكامل و اختبارات وظائف الكبد [مستوى انزيمات الكبد (انزيم ناقل أمين الاسبارتات وانزيم ناقل أمين الألانين وانزيم ناقل جاما جلوتاميل) والالبومين والصفراء في مصل الدم ووقت البروثرومبين].
- قياس مستوى الحمض النووي لفيروس الإلتهاب الكبدى "سى" فى مصل الدم باستخدام التفاعل التسلسلى بأنزيم البوليميريز.
- قياس مستوى بروتين الجين المضيف "أ ن ر" الصغير-١٧ فى بلازما الدم باستخدام طريقة الإنزيم المرتبط بالإمتصاص المناعى (إيليزا).
- اخذ عينات من الكبد من مرضى العدوى المزمنة بفيروس الإلتهاب الكبدى "سى" وعمل الفحص الهستوباثولوجى للأنسجة لتحديد درجة النشاط الهستولوجى ومرحلة التليف الكبدى حسب تقسيم ميتافير وكذلك تحديد درجة التدهن الكبدى.
- وقد تم صبغ عينات الكبد من المرضى باستخدام الصبغة المناعية الهستولوجية الكيميائية بواسطة الأجسام المضادة نحو "بيتنن" والعامل النووي كابا "بى" وقد تم تقسيم درجة الصبغة المناعية كالآنى: "صفر" = عدم وجود صبغة بالخاليا، "١" = ضعيف الصبغة، "٢" = متوسط الصبغة، "٣" = شديد الصبغة.

نتائج البحث:

- أظهر التحليل الاحصائي للبيانات التى تم الحصول عليها من دراسه الحالية النتائج التالية :
- الأعراض التى عانى منها المرضى كالتالى: ألم بالجانب الأيمن الأعلى من البطن فى ١٦ (٥٣,٣٪) من المرضى بينما لم يعاني أيا من المرضى من اليرقان أو الاستسقاء أو نزيف سابق من الجهاز الهضمي.
- أظهر الفحص بالموجات فوق الصوتية للمرضى وجود تضخم بالكبد فى ٦ (٢٠٪) من المرضى، بينما كان حجم الكبد طبيعى فى ١٨ (٦٠٪) من المرضى ومنكمشا فى ٦ (٢٠٪) من المرضى. ووجد لمعان بالكبد فى ٦ (٢٠٪) من المرضى، بينما كانت درجة لمعان الكبد طبيعىة فى ١٤ (٤٦,٧٪) من المرضى ووجد تليف بالكبد فى ١٠ (٣٣,٣٪) من المرضى. وكان هناك تضخم بالطحال فى ١٢ (٤٠٪) من المرضى الذين كانوا جميعا يعانون من التليف الكبدى.
- أظهر متوسط مستوى انزيمات الكبد بمصل الدم ووقت البروثرومبين زيادة ذات دلالة احصائية فى المرضى بالمقارنة بالأشخاص الأصحاء فى حين لم يظهر اختلافا ذو دلالة احصائية فى تركيز الالبومين والصفراء فى مصل الدم بين المجموعتين .
- تراوح مستوى الحمض النووي للفيروس فى مصل الدم فى مرضى العدوى المزمنة بفيروس الإلتهاب الكبدى "سى" بين $10 \times 10^3 - 7400,02$ وحدة عالمية/ مليلتر بمتوسط $1333.02 \pm 1702.40 \times 10^3$ وحدة عالمية/ مليلتر.
- وجدت زيادة ذات دلالة احصائية فى مستوى بروتين الجين المضيف "أ ن ر" الصغير-١٧ فى بلازما الدم فى مرضى العدوى المزمنة بفيروس الإلتهاب الكبدى "سى" بالمقارنة بالأشخاص الأصحاء. كما وجدت زيادة ذات

دلالة احصائية في مستوى البروتين في بلازما الدم في مرضى الإلتهاب الكبدي "سى" المزمن ومرضى التليف الكبدى بالمقارنة بالأشخاص الأصحاء وفى مرضى التليف الكبدى بالمقارنة بمرضى الإلتهاب الكبدي "سى" المزمن.

■ برسم منحني خصائص تشغيل المتلقى (روك) وجد أن حساسية وخصوصية مستوى بروتين الجين المضيف "أ ن ر" الصغير-١٧ في بلازما الدم في التمييز بين مرضى العدوى المزمنة بفيروس الإلتهاب الكبدي "سى" والأشخاص الأصحاء هما ٨٣,٣ ٪ و ١٠٠ ٪ علي التوالي عند مستوي الحد الفاصل ٢٦,٦ بيكوجرام/مللييلتر في التمييز بين مرضى التليف الكبدى ومرضى الإلتهاب الكبدي "سى" المزمن هما ١٠٠ ٪ و ٨٨,٩ ٪ علي التوالي عند مستوي الحد الفاصل ٤٥,٥ بيكوجرام/مللييلتر.

■ تراوحت درجة النشاط الهيستولوجي في عينات الكبد من مرضى العدوى المزمنة بفيروس الإلتهاب الكبدي "سى" بين الدرجة الأولى في ٤ (١٣,٣ ٪) من المرضى والدرجة الثانية في ١٥ (٥٠ ٪) من المرضى والدرجة الثالثة في ١١ (٣٦,٧ ٪) من المرضى. أما مراحل التليف فقد تراوحت بين مرحلة ميتافير ١ في ٣ (١٠ ٪) من المرضى مرحلة ميتافير ٢ في ١١ (٣٦,٧ ٪) من المرضى و مرحلة ميتافير ٣ في ٤ (١٣,٣ ٪) من المرضى و مرحلة ميتافير ٤ في ١٢ (٤٠ ٪) من المرضى. وقد وجد التدهن الكبدي من الدرجة الأولى في ٨ (٢٦,٧ ٪) من المرضى والدرجة الثانية في ٧ (٢٣,٣ ٪) من المرضى والدرجة الثالثة في ٣ (١٠ ٪) من المرضى بينما لم يكن موجودا في ١٢ (٤٠ ٪) من المرضى.

■ وجد أن حساسية وخصوصية مستوى بروتين الجين المضيف "أ ن ر" الصغير-١٧ في بلازما الدم في التمييز بين المرضى الذين لديهم تليف كبدى بسيط (مرحلة ميتافير ١ أو ٢) والذين لديهم تليف كبدى شديد (مرحلة ميتافير ٣ أو ٤) هما ٩٣,٨ ٪ و ٩٢,٩ ٪ علي التوالي عند مستوي الحد الفاصل ٤٠,٣ بيكوجرام/مللييلتر.

■ أظهر استخدام الصبغة المناعية الهستولوجية الكيميائية لعينات الكبد من مرضى العدوى المزمنة بفيروس الإلتهاب الكبدي "سى" أن اظهر "بيتن" في الكبد كان ايجابيا في السيتوبلازم وأحيانا في نواة الخلايا في جميع المرضى. وقد وجد أن شدة الصبغة المناعية كانت ضعيفة في ٧ (٢٣,٣ ٪) من المرضى ومتوسطة في ١١ (٣٦,٧ ٪) من المرضى وشديدة في ١٢ (٤٠ ٪) من المرضى.

■ وجد نقص ذو دلالة احصائية في اظهر "بيتن" في الكبد في مرضى التليف الكبدى بالمقارنة بمرضى الإلتهاب الكبدي "سى" المزمن.

■ كما وجد أن اظهر العامل النووي كابا "بى" في الكبد كان ايجابيا في ٢٧ (٩٠ ٪) من مرضى العدوى المزمنة بفيروس الإلتهاب الكبدي "سى". وقد وجد أن شدة الصبغة المناعية كانت ضعيفة في ٥ (١٦,٧ ٪) من المرضى ومتوسطة في ١٦ (٥٣,٣ ٪) من المرضى وشديدة في ٦ (٢٠ ٪) من المرضى.

■ لم يظهر اختلاف ذو دلالة احصائية في اظهر العامل النووي كابا "بى" في الكبد بين مرضى الإلتهاب الكبدي "سى" المزمن ومرضى التليف الكبدى.

■ اظهر التحليل الاحصائي للعلاقات بين مستوى بروتين الجين المضيف "أ ن ر" الصغير-١٧ في بلازما الدم واطهار "بيتن" والعامل النووي كابا "بى" في الكبد مع العوامل الأخرى التي تمت دراستها في مرضى العدوى المزمنة بفيروس الإلتهاب الكبدي "سى" النتائج التالية:

- لم تظهر علاقة ذات دلالة احصائية بين كلا من مستوى بروتين الجين المضيف "أ ن ر" الصغير-١٧ في بلازما الدم من ناحية وعمر المريض ومدة الإصابة بالفيروس ومستوى الحمض النووي للفيروس في مصل الدم من ناحية أخرى.

- وجدت علاقة طردية ذات دلالة احصائية بين مستوى بروتين الجين المضيف "أ ن ر" الصغير-١٧ في بلازما الدم من ناحية ومستوى انزيم ناقل أمين الاسبارتات وانزيم ناقل أمين الألانين في مصل الدم ودرجة النشاط الهيستولوجي ومرحلة التليف الكبدى ودرجة التدهن الكبدي من ناحية أخرى.

- لم تظهر علاقة ذات دلالة احصائية بين مستوى بروتين الجين المضيف "أ ن ر" الصغير-١٧ في بلازما الدم ومستوى انزيم ناقل جاما جلوتاميل في مصل الدم.

- وجدت علاقة عكسية ذات دلالة احصائية بين مستوى بروتين الجين المضيف "أ ن ر" الصغير-١٧ في بلازما الدم واطهار "بيتين" في الكبد بينما وجدت علاقة طردية ذات دلالة احصائية بين مستوى هذا البروتين في بلازما الدم واطهار العامل النووي كابا "بى" في الكبد.
 - اظهر البحث علاقة عكسية ذات دلالة احصائية بين اظهار "بيتين" في الكبد من ناحية ومستوى انزيم ناقل جاما جلوتاميل في مصل الدم ودرجة النشاط الهيستولوجي ومرحلة التليف الكبدى ودرجة التدهن الكبدى من ناحية اخرى.
 - لم تظهر علاقة ذات دلالة احصائية بين اظهار "بيتين" في الكبد ومستوى انزيم ناقل أمين الاسبارتات وانزيم ناقل أمين الألانين في مصل الدم.
 - وجدت علاقة طردية ذات دلالة احصائية بين اظهار العامل النووي كابا "بى" في الكبد من ناحية ومستوى انزيم ناقل أمين الاسبارتات وانزيم ناقل أمين الألانين في مصل الدم ودرجة النشاط الهيستولوجي ومرحلة التليف الكبدى ودرجة التدهن الكبدى من ناحية اخرى.
 - لم تظهر علاقة ذات دلالة احصائية بين اظهار العامل النووي كابا "بى" في الكبد ومستوى انزيم ناقل جاما جلوتاميل في مصل الدم.
 - اظهر البحث وجود علاقة عكسية ذات دلالة احصائية بين اظهار "بيتين" واطهار العامل النووي كابا "بى" في الكبد.
- من هذه الدراسة يمكن استخلاص أن العدوى المزمنة بفيروس الإلتهاب الكبدى "سى" تؤدي الى تنشيط كتلة "أ ن ر" الصغير ٩٢~١٧ مما قد يؤدي الى حدوث الإلتهاب المزمن والتدهن والتليف الكبدى عن طريق تثبيط "بيتين" وتنشيط العامل النووي كابا "بى" في خلايا الكبد. لذا فإن هناك حاجة لاجراء المزيد من الابحاث لدراسة دور كتلة "أ ن ر" الصغير ٩٢~١٧ في تقدم المرض وحدث السرطان الكبدى الخلوى وكذلك تأثير الأدوية المضادة لفيروس الإلتهاب الكبدى "سى" في تعديل الخلل في نشاط الكتلة. كما أن هناك حاجة ماسة لاجراء الدراسات لتحديد مدى فاعلية استخدام مضادات كتلة "أ ن ر" الصغير ٩٢~١٧ واستخدام مثيل "بيتين" كعلاج لمرضى العدوى المزمنة بفيروس الإلتهاب الكبدى "سى" ومدى تأثيرهما على الإلتهاب المزمن والتدهن والتليف الكبدى. وكذلك دراسة استخدام مستوى بروتين الجين المضيف "أ ن ر" الصغير-١٧ في بلازما الدم كمؤشر سهل القياس لتقدم المرض والتليف الكبدى فى هؤلاء المرضى.

كتلة الحمض النووي الريبوزي الصغير ١٧~٩٢ وهدفه مماثل فوسفاتيز وتنسين (بيتن) في العدوى المزمنة بفيروس الإلتهاب الكبدى سى

رسالة علمية

مقدمة لكلية الطب – جامعة الإسكندرية
إيفاءً جزئياً لشروط الحصول على درجة

الماجستير فى الأمراض الباطنة

مقدمة من

سالى إسماعيل محمد الدميري

بكالوريوس الطب والجراحة

جامعة الإسكندرية

كلية الطب

جامعة الإسكندرية

٢٠١٥

كتلة الحمض النووي الريبوزى الصغير ١٧~٩٢ وهدفه مماثل فوسفاتيز وتنسين (بيتن) فى العدوى المزمنة بفيروس الإلتهاب الكبدى سى
مقدمة من

سالى إسماعيل محمد الدميري
بكالوريوس الطب والجراحة
كلية الطب – جامعة الإسكندرية

للحصول على درجة
الماجستير فى الأمراض الباطنة

لجنة المناقشة والحكم على الرسالة

الاستاذ الدكتور/ أحمد محمد الجوهري
أستاذ الأمراض الباطنة
وحدة امراض الكبد والمرارة
كلية الطب
جامعة الإسكندرية

الاستاذ الدكتور/ هدى عبد المجيد العجان
أستاذ الأمراض الباطنة
وحدة امراض الكبد والمرارة
كلية الطب
جامعة الإسكندرية

الاستاذ الدكتور/ محسن سلامة محمد
أستاذ طب الكبد
معهد الكبد القومي
جامعة المنوفية

موافقون

.....

.....

.....

التاريخ : ٢٠١٥/ ٣ / ٣١

السادة المشرفون

.....
الاستاذ الدكتور/ هدى عبد المجيد العجان

أستاذ الأمراض الباطنة

وحدة أمراض الكبد و المرارة

كلية الطب

جامعة الإسكندرية

.....
الاستاذ الدكتور/ صباح عبد الهادى محمود

استاذ الكيمياء الحيوية الطبية

كلية الطب

جامعة الإسكندرية

.....
الدكتورة / نيفين محمد فريد الديب

أستاذ مساعد الباثولوجيا

كلية الطب

جامعة الإسكندرية

المشرف المشارك

.....
الدكتور/ ايهاب مصطفى حسونة

مدرس الأمراض الباطنة

وحدة أمراض الكبد و المرارة

كلية الطب

جامعة الإسكندرية