Genetic polymorphisms in non-alcoholic fatty liver disease: Clues to pathogenesis and disease progression

Marko Duvnjak, Neven Baršić, Vedran Tomašić, Ivan Lerotić

Duvnjak M, Baršić N, Tomašić V, Lerotić I. Genetic polymorphisms in non-alcoholic fatty liver disease: Clues to pathogenesis and disease progression. World J Gastroenterol 2009; 15(48): 6023-6027 Available from: URL: http://www.wjgnet.com/1007-9327/15/6023.asp DOI: http://dx.doi.org/10.3748/wjg.15.6023

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) has emerged as the most common form of chronic liver disease. The spectrum of NAFLD ranges from simple steatosis through steatohepatitis (NASH) to advanced fibrosis and cirrhosis, and the minority of patients progress to end-stage liver disease requiring liver transplantation or develop hepatocellular carcinoma[1]. However, the vast majority of patients only have simple steatosis with a benign long-term prognosis. It has been observed that even when considering patients with similar environmental and metabolic NAFLD risk factors (diet, exercise, obesity and insulin resistance being the most important factors), they still differ largely in terms of disease phenotype and degree of progression[2]. This led to the research focus more recently being placed on genetic factors that may possibly have a role in NAFLD etiology, and genetic variability is now implied to be one of the most important determinants of disease phenotype and progression in individual patients.

GENETIC INFLUENCES IN NAFLD

Possible genetic risk for advanced NAFLD was initially suggested in studies which showed coexistence of NASH and/or cryptogenic cirrhosis within several kindreds, and it was not invariably associated with similar major metabolic risk factors[3,4]. Further evidence comes from reports of ethnic differences in the prevalence of steatosis, NASH and cryptogenic cirrhosis. The prevalence of all forms of NAFLD was shown to be highest in Hispanic and lowest in African American populations, and this variability did not always correlate with differences in the prevalence of major risk factors[5,6]. Furthermore, it was reported that Asian patients with NAFLD had a significantly lower body mass index (BMI) than all other racial groups[7].

As most of the common diseases today, NAFLD...
is considered to be a genetically complex disorder. In complex diseases, several or many different genes interact with environmental factors in determining disease presence or its phenotype, and individual genes only have a small effect on disease risk and can therefore be very difficult to identify. Methods for detecting genes in complex disorders have included family-based linkage studies, hypothesis-based candidate gene allele association studies, genome-wide single nucleotide polymorphism (SNP) scanning and, recently, microarray and proteomic studies. All of the data available on genes associated with NAFLD has so far come from the candidate gene association studies, where candidate genes are usually selected on the basis of their suggested role in disease pathogenesis, and the frequency of one or more known SNPs within or close to those genes is compared in cases and controls, in the search for a positive or negative association with the disease. Genes that are candidates for study in NAFLD have included genes influencing insulin resistance, fatty acid metabolism, oxidative stress, immune regulation and fibrosis development.

GENETIC POLYMORPHISMS

Peroxisome proliferator-activated receptor γ coactivator 1α (PPARGC1A)

PPARGC1A has been involved with different metabolic pathways, such as regulation of gene expression in glucose and lipid metabolism and transcriptional control of cellular metabolism, mainly through control of mitochondrial function and biogenesis. Several studies have shown that PPARGC1A regulates several key hepatic glucogenetic genes, which are directly involved in the homeostatic control of systemic energy metabolism, and PPARGC1A Gly482Serp polymorphism has also been associated with the development of insulin resistance, obesity and diabetes. PPARGC1A knockout mice are prone to develop hepatostasis due to a combination of reduced mitochondrial respiratory capacity and an increased expression of lipogenic genes. Yoneda et al. therefore examined 15 SNPs in the PPARGC1A gene and found that the rs2290602 polymorphism was significantly associated with NAFLD (more closely with NAFLD than with simple steatosis), and the frequency of the T allele (allele with rs2290602 polymorphism) was significantly higher in the NASH patients than in the control subjects. They also found that intrahepatic PPARGC1A mRNA expression was significantly lower in the TT genotype group than in the GG or GT group. On the other hand, Hui et al. did not find any association between the Gly482Ser variant and NAFLD in Chinese Han people. However, they have reported a correlation between C161T PPAR-γ gene SNP, consequent lower plasma levels of adiponectin and increased susceptibility to NAFLD.

Microsomal triglyceride transfer protein (MTTP)

A higher incidence of -493G/T polymorphism in the MTTP gene promoter has been reported in patients with NAFLD; GG homozygosity was associated with more severe liver histology and has been considered as a risk factor for NAFLD. Gambino et al. suggested that NASH patients with GG homozygosity have more atherogenic postprandial lipoprotein profiles and lipoprotein metabolism, which leads to increased peroxidative liver injury.

Leptin

Leptin is an adipocytokine whose main role is regulation of food intake. It probably has an important role in the pathogenesis of NAFLD; leptin-deficient ob/ob mice develop steatohepatitis when fed with a methionine-choline-deficient diet. Common variants in the human leptin receptor (LEPR) gene have been associated with traits of metabolic syndrome such as obesity, insulin resistance, type 2 diabetes mellitus and altered lipid metabolism, and possibly with NAFLD. The LEPR 3057 variant may link obesity to NAFLD in Chinese patients with type 2 diabetes mellitus through interference with leptin receptor signaling and regulation of lipid metabolism and insulin sensitivity.

Adiponectin

Adiponectin, an adipocyte-derived cytokine has an important role in mobilization, transport and muscle oxidation of free fatty acids leading to improvements in lipid profiles and insulin sensitivity. High levels of tumor necrosis factor-α (TNF-α) mRNA in adipose tissue and high plasma TNF-α concentrations were detected in adiponectin-knockout mice, resulting in severe diet-induced insulin resistance. Musso et al. reported that the adiponectin SNPs 45TT and 276GT/TT were more prevalent in Italian NAFLD patients than in the general population; these polymorphisms independently predicted the severity of liver disease in NASH and exhibited a blunted postprandial adiponectin response and higher postprandial triglyceride levels.

Hepatic lipase

Zhan et al. investigated the prevalence of the hepatic lipase gene promoter polymorphism at position -514 in Chinese patients with NAFLD. They reported a higher frequency of the CC genotype and C allele in the NAFLD group and both the CC genotype and CT genotypes were associated with higher relative risk for development of NAFLD.

Phosphatidylethanolamine N-methyltransferase (PEMT)

Phosphatidylethanolamine is required for hepatic formation and secretion of very low density lipoproteins, and it has been shown that a choline-deficient diet leads to accumulation of fat droplets in hepatocyte cytosol and the development of fatty liver. PEMT catalyzes de novo synthesis of phosphatidylethanolamine and is responsible for approximately 30% of phosphatidylethanolamine formed in liver, the rest of it being synthesized by another pathway from dietary choline. Song et al. showed that SNP (G to A substitution in exon 8) that leads to Val to Met substitution at residue 175 of PEMT is associated
with significantly diminished activity of the enzyme, and determined the frequency of this polymorphism in NAFLD patients and controls. The loss of function AA genotype (Met/Met) occurred more frequently in NAFLD patients than in control subjects, which led to the conclusion that genetically inherited low PEMT activity is an important risk factor for developing NAFLD. This was further proven in a Japanese study published by Dong et al.[3]. Although the polymorphism is much rarer in the Japanese population than in Caucasians, the frequency of A allele was significantly higher in NASH patients compared with controls. NASH patients who were carriers of the Val175Met variant had significantly lower BMI and were more frequently non-obese than NASH patients who were wild-type homozygotes, further proving the role of this polymorphism as an independent risk factor for NAFLD development.

**Methylenetetrahydrofolate reductase (MTHFR)**

Sazci et al.[32] investigated whether the C677T and A1298C polymorphisms of the MTHFR gene which lead to hyperhomocysteinemia and development of liver steatosis were associated with NASH. They found that the MTHFR 1298C allele was associated with increased steatosis were associated with NASH. They found that patients and control subjects. There were no significant differences in the allele frequencies of any of the six polymorphisms among the group of patients with NAFLD and the control group, including the -238 polymorphism which was previously reported to be associated with NAFLD in Italian patients, but this polymorphism was much less frequent in the Japanese population[30]. However, the frequency of the -1031C polymorphism was significantly higher in the NASH group compared to the simple steatosis group, as was the frequency of the -863A polymorphism. The frequency of other polymorphisms did not differ significantly between the two groups. These two polymorphisms were also associated with higher levels of insulin resistance measured by HOMA-IR.

**TNF-α**

TNF-α has long been known to be one of the key cytokines in the development of all chronic liver diseases. In NAFLD, it has been shown that it may cause hepatocyte injury and apoptosis, neutrophil chemotaxis, and hepatic stellate cell activation, as well as contribute to systemic and hepatic insulin resistance[34–36]. Crespo et al.[37] found that obese patients with NASH compared to those without NASH have significantly increased liver expression of TNF-α and its receptor p55, as well as increased expression of TNF-α in adipose tissue. Valenti et al.[38] investigated the relationship between insulin resistance, occurrence of NAFLD and -238 and -308 TNF-α promoter polymorphisms known to be associated with an increased release of this cytokine. The prevalence of the 238 TNF-α polymorphism was higher in subjects with NAFLD than controls, and patients with these polymorphisms had higher insulin resistance indices. Tokushige et al.[39] determined the prevalence of several TNF-α promoter region polymorphisms (positions -1031, -863, -857, -308 and -238) in a group of Japanese NAFLD patients and control subjects. There were no significant differences in the allele frequencies of any of the six polymorphisms among the group of patients with NAFLD and the control group, including the -238 polymorphism which was previously reported to be associated with NAFLD in Italian patients, but this polymorphism was much less frequent in the Japanese population[30]. However, the frequency of the -1031C polymorphism was significantly higher in the NASH group compared to the simple steatosis group, as was the frequency of the -863A polymorphism. The frequency of other polymorphisms did not differ significantly between the two groups. These two polymorphisms were also associated with higher levels of insulin resistance measured by HOMA-IR.

**Transforming growth factor-β1 (TGF-β1) and angiotensin II**

TGF-β1 and angiotensin II are two molecules that have been extensively studied in models of liver fibrogenesis. TGF-β1 has a major role in development of liver fibrosis by activation of hepatic stellate cells and stimulation of production of extracellular matrix proteins[40]. Besides its well-known effects in the cardiovascular and renal systems, angiotensin II also has an established role in liver fibrogenesis, and based on those observations, studies with angiotensin II receptor antagonists have been performed in patients with NASH[41,42]. There have been several suggestions that profibrotic effects of angiotensin II in heart and kidney are mediated by induction of transcription of TGF-β1[43,44]. Considering these data, and based on their previous study in hepatitis C patients, Dixon et al.[45] investigated the relationship between the

---

**Table 1  Studies of genetic polymorphisms in non-alcoholic fatty liver disease (NAFLD) included**

| Gene                                      | Polymorphism | Ref.          | No. of patients with NAFLD included in the study |
|-------------------------------------------|--------------|---------------|--------------------------------------------------|
| Peroxisome proliferator-activated receptor-γ coactivator | rs2290662    | Yoneda et al.[41], 2008 | 115                                                |
| In (PPARGC1A)                             | Gly482Ser    | Hui et al.[47], 2008 | 96                                                 |
| Microsomal triglyceride transfer protein (MTTP) | -499G/T      | Namikawa et al.[49], 2004 | 63                                                 |
| Human leptin receptor                     | G3057A       | Lu et al.[36], 2009 | 104                                                |
| Adiponectin                               | 45C/T and 276G/T | Musso et al.[40], 2008 | 70                                                 |
| Hepatic lipase                            | -514C/T      | Zhan et al.[35], 2008 | 106                                                |
| Phosphatidylethanolamine N-methyltransferase (PEMT) | Val175Met | Song et al.[45], 2005 | 28                                                 |
| Methylenetetrahydrofolate reductase (MTHFR) | C677T and A1298C | Dong et al.[47], 2007 | 107                                                |
| Tumor necrosis factor-α (TNF-α)           | -238 and -308 | Valenti et al., 2002 | 99                                                 |
|                                           | -1031, -863, -857, -308 and -238 | Tokushige et al.[36], 2007 | 102                                                |
| Angiotensinogen                           | G-6A         | Dixon et al.[45], 2003 | 105                                                |
| Transforming growth factor-β1 (TGF-β1)    | Pro25Arg     |               |                                                   |
presence of advanced fibrosis and angiotensinogen G-6A polymorphism or TGF-β1 Pro25Arg polymorphism in a group of severely obese patients. There was no correlation between either high angiotensin or TGF-β1 producing genotypes alone and hepatic fibrosis. However, patients who inherited both high angiotensin and TGF-β1 producing polymorphisms had a higher risk of advanced fibrosis. These data also support the hypothesis that angiotensin II stimulated TGF-β1 production promotes hepatic fibrosis.

A comprehensive list of the above-mentioned polymorphism studies is shown in Table 1.

CONCLUSION

While all this and other evidence clearly indicates that genetic factors have a key role in determining susceptibility to advanced forms of NAFLD and its progression, the majority of studies mentioned here had small sample sizes and therefore limited statistical power, which makes it rather difficult to draw definitive conclusions. However, we believe that the development and wider availability of high throughput genetic technologies together with careful design and performance of large multicenter studies with adequate statistical power will soon provide new insights in this vast and very interesting area. Further study and new data on genetic effects have many potential benefits – advancement in understanding the pathogenesis of NAFLD, identification of new potential treatment targets, and, eventually, categorization of patients with respect to disease prognosis, leading to a change in management approach in specific subgroups of patients. Despite the currently limited data on genetic influences in NAFLD and all the difficulties in studying them, we believe that most of the variability in NAFLD presentation will eventually be attributed to and explained by variations in SNP frequencies and their effects on the function of factors involved in the pathogenesis of the disease.

REFERENCES

1. Duvnjak M, Leočič I, Baršič N, Tomaseč V, Virovič Jukić L, Velagić V. Pathogenesis and management issues for non-alcoholic fatty liver disease. World J Gastroenterol 2007; 13: 4539-4550
2. Wanless IR, Lentz JS. Fatty liver hepatitis (steatohepatitis) and obesity: an autopsy study with analysis of risk factors. Hepatology 1990; 12: 1106-1110
3. Struhen VM, Hespenthalie EE, Caldwell SH. Nonalcoholic steatohepatitis and cryptoic cirrhosis within kindreds. J Am Med 2000; 108: 9-13
4. Willner IR, Waters B, Patil SR, Reuben A, Morelli J, Riely DR. NAFLD: patients with nonalcoholic steatohepatitis: insulin resistance, familial tendency, and severity of disease. Am J Gastroenterol 2001; 96: 2957-2961
5. Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, Grundy SM, Hobbs HH. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. Hepatology 2004; 40: 1387-1395
6. Browning JD, Kuman KS, Saboorian MH, Thiele DL. Ethnic differences in the prevalence of cryptoic cirrhosis. Am J Gastroenterol 2004; 99: 292-298
7. Caldwell SH, Harris DM, Patrie JT, Hespenthalie EE. Is NASH underdiagnosed among African Americans? Am J Gastroenterol 2002; 97: 1496-1500
8. Farrell GC. Non-alcoholic steatohepatitis: what is it, and why is it important in the Asia-Pacific region? J Gastroenterol Hepatol 2003; 18: 124-138
9. Kelly DP. Scarpulla RC. Transcriptional regulatory circuits controlling mitochondrial biogenesis and function. Genes Dev 2004; 18: 357-368
10. Puigserver P, Wu Z, Park CW, Graves R, Wright M, Spiegelman BM. A cold-inducible coactivator of nuclear receptors linked to adaptive thermogenesis. Cell 1998; 92: 829-839
11. Estebaner H, Oberkofer H, Linnemayr V, Iglseder B, Lehman JJ, Finck BN, Schaeffer PJ, Wende W, Waters B, Patil SR, Reuben A, Morelli J, Riely DR. Increased risk of obesity associated with the variant allele of the PPARGC1A Gly482Ser polymorphism in physically inactive elderly men. Diabetologia 2006; 49: 496-500
12. Hara K, Toke B, Okada T, Kadowaki H, Akanuma Y, Ito C, Kimura S, Kadowaki T. A genetic variation in the PGC-1 gene could confer insulin resistance and susceptibility to Type II diabetes. Diabetesologia 2002; 45: 740-743
13. Rådstråle M, Johansson LE, Rastam L, Lindblad U. Increased risk of obesity associated with the variant allele of the PPARGC1A Gly482Ser polymorphism in physically inactive elderly men. Diabetologia 2006; 49: 496-500
14. Xie G, Guo D, Li Y, Liang S, Wu Y. The impact of severity and type of obesity on association of PGC-1α gene with blood pressure and risk of hypertension. BMC Cardiovasc Disord 2007; 7: 33
15. Leone TC, Lehman JJ, Finck BN, Schaeffer PJ, Wende AR, Boudina S, Courtois M, Wozniak D, Sambandam N, Bernal-Mizrachi C, Chen Z, Holloszy JO, Medeiros DM, Schmidt RE, Saffitz JE, Abel ED, Semenovich CF, Kelly DP. PGC-1α deficiency causes multi-system energy metabolic derangements: muscle dysfunction, abnormal weight control and hepatic steatosis. PLoS Biol 2005; 3:e101
16. Yoneda M, Hotta K, Nozaki Y, Endo H, Uchiyama T, Mawatari H, Iida H, Kato S, Hosono K, Fujita K, Yoneda K, Takahashi H, Kikikoshi H, Kobayashi N, Inamori M, Abe Y, Kubota K, Saito S, Maeyama S, Wada K, Nakajima A. Association between PPARGC1A polymorphisms and the occurrence of nonalcoholic fatty liver disease (NAFLD). BMC Gastroenterol 2008; 8: 27
17. Hui Y, Yu-Yuan L, Yu-Qiang N, Wei-Hong S, Yan-Lei D, Xiao-Bo L, Yong-Jian Z. Effect of peroxisome proliferator-activated receptors-gamma and co-activator-1alpha genetic polymorphisms on plasma adiponectin levels and susceptibility of non-alcoholic fatty liver disease in Chinese people. Liver Int 2008; 28: 385-392
18. Namikawa C, Shu-Ping Z, Vyselaar JR, Nozaki Y, Nemoto Y, Ono M, Akisawa N, Saibara T, Hiroi M, Enzan H, Onishi S. Polymorphisms of microsomal triglyceride transfer protein gene and manganese superoxide dismutase gene in non-alcoholic steatohepatitis. J Hepatol 2004; 40: 781-786
19. Gambino R, Cassader M, Pagano G, Durazzo M, Musso G. Polymorphism in microsomal triglyceride transfer protein: a link between liver disease and atherogenic postprandial lipid profile in NASH? Hepatology 2007; 45: 1097-1107
20. Leclercq IA, Farrell GC, Schriemer R, Robertson GR. Leptin is essential for the hepatic fibrogenic response to chronic liver injury. J Hepatol 2002; 37: 206-213
21. Wauters M, Considine RV, Chagnon Y, Mertens I, Rankinen T, Bouchard C, Van Gaal LF. Leptin levels, leptin receptor gene expression, and energy metabolism in women. Obes Res 2002; 10: 594-400
22. Chagnon YC, Rankinen T, Snyder EE, Weisnagel SJ, Pérusse L, Bouchard C. The human obesity gene map: the 2002 update. Obes Res 2003; 11: 313-367
23. Liu CY, Wang YQ, Liu HY, Ji J, Li WH, Bie HL, Li LX. [Relationship of variation 3057 G-->A of exon 20 of leptin receptor gene to lipid metabolism and fat distribution of children with obesity.] Zhonghua Yi Xue Yi Chuan Xuexi Za Zhi
24 Lu H, Sun J, Sun L, Shu X, Xu Y, Xie D. Polymorphism of human leptin receptor gene is associated with type 2 diabetic patients complicated with non-alcoholic fatty liver disease in China. J Gastroenterol Hepatol 2009; 24: 229-232
25 Czaja MJ. Liver injury in the setting of steatosis: crosstalk between adipokine and cytokine. Hepatology 2004; 40: 19-22
26 Mantzoros CS, Li T, Manson JE, Meigs JB, Hu FB. Circulating adiponectin levels are associated with better glycemic control, more favorable lipid profile, and reduced inflammation in women with type 2 diabetes. J Clin Endocrinol Metab 2005; 90: 4542-4548
27 Maeda N, Shimomura I, Kishida K, Nishizawa H, Matsuda M, Nagaretani H, Furuyama N, Kondo H, Takahashi M, Arita Y, Komuro R, Ouchi N, Kihara S, Tochino Y, Okutomi K, Horie M, Takeda S, Aoyama T, Funahashi T, Matsuzawa Y. Diet-induced insulin resistance in mice lacking adiponectin/ACRP30. Nat Med 2002; 8: 731-737
28 Musso G, Gambino R, De Michieli F, Durazzo M, Pagano G, Cassader M. Adiponectin gene polymorphisms modulate acute adiponectin response to dietary fat: Possible pathogenetic role in NASH. Hepatology 2008; 47: 1167-1177
29 Zhan Q, Li YY, Nie YQ, Zhou YJ, DU YL, Sha WH, Wang H. [Association of hepatic lipase gene promoter polymorphism -514C/T with nonalcoholic fatty liver disease] Zhonghua Ganzangbing Zazhi 2008; 16: 375-378
30 Buchman AL, Dubin MD, Moukarzel AA, Jenden DJ, Roch M, Rice KM, Gornbein J, Ament ME. Choline deficiency: a cause of hepatic steatosis during parenteral nutrition that can be reversed with intravenous choline supplementation. Hepatology 1995; 22: 1399-1403
31 Song J, da Costa KA, Fischer LM, Kohlmeier M, Kwock L, Wang S, Zeisel SH. Polymorphism of the PEMT gene and susceptibility to nonalcoholic fatty liver disease (NAFLD). FASEB J 2005; 19: 1266-1271
32 Dong H, Wang J, Li C, Hirose A, Nozaki Y, Takahashi M, Ono M, Akisawa N, Iwasaki S, Saibara T, Onishi S. The phosphatidylethanolamine N-methyltransferase gene V175M single nucleotide polymorphism confers the susceptibility to NASH in Japanese population. J Hepatol 2007; 46: 915-920
33 Sazci A, Ergul E, Aygün C, Akpınar G, Senturk O, Hulagü S. Methylene tetrahydrofolate reductase gene polymorphisms in patients with nonalcoholic steatohepatitis (NASH). Cell Biochem Funct 2008; 26: 291-296
34 Arkan MC, Hevener AL, Gretener FR, Maeda S, Li ZW, Long JM, Wynshaw-Boris A, Poli G, Olefsky J, Karin M. IKK-beta links inflammation to obesity-induced insulin resistance. Nat Med 2005; 11: 191-198
35 Nagai H, Matsumaru K, Fong G, Kaplowitz N. Reduced glutathione depletion causes necrosis and sensitization to tumor necrosis factor-alpha-induced apoptosis in cultured mouse hepatocytes. Hepatology 2002; 36: 55-64
36 Ding WX, Yin XM. Dissection of the multiple mechanisms of TNF-alpha-induced apoptosis in liver injury. J Cell Mol Med 2004; 8: 445-454
37 Crespo J, Cayón A, Fernández-Gil P, Hernández-Guerra M, Mayorga M, Domínguez-Diez A, Fernández-Escalante JC, Pons-Romero F. Gene expression of tumor necrosis factor alpha and TNF-receptors, p55 and p75, in nonalcoholic steatohepatitis patients. Hepatology 2001; 34: 1158-1163
38 Valenti L, Fracanzani AL, Dongiovanni P, Santorelli G, Branchi A, Taioli E, Fiorelli G, Fargion S. Tumor necrosis factor alpha promoter polymorphisms and insulin resistance in nonalcoholic fatty liver disease. Gastroenterology 2002; 122: 274-280
39 Tokushige K, Takakura M, Tsuchiya-Matsushita N, Tanai M, Hashimoto E, Shiratori K. Influence of TNF gene polymorphisms in Japanese patients with NASH and simple steatosis. J Hepatol 2007; 46: 1104-1110
40 Friedman SL. Cytokines and fibrogenesis. Semin Liver Dis 1999; 19: 120-140
41 Bataller R, Sancho-Bru P, Ginés P, Brenner DA. Liver fibrogenesis: a new role for the renin-angiotensin system. Antioxid Redox Signal 2005; 7: 1346-1355
42 Yokohama S, Tokusayi Y, Nakamura K, Tamaki Y, Okamoto S, Okada M, Aso K, Hasegawa T, Aoshima M, Miyokawa N, Haneda M, Yoneda M. Inhibitory effect of angiotensin II receptor antagonist on hepatic stellate cell activation in non-alcoholic steatohepatitis. World J Gastroenterol 2006; 12: 322-326
43 Gibbons GH, Pratt RE, Dzau VJ. Vascular smooth muscle cell hypertrophy vs. hyperplasia. Autocrine transforming growth factor-beta 1 expression determines growth response to angiotensin II. J Clin Invest 1992; 90: 456-461
44 Noble NA. Border WA. Angiotensin II in renal fibrosis: should TGF-beta rather than blood pressure be the therapeutic target? Semin Nephrol 1997; 17: 455-466
45 Dixon JB, Bhathal PS, Jonsson JR, Dixon AF, Powell EE, O’Brien PE. Pro-fibrotic polymorphisms predictive of advanced liver fibrosis in the severely obese. J Hepatol 2003; 39: 967-971