Advanced Research in Gastroenterology & Hepatology
ISSN: 2472-6400

Juniper Publishers
key to the Researchers

Review Article
Volume 5 Issue 1– April 2017
DOI: 10.19080/ARGH.2017.05.555653

Adv Res Gastroentero Hepatol

The Role of Vascular Endothelial Growth Factor (VEGF) in Non-Alcoholic Fatty Liver Disease (NAFLD) Progression: A Systematic Review

Yue Xu[1,2], Lin-Lin Lu[3,4], Yong-Ning Xin[1,2,3*] and Shi-Ying Xuan[1,2,3*]

[1]*Department of Gastroenterology, Dalian Medical University, China*

[2]*Department of Gastroenterology, Qingdao Municipal Hospital, China*

[3]*Digestive Disease Key Laboratory of Qingdao, China*

[4]*Central Laboratories, Qingdao Municipal Hospital, China*

Submission: April 21, 2017; **Published:** April 27, 2017

***Corresponding author:** Shi-Ying Xuan, Department of Gastroenterology, Qingdao Municipal Hospital, 1 Jiaozhou Road, Qingdao 266011, Shandong Province, China, Tel: +86-532-88905508; Fax: +8653288905293; Email: xuansydxy@163.com

Yong-Ning Xin, Department of Gastroenterology, Qingdao Municipal Hospital, 1 Jiaozhou Road, Qingdao 266011, Shandong Province, China, Tel: +86-532-82789463; Fax: +865-3285-968-434; Email:xinyongning@163.com

Abstract

Non-alcoholic fatty liver disease (NAFLD) has been the popular chronic liver disease which incidence rate rises yearly. Many studies showed that patients with NAFLD are characterized by obvious vascular endothelial dysfunction. Vascular endothelial growth factor (VEGF) is a known inducer of angiogenesis, which influence the vascular endothelial function and play a key in coronary artery disease (CAD). However, there was still no systemic discussion on the role of VEGF in the progression of NAFLD. Many studies showed VEGF plays an important role in the fat metabolism of liver, the formation of NAFLD, also the etiology of HCC. This article review will have a specific review.

Keywords: Nonalcoholic fatty liver disease; Vascular endothelial growth factor; Coronary artery disease; Non-alcoholic steatohepatitis; Hepatocellular carcinoma; Genetic polymorphisms

Introduction

Non-alcoholic fatty liver disease (NAFLD) represents a wide histological spectrum of liver disease, ranging from simple steatosis with no or minor inflammation, to non-alcoholic steatohepatitis (NASH), where inflammation and is present, with or without fibrosis [1]. Between 10 and 25% individuals with NAFLD may develop cirrhosis and hepatocellular carcinoma (HCC) [2]. NAFLD is the most common cause of chronic liver disease in all ethnic groups [3]. The global prevalence of NAFLD is 25.24% [4]. Many studies have indicated that NAFLD is a strong independent risk factor for coronary artery disease (CAD) [5-7]. And NAFLD patients are suggested undergo periodic cardiovascular risk assessment. Cardiovascular disease (CVD) is the main reason which caused the death of NAFLD patients [8]. The histologic severity of liver injury and inflammation is strongly associated with an increased cardiovascular risk and an atherogenic lipid profile [9]. A major pathogenic contributor to CAD is atherosclerosis, which is primarily characterized by endothelial dysfunction [10,11]. Also, patients with NAFLD are characterized by obvious vascular endothelial dysfunction [12]. The VEGF is closely related with vascular endothelial dysfunction. Its family contains five members in mammals, VEGF-A, placenta growth factor, VEGF-B, VEGF-C and VEGF-D, which regulate vasculogenesis, angiogenesis and lymphangiogenesis by transducing signals to VEGF receptors [13-16]. Recent investigations have discovered that the decreased expression of VEGF is very common in CAD patients [10,17]. And, Serum VEGF levels were significantly elevated in patients with simple steatosis and borderline significantly

elevated in NASH patients. Hepatic gene expression of VEGF was slightly decreased in NASH patients compared to simple steatosis patients [18]. Besides, with further research on VEGF, the genetic polymorphisms have been found in playing a role in the progression of NAFLD. In this study, we will have a systematic review.

The VEGF influence the fat metabolism according to sinusoidal endothelial cell (SEC) fenestrations and the space of Disse in the liver

VEGF signaling in the liver is essential for the development of the functional sinusoidal vasculature required for efficient plasma lipoprotein uptake. Reduction of VEGF in the liver results in a disrupted vascular network, a lack of sinusoidal endothelial cell (SEC) fenestrations and a non-functional space of Disse [19]. Each hepatocyte is connected with sinusoidal vascular channels, which are lined by sinusoidal endothelial cells (SECs), with the space of Disse separating hepatocytes and sinusoidal cells [20]. The SECs are fenestrated lack a basement membrane, which allows only particles smaller than the fenestrae to reach the parenchymal cells. The fenestrae also allow efficient macromolecules, including lipoproteins and chylomicron remnants, from the blood to the hepatocytes for processing [21]. Cholesterlo-rich lipoproteins are rapidly removed from the circulation by the liver, which occur by receptor-mediated endocytosis on hepatic microvilli within the space of Disse [22]. Morphological studies have highlighted the importance of the space of Disse, and SEC and hepatocyte structural features, such as fenestrations and microvilli, respectively, for effective lipoprotein-remnant passage from the blood to hepatocytes [23]. Furthermore, Kai Sun et.al demonstrated that overexpression of VEGF-A in adipose tissue promoted an increase in lipid clearance and a decrease in high fat diet induced Hepatic Steatosis by inhibiting the activation of vascular endothelial growth factor receptor 2 (VEGFR2) [24]. In short, upregulate the expression of VEGF will make for the transportation of lipoprotein in the liver.

The expression of VEGF influence the progression of NAFLD by leptin and hypoxia

VEGF expression colocalized with leptin receptors (ObR). ObR activation in human hepatic stellate cells (HSCs) promoted the increasing of leptin [25]. Leptin is the first described adipokine [26]. Leptin play an important role in confining the storage of triglycerides to the adipocytes, while limiting triglyceride storage in non-adipose tissues, including the liver, thus protecting them from lipotoxicity and lipoapoptosis [27]. Leptin play an important role in the lipid metabolism, the expression of VEGF is associated with leptin. A recent meta-analysis indicates that circulating leptin levels are higher in patients with NAFLD than in controls, and higher serum leptin levels were associated with an increased severity of NAFLD [28]. This is in agreement with the above-mentioned evidence of inflammatory-mediated damage related to leptin and potential involvement in NASH pathogenesis. Moreover, Hypoxia increases the expression of VEGF by activating hypoxia-inducible factor-1alpha (HIF-1α). And leptin can upregulate HIF to promote the expression of VEGF [29]. *Rosmorduc O* et al. [30] found that hypoxia acts not only as an aggravating factor of cell damage and inflammation, but also as an inhibitor of liver regeneration, a major stimulus of angiogenesis and fibrogenesis, and a promoter of liver carcinogenesis.

VEGF plays an important role in HCC

NAFLD represents an increasingly important etiology of HCC with annual cumulative incidence rates ranging from 2% to 12% in cohorts of NAFLD cirrhosis [31]. From the 1980s to the present, the VEGF-VEGFR system has been demonstrated to be the major regulator of tumor angiogenesis (VEGF2-4). VEGF, also known as VEGF-A, is a protein with vascular permeability activity that was originally purified from a fluid secreted by a tumor [32]. Gao et al. [33] did a research to investigate the effects of the vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR)/K-ras signaling pathways on miRNA21 levels in hepatocellular carcinoma tissues in rats. They made a conclusion that the VEGF/VEGFR/K-ras signaling pathway might promote the occurrence and development of hepatocellular carcinoma cells through regulating expression of miRNA21, which has potential clinical value for the development of therapies against biological targets and determining prognosis for patients with hepatocellular carcinoma. Additionally, VEGF not only promoted the angiogenesis and fibrosis of NAFLD/NASH, but also facilitated the forming of HCC [25]. The patients with HCC have higher VEGF levels, particularly the T allele in VEGF -C936T. VEGF could be a potential biomarker for HCC, while AFP could be used to distinguish between patients with HCC and cirrhosis or hepatitis C virus [34].

VEGF gene polymorphisms involved in NAFLD progression

Genetic polymorphisms are reported to influence predisposition of individuals in NAFLD progression. Hsieh MC showed individuals with the VEGF-C rs1485766 A/A genotype compared to those with wild-type homozygotes had a significantly higher risk for HCC. A high frequency of an advanced stage and a low frequency of being positive for cirrhosis were respectively shown in HCC patients with the VEGF-C rs7664413 CT/TT and rs3775194 GC/CC genotypes [35]. Liu et al. [36] presented the VEGFA 2578C/A polymorphism may play a potential role in the development and clinical outcome of HCC among Chinese Han population. VEGFA 2578C/A polymorphism was significantly associated with decreased risk of HCC. Furthermore, the 2578C/A polymorphism was associated with significantly decreased postoperative recurrence and improved overall survival of resected HCC patients. Recent study have demonstrated that in Hubei Han population VEGF-460 T/C (rs833061), and +936 C/T (rs3025039) polymorphism are associated with the risk of NAFLD [37]. However, VEGF is associated with the progression of fatty liver disease, but we still need to do further research.

How to cite this article: Vikram K. ACL Reconstruction- The Past and the Present. Adv Res Gastroentero Hepatol 2017; 3(3): 555612. DOI: 10.19080/ARGH.2017.05.555653

Conclusion

NAFLD, the hepatic manifestation of metabolic syndrome, is the most common cause of abnormal liver enzymes and has been associated with an increased risk for development of CAD. The decreased expression of VEGF in the liver results in a disrupted vascular network, a lack of SEC fenestrations and a non-functional space of Disse, leading to lipid metabolism disorder. And, VEGF-A suppress the accumulation of lipoproteins. Leptin and hypoxia upregulated the expression of VEGF. And, the elevated leptin levels are associated with the expression of VEGF. Leptin take part in potential involvement in NASH pathogenesis. VEGF is also related with HCC, especially VEGF-A. VEGF may be a potential biomarker of HCC. With further research, VEGF gene polymorphisms have been recognized. VEGF levels play an important role in NAFLD progression. It may be the marker, which can evaluate the progression of NAFLD. We need to pay more attention on it.

Author contribution

Yue Xu, Linlin Lu, Quanjiang Dong and Yongning Xin; drafting of the manuscript: Yue Xu; critical revision of the manuscript for important intellectual content: Linlin Lu and Yongning Xin; study supervision: Yongning Xin, Shiying Xuan.

Acknowledgement

We would like to thank the Qingdao Municipal Hospital for the supports.

Supported by

Dr. Yong-Ning Xin, Prof. Shi-Ying Xuan reported receiving research grants and honoraria from Qingdao Municipal Hospital.

Conflict of Interest

There is no any economic interest or any conflict of interest exists.

References

1. Farrell GC, Larter CZ (2006) Nonalcoholic fatty liver disease: from steatosis to cirrhosis. Hepatology 43(2 Suppl 1): S99-S112.
2. Zain SM, Mohamed R, Cooper DN, Razali R, Rampal S, et al. (2014) Genome-wide analysis of copy number variation identifies candidate gene loci associated with the progression of non-alcoholic fatty liver disease. PLoS One 9: e95604.
3. Setiawan VW, Stram DO, Porcel J, Lu SC, Le Marchand L, et al. (2016) Prevalence of chronic liver disease and cirrhosis by underlying cause in understudied ethnic groups: The multiethnic cohort. Hepatology 64(6): 1969-1977.
4. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, et al. (2016) Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 64(1): 73-84.
5. Choi DH, Lee SJ, Kang CD, Park MO, Choi DW, et al. (2013) Nonalcoholic fatty liver disease is associated with coronary artery disease in Koreans. World J Gastroenterol 19(38): 6453-6457.
6. Kim D, Choi SY, Park EH, Lee W, Kang JH, et al. (2012) Nonalcoholic fatty liver disease is associated with coronary artery calcification. Hepatology 56(2): 605-613.
7. Chiang CH, Huang CC, Chan WL, Chen JW, Leu HB (2010) The severity of non-alcoholic fatty liver disease correlates with high sensitivity C-reactive protein value and is independently associated with increased cardiovascular risk in healthy population. Clin Biochem 43(18): 1399-1404.
8. Ong JP, Pitts A, Younossi ZM (2008) Increased overall mortality and liver-related mortality in non-alcoholic fatty liver disease. J Hepatol 49(4): 608-612.
9. Alkhouri N, Tamimi TA, Yerian L, Lopez R, Zein NN, et al. (2010) The inflamed liver and atherosclerosis: a link between histologic severity of nonalcoholic fatty liver disease and increased cardiovascular risk. Dig Dis Sci 55(9): 2644-2650.
10. Di Y, Zhang D, Hu T, Li D (2015) miR-23 regulate the pathogenesis of patients with coronary artery disease. Int J Clin Exp Med 8(7): 11759-11769.
11. Watt J, Kennedy S, Ahmed N, Hayhurst J, McClure JD, et al. (2016) The relationship between oxidised LDL, endothelial progenitor cells and coronary endothelial function in patients with CHD. Open Heart 3(1): e000342.
12. Sookoian S, Pirola CJ (2008) Non-alcoholic fatty liver disease is strongly associated with carotid atherosclerosis: a systematic review. J Hepatol 49(4): 600-607.
13. Ferrara N, Kerbel RS (2005) Angiogenesis as a therapeutic target. Nature 438(7070): 967-974.
14. Shibuya M (2011) Involvement of Flt-1 (VEGF receptor-1) in cancer and preeclampsia. Proc Jpn Acad Ser B Phys Biol Sci 87(4): 167-178.
15. Shibuya M, Claesson-Welsh L (2006) Signal transduction by VEGF receptors in regulation of angiogenesis and lymphangiogenesis. Exp Cell Res 312(5): 549-560.
16. Alitalo K, Carmeliet P (2002) Molecular mechanisms of lymphangiogenesis in health and disease. Cancer Cell 1(3): 219-227.
17. Qin W, Xie W, Xia N, He Q, Sun T (2016) Silencing of Transient Receptor Potential Channel 4 Alleviates oxLDL-induced Angiogenesis in Human Coronary Artery Endothelial Cells by Inhibition of VEGF and NF-kappaB. Med Sci Monit 22: 930-936.
18. Coulon S, Francque S, Colle I, Verrijken A, Blomme B, et al. (2012) Evaluation of inflammatory and angiogenic factors in patients with non-alcoholic fatty liver disease. Cytokine 59(2): 442-449.
19. Carpenter B, Lin Y, Stoll S, Raffai RL, McCuskey R, et al. (2005) VEGF is crucial for the hepatic vascular development required for lipoprotein uptake. Development 132(4): 3293-3303.
20. McCuskey RS, Reilly FD (1993) Hepatic microvasculature: dynamic structure and its regulation. Semin Liver Dis 13(1): 1-12.
21. Smedsrod B, De Bleser PJ, Braet F, Lovisetti P, Vanderkerken K, et al. (1994) Cell biology of liver endothelial and Kupffer cells. Gut 35(11): 1509-1516.
22. Cooper AD (1997) Hepatic uptake of chylomicron remnants. J Lipid Res 38(11): 2173-2192.
23. Fraser R, Dobbs BR, Rogers GW (1995) Lipoproteins and the liver sieve: the role of the fenestrated sinusoidal endothelium in lipoprotein metabolism, atherosclerosis, and cirrhosis. Hepatology 21(3): 863-874.
24. Sun K, Wernstedt Asterholm I, Kusminski CM, Bueno AC, Wang ZV, et al.

 How to cite this article: Vikram K. ACL Reconstruction- The Past and the Present. Adv Res Gastroentero Hepatol 2017; 3(3): 555612. DOI: 10.19080/ARGH.2017.05.555653

(2012) Dichotomous effects of VEGF-A on adipose tissue dysfunction. Proc Natl Acad Sci U S A 109(15): 5874-5879.

25. Aleffi S, Petrai I, Bertolani C, Parola M, Colombatto S, et al. (2005) Upregulation of proinflammatory and proangiogenic cytokines by leptin in human hepatic stellate cells. Hepatology 42(6): 1339-1348.
26. Halaas JL, Gajiwala KS, Maffei M, Cohen SL, Chait BT, et al. (1995) Weight-reducing effects of the plasma protein encoded by the obese gene. Science 269(5223): 543-546.
27. Unger RH, Zhou YT, Orci L (1999) Regulation of fatty acid homeostasis in cells: novel role of leptin. Proc Natl Acad Sci U S A 96: 2327-2332.
28. Polyzos SA, Aronis KN, Kountouras J, Raptis DD, Vasiloglou MF, et al. (2016) Circulating leptin in non-alcoholic fatty liver disease: a systematic review and meta-analysis. Diabetologia 59(1): 30-43.
29. Matsumoto K, Imagawa S, Obara N, Suzuki N, Takahashi S, et al. (2006) 2-Oxoglutarate downregulates expression of vascular endothelial growth factor and erythropoietin through decreasing hypoxia-inducible factor-1alpha and inhibits angiogenesis. J Cell Physiol 209(2): 333-340.
30. Rosmorduc O, Housset C (2010) Hypoxia: a link between fibrogenesis, angiogenesis, and carcinogenesis in liver disease. Semin Liver Dis 30(3): 258-270.
31. Wong CR, Nguyen MH, Lim JK (2016) Hepatocellular carcinoma in patients with non-alcoholic fatty liver disease. World J Gastroenterol 22(7): 8294-8303.
32. Senger DR, Galli SJ, Dvorak AM, Perruzzi CA, Harvey VS, et al. (1983) Tumor cells secrete a vascular permeability factor that promotes accumulation of ascites fluid. Science 219(4587): 983-985.
33. Gao JZ, Wang YL, Li J, Wei LX (2015) Effects of VEGF/VEGFR/K-ras signaling pathways on miRNA21 levels in hepatocellular carcinoma tissues in rats. Genet Mol Res 14(1): 671-679.
34. Yvamoto EY, Ferreira RF, Nogueira V, Pinhe MA, Tenani GD, et al. (2015) Influence of vascular endothelial growth factor and alpha-fetoprotein on hepatocellular carcinoma. Genet Mol Res 14(4): 17453-17462.
35. Hsieh MC, Hsu HT, Hsiao PC, Yang SF, Yeh CB, et al. (2014) Role of VEGF-C gene polymorphisms in susceptibility to hepatocellular carcinoma and its pathological development. J Clin Lab Anal 28(3): 237-244.
36. Liu F, Luo L, Wei Y, Wang W, Wen T, et al. (2017) Association of VEGFA polymorphisms with susceptibility and clinical outcome of hepatocellular carcinoma in a Chinese han population. Oncotarget 8(10): 16488-16497.
37. Wu P, Hua Y, Tan S, Li M, Yongxiang S, et al. (2015) Interactions of smoking with rs833061 polymorphism on the risk of non-alcoholic fat liver disease in Hubei Han population: a preliminary case-control study. Iran J Basic Med Sci 18(11): 1112-1117.

DOI: 10.19080/ARGH.2017.05.555653