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EDITORIAL

Is there a role for adaptive immunity in nonalcoholic steatohepatitis?

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Abstract

The growing diffusion of nonalcoholic fatty liver disease (NAFLD) is a consequence of the worldwide increase in the prevalence of obesity. Oxidative stress is widely recognized to play a pivotal role in NAFLD evolution to nonalcoholic steatohepatitis (NASH). Here we review recent evidence suggesting that oxidative stress-derived antigens originating within fatty livers stimulate both humoral and cellular adaptive immune responses and the possible mechanisms involved in sustaining hepatic inflammation in NASH.

Key words: Liver; Adaptive immunity; Nonalcoholic steatohepatitis; Hepatic inflammation; Nonalcoholic fatty liver disease

Core tip: Nonalcoholic fatty liver disease (NAFLD) is becoming one of the most common hepatic diseases, yet the factors responsible for the wide inter-individual variability in NAFLD evolution to nonalcoholic steatohepatitis are still poorly understood. In this Editorial, we comment on recent evidence suggesting the involvement of adaptive immune responses in sustaining hepatic inflammation during NAFLD evolution.

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INTRODUCTION

One of the consequences of the epidemical worldwide diffusion of obesity is the growing prevalence of nonalcoholic fatty liver disease (NAFLD) that has become the most frequent hepatic lesion in western countries[1-3]. Although NAFLD is most often benign, in about 20%-30% of the patients steatosis evolves to nonalcoholic steatohepatitis (NASH) and fibrosis[1-3], making NAFLD an increasingly important cause of hepatic cirrhosis. In recent past, many studies have investigated the

pathogenesis of NAFLD/NASH[4]. However, several issues concerning the mechanisms responsible for promoting lobular inflammation are still incompletely understood. In particular, it is unclear why only a fraction of NAFLD patients develop steatohepatitis and what are the factors responsible for the large inter-individual variability in the disease evolution to fibrosis. Lymphocytes represent along with macrophages the most frequent inflammatory cells in lobular and periportal infiltrates of NASH[5]. This has several analogies with that observed in the adipose tissue of obese subjects where lymphocyte infiltration has emerged as an important player in orchestrating inflammation[6,7]. In fact, chemokines released by fat-resident macrophages recruit to the adipose tissue $CD4^+$/$CD8^+$ T-lymphocytes and natural killer T-cells (NKT), that, in turn, stimulate macrophage activation and the release of pro-inflammatory mediators[6,7]. B-cell are also involved in the process by driving T-cell activation and secreting pro-inflammatory cyto/chemokines[8]. Accordingly, T- or B-cell-null mice are less susceptible to fat inflammation and insulin resistance when fed a high fat diet[9,10].

ROLE OF OXIDATIVE STRESS-MEDIATED IMMUNE RESPONSES IN NAFLD EVOLUTION

In spite of the growing importance of adaptive immunity in stimulating adipose tissue inflammation, so far little attention has been paid to the possible involvement of similar mechanisms in NASH. Oxidative stress is a key feature of NAFLD/NASH[11,12] and many data show that lipid peroxidation products arisen from the oxidation of phospholipids can elicit humoral and cellular immune responses by forming immunogenic adducts through the interaction with cellular proteins[13]. In this regard, our experimental data have shown that 40%-60% of both adults and children with NAFLD/NASH have circulating antibodies against lipid peroxidation-derived antigens, namely malonyldialdehyde (MDA) and 4-hydroxynonenal[14,15]. Noteworthy, high titres of these antibodies are also associated with increased hepatic inflammation, and advanced fibrosis in, respectively children[15] and adults[14]. Similar antibodies against lipid peroxidation-derived antigens are detectable in a dietary rat model of NAFLD and reducing lipid peroxidation by supplementation with the antioxidant N-acetylcysteine prevents antibody response and ameliorates hepatic injury[16]. In line with these observations, experiments using mice with NASH induced by feeding a methionine and choline deficient (MCD) diet demonstrate that $CD4^+$ and $CD8^+$ T-lymphocytes are recruited within the liver and their prevalence parallels the worsening of parechymal injury and lobular inflammation[17]. Both lymphocyte subsets express the CD69 activation marker and $CD4^+$ T-cells show an increased interferon-γ (IFN-γ) production indicating that liver infiltrating lymphocytes have an activated phenotype[17]. Concomitantly, we have also observed a stimulation of humoral immunity with an increase of circulating IgG recognizing antigens derived from protein modification by lipid peroxidation derived adducts[17]. Interestingly, the same antigens are also recognized by hepatic T-cells confirming that oxidative stress can represent the source of neo-antigens able to promote adaptive immune responses[17]. The characterization of the epitopes recognized by circulating antibodies associated with human NASH has revealed that they mainly interact with the cyclic methyl-1,4-dihydroxypyridine-3,5-dicarbaldehyde adducts also known as malonyldialdehyde-acetaldehyde (MAA) adducts[14] which originate by the combined interaction of these aldehydes with protein lysine ε-amino groups[18]. MAA adducts are known to be very antigenic[18]. Furthermore, a recent study by Henning *et al*[19] has shown that the development of MCD-induced NASH is associated with an early expansion in hepatic mature myeloid dendritic cells, which acquire the capacity to specifically stimulate $CD4^+$ T-cells. Thus, this combination can likely drive the activation of adaptive immunity during the onset of NASH. It is noteworthy that immune reactions toward lipid peroxidation-derived epitopes, including the MAA adducts, characterize alcoholic liver disease in both humans and experimental animals[20-22]. In heavy drinkers elevated titres of IgG recognizing lipid peroxidation-related antigens are associated with a 5-fold increase in circulating tumor necrosis factor (TNF)-α levels as compared to subjects without these antibodies and with an enhanced probability to progress to more severe liver injury[23]. Moreover, antigens derived from oxidative modification of low density lipoprotein are also among the triggers of adaptive immune mechanisms involved in the evolution of atherosclerosis and anti-MAA antibodies predict coronary artery disease in atherosclerotic patients[24]. This latter analogy might have clinical relevance in the light of the data suggesting that NAFLD/NASH and atherosclerosis share common pathogenetic mechanisms and the presence of NASH increases the risk of atherosclerotic ischemic complications[25].

INTERACTION BETWEEN INNATE AND ADAPTIVE IMMUNITY IN NASH EVOLUTION

More insides in understanding of the possible role of adaptive immunity in sustaining NASH-associated hepatic inflammation have been obtained by immunizing mice with MDA-derived protein adducts, that are among the antigens related to oxidative stress detected in both in human and experimental NASH. By this approach, we have observed that the stimulation of immune responses worsens parenchymal injury and lobular inflammation in mice receiving the MCD diet and that these effects are associated with an enhanced hepatic lymphocyte infiltration[17]. In these animals, $CD4^+$ T-cell depletion with specific antibodies demonstrates that Th-1 polarized $CD4^+$ T-cells are able to stimulate

hepatic macrophages through the expression of CD40 ligand and IFN-γ[17]. On their turn, by releasing TNF-α, interleukin 12 (IL-12), reactive oxygen species and nitric oxide macrophages further contributes in promoting lymphocyte functions, oxidative stress and parenchymal injury. In fact, $CD4^+$ T-cell ablation in MCD-fed MDA-immunized mice significantly improves liver damage and lobular inflammation[17]. Interestingly, IFN-γ deficiency attenuates steatohepatitis and hepatic fibrosis in mice fed with the MCD diet[26], while interference with CD40/CD154 dyad reduces adipose tissue inflammation in obese mice[27]. Altogether, these results indicate that Th-1 $CD4^+$ T cells activation might represent one of the mechanisms by which adaptive immunity can sustain hepatic inflammation during NASH progression. Overall, these findings are relevant for the human disease since both paediatric and adult NASH are characterized by an up-regulation in liver IFN-γ expression and an increase in circulating $CD4^+$ T-cells producing IFN-γ[28,29]. This does not exclude that additional mechanisms might also be involved. For instance, Tank *et al*[30] have recently reported an increase in Th-17 $CD4^+$ T-cells in mice with steatosis induced by feeding a high fat diet. They also have observed an up-regulation of Th-17 related cytokines (IL-17, IL-21, IL-23) in liver biopsies of NASH patients[30]. In our hands, $CD4^+$ T cells activation in MCD-fed MDA-immunized mice does not affect ROR-γt as well as IL-17a hepatic gene expression[17]. Nonetheless, the actual role of $CD4^+$ Th-17 T-cells in the pathogenesis of NASH requires further investigations, as IL-17 up-regulation has been associated to the pathogenesis of liver fibrosis in mice[31].

Although B-cell depletion reduces fat inflammation in obese mice[10], so far the role of humoral immunity in NASH is poorly investigated. Our preliminary results indicate that in MCD-induced steatohepatitis the presence of antibodies recognizing MDA-antigens is associated with IgG deposition within the inflammatory infiltrates suggesting the possibility that these antibodies may contribute to hepatic damage by inducing antibody-dependent cytotoxicity or complement activation. On this latter respect, Rensen *et al*[32] have recently reported extensive complement activation in liver biopsies of NASH patients, which in turn is associated with enhanced hepatocyte death, granulocyte infiltration and higher liver expression of IL-1β, IL-6 and IL-8 mRNAs. Furthermore, in the livers of immunized mice we have observed that the up-regulation in the B-cell markers parallel with that of pro-inflammatory cytokines. Nonetheless, further investigations are needed to better clarify the possible involvement of humoral responses in NASH.

IS THERE A ROLE OF ADAPTIVE IMMUNITY IN NASH PROGRESSION TO FIBROSIS AND HEPATOCELLULAR CARCINOMA?

In recent years, NAFLD/NASH has not only been recognized to be an important cause of hepatic fibrosis/cirrhosis, but has also been associated with the growing prevalence of the hepatocellular-carcinoma (HCC)[33]. In this latter respect, the possible relevance of adaptive immune mechanisms has emerged from a recent report showing that lymphocyte responses promote HCC development in a dietary model of NASH consisting in mice feeding with a choline deficient high fat diet (CD-HFD)[34]. In this study, Wolf *et al*[34] have observed that NASH and hepatic fibrosis parallel with the liver recruitment of activated $CD4^+$, $CD8^+$ T and NKT cells. Moreover, after 12 mo a substantial fraction CD-HCF-fed animals develops HCC, while $\beta 2m^{-/-}$ mice lacking $CD8^+$ T- and NKT cells are protected from both NASH and HCC[34]. These findings are in line with recent data pointing to an involvement of NKT-cells in the evolution of chronic liver disease[35]. In particular, NKT cell expansion characterizes advanced NASH in both humans and rodents, while MCD-fed NKT cells deficient mice show lower hepatic inflammation and fibrosis than wild type littermates[36,37]. On the same line, we have reported that an increased prevalence of hepatic NKT cells is associated with the worsening of steatohepatitis in MDA-immunized mice receiving the MCD diet[17]. A stimulation in the macrophage production of CXCL16, a chemokine specifically involved in NKT cell recruitment along with an elevation in hepatic levels of IL-15 have been proposed to regulate NKT cell pool in NASH[38,39]. In accord with the importance of IL-15 in supporting T- and NKT cell differentiation and survival[40], we have observed that IL-15 is selectively up-regulated in MDA-immunized MCD-fed mice concomitantly with the expansion of NKT cells, while $CD4^+$ T cell ablation significantly lower the intrahepatic IL-15 mRNA level[17]. This suggests that Th-1 responses might promote NKT cell expansion through IL-15 up-regulation. At present, the mechanisms by which NKT cells contribute to liver injury in NASH are still poorly understood. Syn *et al*[41] have proposed that osteopontin (OPN) producing NKT cells can sustain NASH evolution to fibrosis. An over-expression of liver OPN has been described both in humans and rodents suffering from advanced NASH[41-43], whereas OPN-deficient mice are protected from the development of steatohepatitis and fibrosis induced by the MCD diet[42,44]. In our hands, liver OPN content is selectively up-regulated in immunized MCD-fed mice concurrently with NKT cell recruitment and OPN-producing NKT cells are also increased in the livers of these animals[17]. This could explain the stimulation in collagen deposition that is evident in these animals, as OPN can directly promote collagen production by activated hepatic stellate cells[45]. OPN has also been proposed to induce ductular reaction[46] that is associated with an increased risk of fibrosis evolution in NASH patients[47,48].

CONCLUSION

Available evidence indicates that immune responses stimulated by oxidative stress-related antigens can

sustain the progression of experimental NASH through the Th-1 activation of $CD4^+$ T-cells, which, in turn, stimulate macrophage M1 responses and liver $CD8^+$ T- and NKT cell recruitment. These data along with the findings in humans support the possible contribution of adaptive immunity in the processes driving NAFLD evolution. However, further researches are required to better characterize the interaction between innate and adaptive immunity in sustaining hepatic inflammation and to evaluate the possible application to NASH therapy of the large variety of molecules already under study in other conditions characterized by impaired immune regulation or autoimmunity.

REFERENCES

1 **Neuschwander-Tetri BA**, Caldwell SH. Nonalcoholic steatohepatitis: summary of an AASLD Single Topic Conference. *Hepatology* 2003; **37**: 1202-1219 [PMID: 12717402]
2 **Fabbrini E**, Sullivan S, Klein S. Obesity and nonalcoholic fatty liver disease: biochemical, metabolic, and clinical implications. *Hepatology* 2010; **51**: 679-689 [PMID: 20041406]
3 **Farrell GC**, Larter CZ. Nonalcoholic fatty liver disease: from steatosis to cirrhosis. *Hepatology* 2006; **43**: S99-S112 [PMID: 16447287]
4 **Tilg H**, Moschen AR. Evolution of inflammation in nonalcoholic fatty liver disease: the multiple parallel hits hypothesis. *Hepatology* 2010; **52**: 1836-1846 [PMID: 21038418]
5 **Brunt EM**. Pathology of nonalcoholic fatty liver disease. *Nat Rev Gastroenterol Hepatol* 2010; **7**: 195-203 [PMID: 20195271]
6 **Kaminski DA**, Randall TD. Adaptive immunity and adipose tissue biology. *Trends Immunol* 2010; **31**: 384-390 [PMID: 20817556]
7 **Sell H**, Habich C, Eckel J. Adaptive immunity in obesity and insulin resistance. *Nat Rev Endocrinol* 2012; **8**: 709-716 [PMID: 22847239]
8 **Winer DA**, Winer S, Chng MH, Shen L, Engleman EG. B Lymphocytes in obesity-related adipose tissue inflammation and insulin resistance. *Cell Mol Life Sci* 2014; **71**: 1033-1043 [PMID: 24127133]
9 **Nishimura S**, Manabe I, Nagasaki M, Eto K, Yamashita H, Ohsugi M, Otsu M, Hara K, Ueki K, Sugiura S, Yoshimura K, Kadowaki T, Nagai R. CD8+ effector T cells contribute to macrophage recruitment and adipose tissue inflammation in obesity. *Nat Med* 2009; **15**: 914-920 [PMID: 19633658]
10 **DeFuria J**, Belkina AC, Jagannathan-Bogdan M, Snyder-Cappione J, Carr JD, Nersesova YR, Markham D, Strissel KJ, Watkins AA, Zhu M, Allen J, Bouchard J, Toraldo G, Jasuja R, Obin MS, McDonnell ME, Apovian C, Denis GV, Nikolajczyk BS. B cells promote inflammation in obesity and type 2 diabetes through regulation of T-cell function and an inflammatory cytokine profile. *Proc Natl Acad Sci USA* 2013; **110**: 5133-5138 [PMID: 23479618]
11 **Seki S**, Kitada T, Yamada T, Sakaguchi H, Nakatani K, Wakasa K. In situ detection of lipid peroxidation and oxidative DNA damage in non-alcoholic fatty liver diseases. *J Hepatol* 2002; **37**: 56-62 [PMID: 12076862]
12 **Chalasani N**, Deeg MA, Crabb DW. Systemic levels of lipid peroxidation and its metabolic and dietary correlates in patients with nonalcoholic steatohepatitis. *Am J Gastroenterol* 2004; **99**: 1497-1502 [PMID: 15307867]
13 **Witztum JL**, Lichtman AH. The influence of innate and adaptive immune responses on atherosclerosis. *Annu Rev Pathol* 2014; **9**: 73-102 [PMID: 23937439]
14 **Albano E**, Mottaran E, Vidali M, Reale E, Saksena S, Occhino G, Burt AD, Day CP. Immune response towards lipid peroxidation products as a predictor of progression of non-alcoholic fatty liver disease to advanced fibrosis. *Gut* 2005; **54**: 987-993 [PMID: 15951547]
15 **Nobili V**, Parola M, Alisi A, Marra F, Piemonte F, Mombello C, Sutti S, Povero D, Maina V, Novo E, Albano E. Oxidative stress parameters in paediatric non-alcoholic fatty liver disease. *Int J Mol Med* 2010; **26**: 471-476 [PMID: 20818484]
16 **Baumgardner JN**, Shankar K, Hennings L, Albano E, Badger TM, Ronis MJ. N-acetylcysteine attenuates progression of liver pathology in a rat model of nonalcoholic steatohepatitis. *J Nutr* 2008; **138**: 1872-1879 [PMID: 18806095]
17 **Sutti S**, Jindal A, Locatelli I, Vacchiano M, Gigliotti L, Bozzola C, Albano E. Adaptive immune responses triggered by oxidative stress contribute to hepatic inflammation in NASH. *Hepatology* 2014; **59**: 886-897 [PMID: 24115128]
18 **Thiele GM**, Klassen LW, Tuma DJ. Formation and immunological properties of aldehyde-derived protein adducts following alcohol consumption. *Methods Mol Biol* 2008; **447**: 235-257 [PMID: 18369923]
19 **Henning JR**, Graffeo CS, Rehman A, Fallon NC, Zambirinis CP, Ochi A, Barilla R, Jamal M, Deutsch M, Greco S, Ego-Osuala M, Bin-Saeed U, Rao RS, Badar S, Quesada JP, Acehan D, Miller G. Dendritic cells limit fibroinflammatory injury in nonalcoholic steatohepatitis in mice. *Hepatology* 2013; **58**: 589-602 [PMID: 23322710]
20 **Xu D**, Thiele GM, Beckenhauer JL, Klassen LW, Sorrell MF, Tuma DJ. Detection of circulating antibodies to malondialdehyde-acetaldehyde adducts in ethanol-fed rats. *Gastroenterology* 1998; **115**: 686-692 [PMID: 9721166]
21 **Rolla R**, Vay D, Mottaran E, Parodi M, Traverso N, Aricó S, Sartori M, Bellomo G, Klassen LW, Thiele GM, Tuma DJ, Albano E. Detection of circulating antibodies against malondialdehyde-acetaldehyde adducts in patients with alcohol-induced liver disease. *Hepatology* 2000; **31**: 878-884 [PMID: 10733543]
22 **Vidali M**, Stewart SF, Albano E. Interplay between oxidative stress and immunity in the progression of alcohol-mediated liver injury. *Trends Mol Med* 2008; **14**: 63-71 [PMID: 18222109]
23 **Vidali M**, Occhino G, Ivaldi A, Rigamonti C, Sartori M, Albano E. Combination of oxidative stress and steatosis is a risk factor for fibrosis in alcohol-drinking patients with chronic hepatitis C. *Am J Gastroenterol* 2008; **103**: 147-153 [PMID: 18184121]
24 **Anderson DR**, Duryee MJ, Shurmur SW, Um JY, Bussey WD, Hunter CD, Garvin RP, Sayles HR, Mikuls TR, Klassen LW, Thiele GM. Unique antibody responses to malondialdehyde-acetaldehyde (MAA)-protein adducts predict coronary artery disease. *PLoS One* 2014; **9**: e107440 [PMID: 25210746 DOI: 10.1371/journal.pone.0107440]
25 **Bieghs V**, Rensen PC, Hofker MH, Shiri-Sverdlov R. NASH and atherosclerosis are two aspects of a shared disease: central role for macrophages. *Atherosclerosis* 2012; **220**: 287-293 [PMID: 21930273]
26 **Luo XY**, Takahara T, Kawai K, Fujino M, Sugiyama T, Tsuneyama K, Tsukada K, Nakae S, Zhong L, Li XK. IFN-γ deficiency attenuates hepatic inflammation and fibrosis in a steatohepatitis model induced by a methionine- and choline-deficient high-fat diet. *Am J Physiol Gastrointest Liver Physiol* 2013; **305**: G891-G899 [PMID: 24136786]
27 **Poggi M**, Engel D, Christ A, Beckers L, Wijnands E, Boon L, Driessen A, Cleutjens J, Weber C, Gerdes N, Lutgens E. CD40L deficiency ameliorates adipose tissue inflammation and metabolic manifestations of obesity in mice. *Arterioscler Thromb Vasc Biol* 2011; **31**: 2251-2260 [PMID: 21817098]
28 **Inzaugarat ME**, Ferreyra Solari NE, Billordo LA, Abecasis R, Gadano AC, Cherñavsky AC. Altered phenotype and functionality of circulating immune cells characterize adult patients with nonalcoholic steatohepatitis. *J Clin Immunol* 2011; **31**: 1120-1130 [PMID: 21845516]
29 **Ferreyra Solari NE**, Inzaugarat ME, Baz P, De Matteo E, Lezama C, Galoppo M, Galoppo C, Cherñavsky AC. The role of innate cells is coupled to a Th1-polarized immune response in pediatric nonalcoholic steatohepatitis. *J Clin Immunol* 2012; **32**: 611-621 [PMID: 22228550]
30 **Tang Y**, Bian Z, Zhao L, Liu Y, Liang S, Wang Q, Han X, Peng Y,

Chen X, Shen L, Qiu D, Li Z, Ma X. Interleukin-17 exacerbates hepatic steatosis and inflammation in non-alcoholic fatty liver disease. *Clin Exp Immunol* 2011; **166**: 281-290 [PMID: 21985374]
31 **Meng F**, Wang K, Aoyama T, Grivennikov SI, Paik Y, Scholten D, Cong M, Iwaisako K, Liu X, Zhang M, Osterreicher CH, Stickel F, Ley K, Brenner DA, Kisseleva T. Interleukin-17 signaling in inflammatory, Kupffer cells, and hepatic stellate cells exacerbates liver fibrosis in mice. *Gastroenterology* 2012; **143**: 765-76.e1-3 [PMID: 22687286]
32 **Rensen SS**, Slaats Y, Driessen A, Peutz-Kootstra CJ, Nijhuis J, Steffensen R, Greve JW, Buurman WA. Activation of the complement system in human nonalcoholic fatty liver disease. *Hepatology* 2009; **50**: 1809-1817 [PMID: 19821522]
33 **Baffy G**, Brunt EM, Caldwell SH. Hepatocellular carcinoma in non-alcoholic fatty liver disease: an emerging menace. *J Hepatol* 2012; **56**: 1384-1391 [PMID: 22326465]
34 **Wolf MJ**, Adili A, Piotrowitz K, Abdullah Z, Boege Y, Stemmer K, Ringelhan M, Simonavicius N, Egger M, Wohlleber D, Lorentzen A, Einer C, Schulz S, Clavel T, Protzer U, Thiele C, Zischka H, Moch H, Tschöp M, Tumanov AV, Haller D, Unger K, Karin M, Kopf M, Knolle P, Weber A, Heikenwalder M. Metabolic activation of intrahepatic CD8+ T cells and NKT cells causes nonalcoholic steatohepatitis and liver cancer via cross-talk with hepatocytes. *Cancer Cell* 2014; **26**: 549-564 [PMID: 25314080]
35 **Gao B**, Radaeva S. Natural killer and natural killer T cells in liver fibrosis. *Biochim Biophys Acta* 2013; **1832**: 1061-1069 [PMID: 23022478]
36 **Syn WK**, Oo YH, Pereira TA, Karaca GF, Jung Y, Omenetti A, Witek RP, Choi SS, Guy CD, Fearing CM, Teaberry V, Pereira FE, Adams DH, Diehl AM. Accumulation of natural killer T cells in progressive nonalcoholic fatty liver disease. *Hepatology* 2010; **51**: 1998-2007 [PMID: 20512988]
37 **Tajiri K**, Shimizu Y, Tsuneyama K, Sugiyama T. Role of liver-infiltrating CD3+CD56+ natural killer T cells in the pathogenesis of nonalcoholic fatty liver disease. *Eur J Gastroenterol Hepatol* 2009; **21**: 673-680 [PMID: 19318971]
38 **Kremer M**, Thomas E, Milton RJ, Perry AW, van Rooijen N, Wheeler MD, Zacks S, Fried M, Rippe RA, Hines IN. Kupffer cell and interleukin-12-dependent loss of natural killer T cells in hepatosteatosis. *Hepatology* 2010; **51**: 130-141 [PMID: 20034047]
39 **Wehr A**, Baeck C, Heymann F, Niemietz PM, Hammerich L, Martin C, Zimmermann HW, Pack O, Gassler N, Hittatiya K, Ludwig A, Luedde T, Trautwein C, Tacke F. Chemokine receptor CXCR6-dependent hepatic NK T Cell accumulation promotes inflammation and liver fibrosis. *J Immunol* 2013; **190**: 5226-5236 [PMID: 23596313]
40 **Correia MP**, Cardoso EM, Pereira CF, Neves R, Uhrberg M, Arosa FA. Hepatocytes and IL-15: a favorable microenvironment for T cell survival and CD8+ T cell differentiation. *J Immunol* 2009; **182**: 6149-6159 [PMID: 19414768]
41 **Syn WK**, Agboola KM, Swiderska M, Michelotti GA, Liaskou E, Pang H, Xie G, Philips G, Chan IS, Karaca GF, Pereira Tde A, Chen Y, Mi Z, Kuo PC, Choi SS, Guy CD, Abdelmalek MF, Diehl AM. NKT-associated hedgehog and osteopontin drive fibrogenesis in non-alcoholic fatty liver disease. *Gut* 2012; **61**: 1323-1329 [PMID: 22427237]
42 **Syn WK**, Choi SS, Liaskou E, Karaca GF, Agboola KM, Oo YH, Mi Z, Pereira TA, Zdanowicz M, Malladi P, Chen Y, Moylan C, Jung Y, Bhattacharya SD, Teaberry V, Omenetti A, Abdelmalek MF, Guy CD, Adams DH, Kuo PC, Michelotti GA, Whitington PF, Diehl AM. Osteopontin is induced by hedgehog pathway activation and promotes fibrosis progression in nonalcoholic steatohepatitis. *Hepatology* 2011; **53**: 106-115 [PMID: 20967826]
43 **Locatelli I**, Sutti S, Vacchiano M, Bozzola C, Albano E. NF-κB1 deficiency stimulates the progression of non-alcoholic steatohepatitis (NASH) in mice by promoting NKT-cell-mediated responses. *Clin Sci* (Lond) 2013; **124**: 279-287 [PMID: 22970906]
44 **Sahai A**, Malladi P, Melin-Aldana H, Green RM, Whitington PF. Upregulation of osteopontin expression is involved in the development of nonalcoholic steatohepatitis in a dietary murine model. *Am J Physiol Gastrointest Liver Physiol* 2004; **287**: G264-G273 [PMID: 15044174]
45 **Urtasun R**, Lopategi A, George J, Leung TM, Lu Y, Wang X, Ge X, Fiel MI, Nieto N. Osteopontin, an oxidant stress sensitive cytokine, up-regulates collagen-I via integrin α(V)β(3) engagement and PI3K/pAkt/NFκB signaling. *Hepatology* 2012; **55**: 594-608 [PMID: 21953216]
46 **Wang X**, Lopategi A, Ge X, Lu Y, Kitamura N, Urtasun R, Leung TM, Fiel MI, Nieto N. Osteopontin induces ductular reaction contributing to liver fibrosis. *Gut* 2014; **63**: 1805-1818 [PMID: 24496779]
47 **Williams MJ**, Clouston AD, Forbes SJ. Links between hepatic fibrosis, ductular reaction, and progenitor cell expansion. *Gastroenterology* 2014; **146**: 349-356 [PMID: 24315991]
48 **Richardson MM**, Jonsson JR, Powell EE, Brunt EM, Neuschwander-Tetri BA, Bhathal PS, Dixon JB, Weltman MD, Tilg H, Moschen AR, Purdie DM, Demetris AJ, Clouston AD. Progressive fibrosis in nonalcoholic steatohepatitis: association with altered regeneration and a ductular reaction. *Gastroenterology* 2007; **133**: 80-90 [PMID: 17631134]

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