

References:

1. Kojima H, Sakurai S, Uemura M, et al. Difference and similarity between non-alcoholic steatohepatitis and alcoholic liver disease. *Alcohol Clin Exp Res* 2005;29:259S– 263S
2. Farrell GC, Larter CZ. Nonalcoholic fatty liver disease: from steatosis to cirrhosis. *Hepatology* 2006;43:S99–S112
3. Clark JM. The epidemiology of nonalcoholic fatty liver disease in adults. *J Clin Gastroenterol* 2006;40(suppl 1):S5– S10
4. Day CP. From fat to inflammation. *Gastroenterology* 2006;130:207–210
5. Lieber CS. Alcoholic liver disease: new insights in pathogenesis lead to new treatments. *J Hepatol* 2000;32:113–128
6. Molina PE, McClain C, Valla D, et al. Molecular pathology and clinical aspects of alcohol-induced tissue injury. *Alcohol Clin Exp Res* 2002;26:120–128
7. Lumeng L, Crabb DW. Genetic aspects and risk factors in alcoholism and alcoholic liver disease. *Gastroenterology* 1994;107:572–588
8. Harrison SA, Diehl AM. Fat and the liver: a molecular overview. *Semin Gastrointest Dis* 2002;13:3–16
9. Yang S, Lin H, Diehl AM. Fatty liver vulnerability to endotoxin-induced damage despite NF-kappaB induction and inhibited caspase 3 activation. *Am J Physiol Gastrointest Liver Physiol* 2001;281:G382–G392
10. Day CP. Natural history of NAFLD: remarkably benign in the absence of cirrhosis. *Gastroenterology* 2005;129:375– 378
11. Adams LA, Angulo P. Recent concepts in non-alcoholic fatty liver disease. *Diabet Med* 2005;22:1129–1133
12. Reddy JK, Rao MS. Lipid metabolism and liver inflammation: II. Fatty liver disease and fatty acid oxidation. *Am J Physiol Gastrointest Liver Physiol* 2006;290:G852–G858
13. McCullough AJ. Pathophysiology of nonalcoholic steatohepatitis. *J Clin Gastroenterol* 2006;40:S17–S29
14. Feldstein AE, Werneburg NW, Canbay A, et al. Free fatty acids promote hepatic lipotoxicity by stimulating TNFalpha expression via a lysosomal pathway. *Hepatology* 2004; 40:185–194
15. Feldstein AE, Gores GJ. Apoptosis in alcoholic and nonalcoholic steatohepatitis. *Front Biosci* 2005;10:3093– 3099
16. Mari M, Caballero F, Colell A, et al. Mitochondrial free cholesterol loading sensitizes to TNF- and Fas-mediated steatohepatitis. *Cell Metab* 2006;4:185–198
17. Mundt B, Wirth T, Zender L, et al. Tumour necrosis factor related apoptosis inducing ligand (TRAIL) induces hepatic steatosis in viral hepatitis and after alcohol intake. *Gut* 2005; 54:1590–1596

18. Bradbury MW. Lipid metabolism and liver inflammation: I. Hepatic fatty acid uptake: possible role in steatosis. *Am J Physiol Gastrointest Liver Physiol* 2006;290:G194–G198
19. Leclercq IA, Farrell GC, Field J, Bell DR, Gonzalez FJ, Robertson GR. CYP2E1 and CYP4A as microsomal catalysts of lipid peroxides in murine nonalcoholic steatohepatitis. *J Clin Invest* 2000;105:1067–1075
20. Robertson G, Leclercq I, Farrell GC. Nonalcoholic steatosis and steatohepatitis: II. Cytochrome P-450 enzymes and oxidative stress. *Am J Physiol Gastrointest Liver Physiol* 2001;281:G1135–G1139
21. Hubscher SG. Histological assessment of non-alcoholic fatty liver disease. *Histopathology* 2006;49:450–465
22. Falck-Ytter Y, Younossi ZM, Marchesini G, McCullough AJ. Clinical features and natural history of nonalcoholic steatosis syndromes. *Semin Liver Dis* 2001;21:17–26
23. Chedid A, Mendenhall CL, Gartside P, French SW, Chen T, Rabin L. Prognostic factors in alcoholic liver disease. The VA Cooperative Study Group. *Am J Gastroenterol* 1991;86:210–216
24. Wanless IR, Shiota K. The pathogenesis of nonalcoholic steatohepatitis and other fatty liver diseases: a four-step model including the role of lipid release and hepatic venular obstruction in the progression to cirrhosis. *Semin Liver Dis* 2004;24:99–106
25. French SW, Nash J, Shitabata P, et al. Pathology of alcoholic liver disease. The VA Cooperative Group. *Semin Liver Dis* 1993;13:154–169
26. Day CP. Who gets alcoholic liver disease: nature or nurture? *J R Coll Physicians Lond* 2000;34:557–562
27. Aloisi F, Pujol-Borrell R. Lymphoid neogenesis in chronic inflammatory diseases. *Nat Rev Immunol* 2006;6:205–217
28. Savill J, Dransfield I, Gregory C, Haslett C. A blast from the past: clearance of apoptotic cells regulates immune responses. *Nat Rev Immunol* 2002;2:965–975
29. Crispe IN. Hepatic T cells and liver tolerance. *Nat Rev Immunol* 2003;3:51–62
30. Mehal WZ, Juedes AE, Crispe IN. Selective retention of activated CD8pT cells by the normal liver. *J Immunol* 1999;163:3202–3210
31. Adams DH, Eksteen B. Aberrant homing of mucosal T cells and extra-intestinal manifestations of inflammatory bowel disease. *Nat Rev Immunol* 2006;6:244–251
32. Klugewitz K, Adams DH, Emoto M, Eulenburg K, Hamann A. The composition of intrahepatic lymphocytes: shaped by selective recruitment? *Trends Immunol* 2004;25:590–594
33. International Group. Alcoholic liver disease: morphological manifestations. *Lancet* 1981;1:707–771
34. Bonder CS, Ajuebor MN, Zbytnuik LD, Kubes P, Swain MG. Essential role for neutrophil recruitment to the liver in concanavalin A-induced hepatitis. *J Immunol* 2004;172:45–53
35. Jaeschke H. Neutrophil-mediated tissue injury in alcoholic hepatitis. *Alcohol* 2002;27:23–27

36. Natori S, Rust C, Stadheim LM, Srinivasan A, Burgart LJ, Gores GJ. Hepatocyte apoptosis is a pathologic feature of human alcoholic hepatitis. *J Hepatol* 2001;34: 248–253
37. Taieb J, Mathurin P, Elbim C, et al. Blood neutrophil functions and cytokine release in severe alcoholic hepatitis: effect of corticosteroids. *J Hepatol* 2000;32:579–586
38. Maltby J, Wright S, Bird G, Sheron N. Chemokine levels in human liver homogenates: associations between gro alpha and histopathological evidence of alcoholic hepatitis. *Hepatology* 1996;24:1156–1160
39. Burra P, Hubscher SG, Shaw J, Elias E, Adams DH. Is the intercellular adhesion molecule-1/leukocyte function associated antigen 1 pathway of leukocyte adhesion involved in the tissue damage of alcoholic hepatitis? *Gut* 1992;33:268–271
40. Hui AY, Friedman SL. Molecular basis of hepatic fibrosis. *Expert Rev Mol Med* 2003;2003:1–23
41. Tsukamoto H, Lu SC. Current concepts in the pathogenesis of alcoholic liver injury. *FASEB J* 2001;15:1335–1349
42. Stewart SF, Vidali M, Day CP, Albano E, Jones DE. Oxidative stress as a trigger for cellular immune responses in patients with alcoholic liver disease. *Hepatology* 2004;39: 197–203
43. Chedid A, Mendenhall CL, Moritz TE, et al. Cellmediated hepatic injury in alcoholic liver disease. Veterans Affairs Cooperative Study Group 275. *Gastroenterology* 1993;105:254–266
44. Haydon G, Lalor PF, Hubscher SG, Adams DH. Lymphocyte recruitment to the liver in alcoholic liver disease. *Alcohol* 2002;27:29–36
45. Adams DH, Afford SC. Effector mechanisms of nonsuppurative destructive cholangitis in graft-versus-host disease and allograft rejection. *Semin Liver Dis* 2005;25: 281–297
46. Afford SC, Randhawa S, Eliopoulos AG, Hubscher SG, Young LS, Adams DH. CD40 activation induces apoptosis in cultured human hepatocytes via induction of cell surface fas ligand expression and amplifies fas-mediated hepatocyte death during allograft rejection. *J Exp Med* 1999;189:441–446
47. Galle PR, Hofmann WJ, Walczak H, et al. Involvement of the CD95 (APO-1/Fas) receptor and ligand in liver damage. *J Exp Med* 1995;182:1223–1230
48. Friedman SL. Molecular regulation of hepatic fibrosis, an integrated cellular response to tissue injury. *J Biol Chem* 2000;275:2247–2250
49. Cassiman D, Libbrecht L, Desmet V, Denef C, Roskams T. Hepatic stellate cell/myofibroblast subpopulations in fibrotic human and rat livers. *J Hepatol* 2002;36:200–209
50. Buckley CD, Pilling D, Lord JM, Akbar AN, Scheel-Toellner D, Salmon M. Fibroblasts regulate the switch from acute resolving to chronic persistent inflammation. *Trends Immunol* 2001;22:199–204
51. Parsonage G, Filer AD, Haworth O, et al. A stromal address code defined by fibroblasts. *Trends Immunol* 2005; 26:150–156

52. Iredale JP, Benyon RC, Pickering J, et al. Mechanisms of spontaneous resolution of rat liver fibrosis: hepatic stellate cell apoptosis and reduced hepatic expression of metalloproteinase inhibitors. *J Clin Invest* 1998;102:538–549
53. Duffield JS, Forbes SJ, Constandinou CM, et al. Selective depletion of macrophages reveals distinct, opposing roles during liver injury and repair. *J Clin Invest* 2005;115:56–65
54. Gordon S. Alternative activation of macrophages. *Nat Rev Immunol* 2003;3:23–35
55. Sandler NG, Mentink-Kane MM, Cheever AW, Wynn TA. Global gene expression profiles during acute pathogen-induced pulmonary inflammation reveal divergent roles for Th1 and Th2 responses in tissue repair. *J Immunol* 2003; 171:3655–3667
56. Novobrantseva TI, Majeau GR, Amatucci A, et al. Attenuated liver fibrosis in the absence of B cells. *J Clin Invest* 2005;115:3072–3082
57. Safadi R, Ohta M, Alvarez CE, et al. Immune stimulation of hepatic fibrogenesis by CD8 cells and attenuation by transgenic interleukin-10 from hepatocytes. *Gastroenterology* 2004;127:870–882
58. Wyler DJ. Schistosomes, fibroblasts, and growth factors: how a worm causes liver scarring. *New Biol* 1991;3:734–740
59. Chiaramonte MG, Donaldson DD, Cheever AW, Wynn TA. An IL-13 inhibitor blocks the development of hepatic fibrosis during a T-helper type 2-dominated inflammatory response. *J Clin Invest* 1999;104:777–785
60. Fichtner-Feigl S, Strober W, Kawakami K, Puri RK, Kitani A. IL-13 signaling through the IL-13 α (2) receptor is involved in induction of TGF- β (1) production and fibrosis. *Nat Med* 2006;12:99–106
61. Kremer M, Hines IN, Milton RJ, Wheeler MD. Favored T helper 1 response in a mouse model of hepatosteatosis is associated with enhanced T cell-mediated hepatitis. *Hepatology* 2006;44:216–227
62. Hoffmann KF, McCarty TC, Segal DH, et al. Disease fingerprinting with cDNA microarrays reveals distinct gene expression profiles in lethal type 1 and type 2 cytokine-mediated inflammatory reactions. *FASEB J* 2001;15:2545–2547
63. Tilg H, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. *Nat Rev Immunol* 2006;6:772–783
64. Ikejima K, Takei Y, Honda H, et al. Leptin receptor-mediated signaling regulates hepatic fibrogenesis and remodeling of extracellular matrix in the rat. *Gastroenterology* 2002;122:1399–1410
65. Diehl AM, Li ZP, Lin HZ, Yang SQ. Cytokines and the pathogenesis of non-alcoholic steatohepatitis. *Gut* 2005;54: 303–306
66. Emoto M, Kaufmann SH. Liver NKT cells: an account of heterogeneity. *Trends Immunol* 2003;24:364–369
67. Ajuebor MN, Aspinall AI, Zhou F, et al. Lack of chemokine receptor CCR5 promotes murine fulminant liver failure by preventing the apoptosis of activated CD1d-restricted NKT cells. *J Immunol* 2005;174:8027–8037

68. Li Z, Lin H, Yang S, Diehl AM. Murine leptin deficiency alters Kupffer cell production of cytokines that regulate the innate immune system. *Gastroenterology* 2002;123:1304–1310
69. Elinav E, Pappo O, Sklair-Levy M, et al. Adoptive transfer of regulatory NKT lymphocytes ameliorates non-alcoholic steatohepatitis and glucose intolerance in ob/ob mice and is associated with intrahepatic CD8 trapping. *J Pathol* 2006; 209:121–128
70. Li Z, Oben JA, Yang S, et al. Norepinephrine regulates hepatic innate immune system in leptin-deficient mice with nonalcoholic steatohepatitis. *Hepatology* 2004;40:434–441
71. Margalit M, Shalev Z, Pappo O, et al. Glucocerebroside ameliorates the metabolic syndrome in OB/OB mice. *J Pharmacol Exp Ther* 2006;319:105–110
72. Sakaguchi S. Naturally arising CD4⁺regulatory T cells for immunologic self-tolerance and negative control of immune responses. *Annu Rev Immunol* 2004;22:531–562
73. Hori S, Nomura T, Sakaguchi S. Control of regulatory T cell development by the transcription factor Foxp3. *Science* 2003;299:1057–1061
74. Maloy KJ, Salaun L, Cahill R, Dougan G, Saunders NJ, Powrie F. CD4⁺CD25⁺T(R) cells suppress innate immune pathology through cytokine-dependent mechanisms. *J Exp Med* 2003;197:111–119
75. von Herrath MG, Harrison LC. Antigen-induced regulatory T cells in autoimmunity. *Nat Rev Immunol* 2003;3: 223–232
76. Goddard S, Youster J, Morgan E, Adams DH. Interleukin- 10 secretion differentiates dendritic cells from human liver and skin. *Am J Pathol* 2004;164:511–519
77. Eksteen B, Miles A, Curbishley SM, et al. Epithelial inflammation is associated with CCL28 production and the recruitment of regulatory T cells expressing CCR10. *J Immunol* 2006;177:593–603
78. Accapezzato D, Francavilla V, Paroli M, et al. Hepatic expansion of a virus-specific regulatory CD8⁺ T cell population in chronic hepatitis C virus infection. *J Clin Invest* 2004;113:963–972
79. Bruder D, Westendorf AM, Geffers R, et al. CD4⁺ T Lymphocyte-mediated lung disease: steady state between pathological and tolerogenic immune reactions. *Am J Respir Crit Care Med* 2004;170:1145–1152
80. Westendorf AM, Templin M, Geffers R, et al. CD4⁺T cell mediated intestinal immunity: chronic inflammation versus immune regulation. *Gut* 2005;54:60–69
81. von Andrian UH, Mackay CR. T-cell function and migration: two sides of the same coin. *N Engl J Med* 2000;343:1020–1034
82. Agace WW. Tissue-tropic effector T cells: generation and targeting opportunities. *Nat Rev Immunol* 2006;6:682–692
83. Middleton J, Patterson AM, Gardner L, Schmutz C, Ashton BA. Leukocyte extravasation: chemokine transport and presentation by the endothelium. *Blood* 2002;100: 3853–3860
84. Takasaki S, Hano H. Three-dimensional observations of the human hepatic artery (arterial system in the liver). *J Hepatol* 2001;34:455–466

85. Lalor PF, Lai WK, Curbishley SM, Shetty S, Adams DH. Human hepatic sinusoidal endothelial cells can be distinguished by expression of phenotypic markers related to their specialised functions in vivo. *World J Gastroenterol* 2006; 12:5429–5439
86. Elvevold KH, Nedredal GI, Revhaug A, Smedsrod B. Scavenger properties of cultivated pig liver endothelial cells. *Comp Hepatol* 2004;3:4
87. Steinhoff G, Behrend M, Schrader B, Duijvestijn AM, Wonigeit K. Expression patterns of leukocyte adhesion ligand molecules on human liver endothelia: lack of ELAM- 1 and CD62 inducibility on sinusoidal endothelia and distinct distribution of VCAM-1, ICAM-1, ICAM-2 and LFA-3. *Am J Pathol* 1993;142:481–488
88. Scoazec JY, Feldmann G. In situ immunophenotyping study of endothelial cells of the human hepatic sinusoid: results and functional implications. *Hepatology* 1991;14:789–797
89. Wong J, Johnston B, Lee SS, et al. A minimal role for selectins in the recruitment of leukocytes into the inflamed liver microvasculature. *J Clin Invest* 1997;99:2782–2790
90. Steinhoff G, Behrend M, Schrader B, Pichlmayr R. Intercellular immune adhesion molecules in human liver transplants: overview on expression patterns of leukocyte receptor and ligand molecules. *Hepatology* 1993;18:440–453
91. Adams DH, Hubscher SG, Fisher NC, Williams A, Robinson M. Expression of E-selectin and E-selectin ligands in human liver inflammation. *Hepatology* 1996;24: 533–538
92. Jalkanen S, Salmi M. Cell surface monoamine oxidases: enzymes in search of a function. *EMBO J* 2001;20:3893– 3901
93. McNab G, Reeves JL, Salmi M, Hubscher S, Jalkanen S, Adams DH. Vascular adhesion protein 1 mediates binding of T cells to human hepatic endothelium. *Gastroenterology* 1996;110:522–528
94. Yoong KF, McNab G, Hubscher SG, Adams DH. Vascular adhesion protein-1 and ICAM-1 support the adhesion of tumor-infiltrating lymphocytes to tumor endothelium in human hepatocellular carcinoma. *J Immunol* 1998;160: 3978–3988
95. Lalor PF, Edwards S, McNab G, Salmi M, Jalkanen S, Adams DH. Vascular adhesion protein-1 mediates adhesion and transmigration of lymphocytes on human hepatic endothelial cells. *J Immunol* 2002;169:983–992
96. Ostermann G, Weber KS, Zerneck A, Schroder A, Weber C. JAM-1 is a ligand of the beta(2) integrin LFA-1 involved in transendothelial migration of leukocytes. *Nat Immunol* 2002;3:151–158
97. Chosay JG, Essani NA, Dunn CJ, Jaeschke H. Neutrophil margination and extravasation in sinusoids and venules of liver during endotoxin-induced injury. *Am J Physiol* 1997;272:G1195–G1200
98. Smith DJ, Salmi M, Bono P, Hellman J, Leu T, Jalkanen S. Cloning of vascular adhesion protein 1 reveals a novel multifunctional adhesion molecule. *J Exp Med* 1998;188:17–27
99. Salmi M, Yegutkin GG, Lehvonen R, Koskinen K, Salminen T, Jalkanen S. A cell surface amine oxidase directly controls lymphocyte migration. *Immunity* 2001;14: 265–276

100. Lalor PF, Sun PJ, Weston CJ, Martin-Santos A, Wakelam MJ, Adams DH. Activation of vascular adhesion protein-1 on liver endothelium results in an NF-kappaB-dependent increase in lymphocyte adhesion. *Hepatology* 2007;45:465– 474
101. Kurkijarvi R, Yegutkin GG, Gunson BK, Jalkanen S, Salmi M, Adams DH. Circulating soluble vascular adhesion protein 1 accounts for the increased serum monoamine oxidase activity in chronic liver disease. *Gastroenterology* 2000;119:1096–1103
102. O’Sullivan J, Unzeta M, Healy J, O’Sullivan MI, Davey G, Tipton KF. Semicarbazide-sensitive amine oxidases: enzymes with quite a lot to do. *Neurotoxicology* 2004; 25:303–315
103. Yu PH, Lu LX, Fan H, et al. Involvement of semicarbazidesensitive amine oxidase-mediated deamination in lipopolysaccharide- induced pulmonary inflammation. *Am J Pathol* 2006;168:718–726
104. Enrique-Tarancon G, Castan I, Morin N, et al. Substrates of semicarbazide-sensitive amine oxidase co-operate with vanadate to stimulate tyrosine phosphorylation of insulinreceptor- substrate proteins, phosphoinositide 3-kinase activity and GLUT4 translocation in adipose cells. *Biochem J* 2000;350:171–180
105. Stolen CM, Madanat R, Marti L, et al. Semicarbazide sensitive amine oxidase overexpression has dual consequences: insulin mimicry and diabetes-like complications. *FASEB J* 2004;18:702–704
106. Adams DH, Burra P, Hubscher SG, Elias E, Newman W. Endothelial activation and circulating vascular adhesion molecules in alcoholic liver disease. *Hepatology* 1994;19: 588–594
107. Jaeschke H. Chemokines, neutrophils, and inflammatory liver injury. *Shock* 1996;6:403–404
108. Kurkijarvi R, Adams DH, Leino R, Mottonen T, Jalkanen S, Salmi M. Circulating form of human vascular adhesion protein-1 (VAP-1): increased serum levels in inflammatory liver diseases. *J Immunol* 1998;161:1549–1557
109. Bonacchi A, Petrai I, Defranco RM, et al. The chemokine CCL21 modulates lymphocyte recruitment and fibrosis in chronic hepatitis C. *Gastroenterology* 2003;125:1060–1076
110. Efsen E, Bonacchi A, Pastacaldi S, et al. Agonist-specific regulation of monocyte chemoattractant protein-1 expression by cyclooxygenase metabolites in hepatic stellate cells. *Hepatology* 2001;33:713–721
111. Marra F, DeFranco R, Grappone C, et al. Increased expression of monocyte chemotactic protein-1 during active hepatic fibrogenesis: correlation with monocyte infiltration. *Am J Pathol* 1998;152:423–430
112. Morland CM, Fear J, McNab G, Joplin R, Adams DH. Promotion of leukocyte transendothelial cell migration by chemokines derived from human biliary epithelial cells in vitro. *Proc Assoc Am Physicians* 1997;109:372–382
113. Maher JJ. Rat hepatocytes and Kupffer cells interact to produce interleukin-8 (cinc) in the setting of ethanol. *Am J Physiol* 1995;269:G518–G523

114. Shields PL, Morland CM, Salmon M, Qin S, Hubscher SG, Adams DH. Chemokine and chemokine receptor interactions provide a mechanism for selective T cell recruitment to specific liver compartments within hepatitis C-infected liver. *J Immunol* 1999;163:6236–6243
115. Narumi S, Tominaga Y, Tamaru M, et al. Expression of IFN-inducible protein-10 in chronic hepatitis. *J Immunol* 1997;158:5536–5544
116. Afford SC, Fisher NC, Neil DA, et al. Distinct patterns of chemokine expression are associated with leukocyte recruitment in alcoholic hepatitis and alcoholic cirrhosis. *J Pathol* 1998;186:82–89
117. Kugelman M, Hill DB, Vivian B, Marsano L, McClain CJ. Cytokines and NASH: a pilot study of the effects of lifestyle modification and vitamin E. *Hepatology* 2003;38:413–419
118. Abiru S, Migita K, Maeda Y, et al. Serum cytokine and soluble cytokine receptor levels in patients with nonalcoholic steatohepatitis. *Liver Int* 2006;26:39–45
119. Haukeland JW, Damas JK, Konopski Z, et al. Systemic inflammation in nonalcoholic fatty liver disease is characterized by elevated levels of CCL2. *J Hepatol* 2006;44: 1167–1174
120. Heydtmann M, Hardie D, Shields PL, et al. Detailed analysis of intrahepatic CD8 T cells in the normal and hepatitis C-infected liver reveals differences in specific populations of memory cells with distinct homing phenotypes. *J Immunol* 2006;177:729–738
121. Debes GF, Arnold CN, Young AJ, et al. Chemokine receptor CCR7 required for T lymphocyte exit from peripheral tissues. *Nat Immunol* 2005;6:889–894
122. Fisher NC, Neil DA, Williams A, Adams DH. Serum concentrations and peripheral secretion of the beta chemokines monocyte chemoattractant protein 1 and macrophage inflammatory protein 1alpha in alcoholic liver disease. *Gut* 1999;45:416–420
123. Aleffi S, Petrai I, Bertolani C, et al. Upregulation of proinflammatory and proangiogenic cytokines by leptin in human hepatic stellate cells. *Hepatology* 2005;42:1339– 1348
124. Zamara E, Galastri S, Aleffi S, et al. Prevention of severe toxic liver injury and oxidative stress in MCP-1-deficient mice. *J Hepatol* 2007;46:230–238
125. Bertolani C, Sancho-Bru P, Failli P, et al. Resistin as an intrahepatic cytokine: overexpression during chronic injury and induction of proinflammatory actions in hepatic stellate cells. *Am J Pathol* 2006;169:2042–2053
126. Kanda H, Tateya S, Tamori Y, et al. MCP-1 contributes to macrophage infiltration into adipose tissue, insulin resistance, and hepatic steatosis in obesity. *J Clin Invest* 2006; 116:1494–1505
127. Boisvert J, Kunkel EJ, Campbell JJ, Keeffe EB, Butcher EC, Greenberg HB. Liver-infiltrating lymphocytes in end-stage hepatitis C virus: subsets, activation status, and chemokine receptor phenotypes. *J Hepatol* 2003;38:67–75
128. Coulomb-L'Hermin A, Amara A, Schiff C, et al. Stromal cell-derived factor 1 (SDF-1) and antenatal human B cell lymphopoiesis: expression of SDF-1 by mesothelial

- cells and biliary ductal plate epithelial cells. *Proc Natl Acad Sci USA* 1999;96:8585–8590
129. Heydtmann M, Lalor PF, Eksteen JA, Hubscher SG, Briskin M, Adams DH. CXC chemokine ligand 16 promotes integrin-mediated adhesion of liver-infiltrating lymphocytes to cholangiocytes and hepatocytes within the inflamed human liver. *J Immunol* 2005;174:1055–1062
 130. Sato T, Thorlacius H, Johnston B, et al. Role for CXCR6 in recruitment of activated CD8⁺ lymphocytes to inflamed liver. *J Immunol* 2005;174:277–283
 131. Goddard S, Williams A, Morland C, et al. Differential expression of chemokines and chemokine receptors shapes the inflammatory response in rejecting human liver transplants. *Transplantation* 2001;72:1957–1967
 132. Isse K, Harada K, Zen Y, et al. Fractalkine and CX3CR1 are involved in the recruitment of intraepithelial lymphocytes of intrahepatic bile ducts. *Hepatology* 2005;41:506–516
 133. Curbishley SM, Eksteen B, Gladue RP, Lalor P, Adams DH. CXCR3 activation promotes lymphocyte transendothelial migration across human hepatic endothelium under fluid flow. *Am J Pathol* 2005;167:887–899
 134. Leroy V, Vigan I, Mosnier JF, et al. Phenotypic and functional characterization of intrahepatic T lymphocytes during chronic hepatitis C. *Hepatology* 2003;38:829–841
 135. Bonacchi A, Romagnani P, Romanelli RG, et al. Signal transduction by the chemokine receptor CXCR3: activation of Ras/ERK, Src, and phosphatidylinositol 3-kinase/Akt controls cell migration and proliferation in human vascular pericytes. *J Biol Chem* 2001;276:9945–9954
 136. Dela Pena A, Leclercq I, Field J, George J, Jones B, Farrell G. NF-kappaB activation, rather than TNF, mediates hepatic inflammation in a murine dietary model of steatohepatitis. *Gastroenterology* 2005;129:1663–1674
 137. Boden G, She P, Mozzoli M, et al. Free fatty acids produce insulin resistance and activate the proinflammatory nuclear factor-kappaB pathway in rat liver. *Diabetes* 2005;54:3458–3465
 138. Bird GLA, Sheron N, Goka AKJ, Alexander GJM, Williams R. Increased plasma tumour necrosis factor in severe alcoholic hepatitis. *Ann Intern Med* 1990;112:917–920
 139. Khoruts A, Stahnke L, McClain CJ, Logan G, Allen JI. Circulating tumor necrosis factor, interleukin-1 and interleukin-6 concentrations in chronic alcoholic patients. *Hepatology* 1991;13:267–276
 140. Gebhard HH, Zysk SP, Schmitt-Sody M, Jansson V, Messmer K, Veihelmann A. The effects of Celecoxib on inflammation and synovial microcirculation in murine antigen-induced arthritis. *Clin Exp Rheumatol* 2005;23: 63–70
 141. Nanji AA, Miao L, Thomas P, et al. Enhanced cyclooxygenase-2 gene expression in alcoholic liver disease in the rat. *Gastroenterology* 1997;112:943–951
 142. Yu J, Ip E, Dela PA, et al. COX-2 induction in mice with experimental nutritional steatohepatitis: role as pro-inflammatory mediator. *Hepatology* 2006;43:826–836
 143. Tilg H, Diehl AM. Cytokines in alcoholic and nonalcoholic steatohepatitis. *N Engl J Med* 2000;343:1467–1476

144. Wigg AJ, Roberts-Thomson IC, Dymock RB, McCarthy PJ, Grose RH, Cummins AG. The role of small intestinal bacterial overgrowth, intestinal permeability, endotoxaemia, and tumour necrosis factor alpha in the pathogenesis of nonalcoholic steatohepatitis. *Gut* 2001;48:206–211
145. Crespo J, Cayon A, Fernandez-Gil P, et al. Gene expression of tumor necrosis factor alpha and TNF-receptors, p55 and p75, in nonalcoholic steatohepatitis patients. *Hepatology* 2001;34:1158–1163
146. Hui JM, Hodge A, Farrell GC, Kench JG, Kriketos A, George J. Beyond insulin resistance in NASH: TNF-alpha or adiponectin? *Hepatology* 2004;40:46–54
147. Poniachik J, Csendes A, Diaz JC, et al. Increased production of IL-1alpha and TNF-alpha in lipopolysaccharide- stimulated blood from obese patients with nonalcoholic fatty liver disease. *Cytokine* 2006;33:252–257
148. Tomita K, Tamiya G, Ando S, et al. Tumour necrosis factor alpha signalling through activation of Kupffer cells plays an essential role in liver fibrosis of non-alcoholic steatohepatitis in mice. *Gut* 2006;55:415–424
149. Koppe SW, Sahai A, Malladi P, Whittington PF, Green RM. Pentoxifylline attenuates steatohepatitis induced by the methionine choline deficient diet. *J Hepatol* 2004;41:592–598
150. Satapathy SK, Garg S, Chauhan R, et al. Beneficial effects of tumor necrosis factor-alpha inhibition by pentoxifylline on clinical, biochemical, and metabolic parameters of patients with nonalcoholic steatohepatitis. *Am J Gastroenterol* 2004;99:1946–1952
151. Adams LA, Zein CO, Angulo P, Lindor KD. A pilot trial of pentoxifylline in nonalcoholic steatohepatitis. *Am J Gastroenterol* 2004;99:2365–2368
152. Anty R, Bekri S, Luciani N, et al. The inflammatory C-reactive protein is increased in both liver and adipose tissue in severely obese patients independently from metabolic syndrome, type 2 diabetes, and NASH. *Am J Gastroenterol* 2006;101:1824–1833
153. Fox-Robichaud A, Kubes P. Molecular mechanisms of tumor necrosis factor alpha-stimulated leukocyte recruitment into the murine hepatic circulation. *Hepatology* 2000;31:1123–1127
154. La Cava A, Matarese G. The weight of leptin in immunity. *Nat Rev Immunol* 2004;4:371–379
155. Verma S, Li SH, Wang CH, et al. Resistin promotes endothelial cell activation: further evidence of adipokine-endothelial interaction. *Circulation* 2003;108:736–740
156. Parish CR. The role of heparan sulphate in inflammation. *Nat Rev Immunol* 2006;6:633–643
157. Shiratori Y, Takada H, Hikiba Y, et al. Production of chemotactic factor, interleukin-8, from hepatocytes exposed to ethanol. *Hepatology* 1993;18:1477–1482
158. Armendariz-Borunda J, Seyer JM, Postlethwaite AE, Kang AH. Kupffer cells from carbon tetrachloride-injured rat liver produce chemotactic factors for fibroblasts and monocytes: the role of tumour necrosis factor-alpha. *Hepatology* 1991; 14:895–900

159. Edwards S, Lalor PF, Nash GB, Rainger GE, Adams DH. Lymphocyte traffic through sinusoidal endothelial cells is regulated by hepatocytes. *Hepatology* 2005;41:451–459
160. Lieber CS. Alcohol and the liver: metabolism of alcohol and its role in hepatic and extrahepatic diseases. *Mt Sinai J Med* 2000;67:84–94
161. Lauterburg BH, Davies S, Mitchell JR. Ethanol suppresses hepatic glutathione synthesis in rats in vivo. *J Pharmacol Exp Ther* 1984;230:7–11
162. Lieber CS. Role of oxidative stress and antioxidant therapy in alcoholic and nonalcoholic liver diseases. *Adv Pharmacol* 1997;38:601–628
163. Lieber CS. Biochemical factors in alcoholic liver disease. *Semin Liver Dis* 1993;13:136–153
164. Kessova I, Cederbaum AI. CYP2E1: biochemistry, toxicology, regulation and function in ethanol-induced liver injury. *Curr Mol Med* 2003;3:509–518
165. Nanji AA. Role of Kupffer cells in alcoholic hepatitis. *Alcohol* 2002;27:13–15
166. Purohit V, Brenner DA. Mechanisms of alcohol-induced hepatic fibrosis: a summary of the Ron Thurman Symposium. *Hepatology* 2006;43:872–878
167. Yokoyama H, Fukuda M, Okamura Y, et al. Superoxide anion release into the hepatic sinusoid after an acute ethanol challenge and its attenuation by Kupffer cell depletion. *Alcohol Clin Exp Res* 1999;23:71S–75S
168. Deaciuc IV, D'Souza NB, Spitzer JJ. Tumor necrosis factor alpha cell-surface receptors of liver parenchymal and nonparenchymal cells during acute and chronic alcohol administration to rats. *Alcohol Clin Exp Res* 1995;19:332–338
169. Saeed RW, Varma S, Peng T, Tracey KJ, Sherry B, Metz CN. Ethanol blocks leukocyte recruitment and endothelial cell activation in vivo and in vitro. *J Immunol* 2004;173: 6376–6383
170. Yamaguchi T, Dayton C, Shigematsu T, et al. Preconditioning with ethanol prevents postischemic leukocyte-endothelial cell adhesive interactions. *Am J Physiol Heart Circ Physiol* 2002;283:H1019–H1030
171. Bautista AP. Chronic alcohol intoxication induces hepatic injury through enhanced macrophage inflammatory protein-2 production and intercellular adhesion molecule-1 expression in the liver. *Hepatology* 1997;25:335–342
172. Ohki E, Kato S, Ohgo H, et al. Effect of chronic ethanol feeding on endotoxin-induced hepatic injury: role of adhesion molecules on leukocytes and hepatic sinusoid. *Alcohol Clin Exp Res* 1998;22:129S–132S
173. Thurman RG, Bradford BU, Imuro Y, et al. The role of gut-derived bacterial toxins and free radicals in alcohol-induced liver injury. *J Gastroenterol Hepatol* 1998;13(suppl):S39–S50
174. Thurman RG II. Alcoholic liver injury involves activation of Kupffer cells by endotoxin. *Am J Physiol* 1998;275:G605–G611
175. John B, Klein I, Crispe IN. Immune role of hepatic TLR-4 revealed by orthotopic mouse liver transplantation. *Hepatology* 2007;45:178–186

176. Tuma DJ, Thiele GM, Xu D, Klassen LW, Sorrell MF. Acetaldehyde and malondialdehyde react together to generate distinct protein adducts in the liver during long-term ethanol administration. *Hepatology* 1996;23:872–880
177. Rolla R, Vay D, Mottaran E, et al. Detection of circulating antibodies against malondialdehyde-acetaldehyde adducts in patients with alcohol-induced liver disease. *Hepatology* 2000;31:878–884
178. Duryee MJ, Klassen LW, Freeman TL, Willis MS, Tuma DJ, Thiele GM. Lipopolysaccharide is a cofactor for malondialdehyde-acetaldehyde adduct-mediated cytokine/chemokine release by rat sinusoidal liver endothelial and Kupffer cells. *Alcohol Clin Exp Res* 2004;28:1931–1938
179. Nelson S, Bagby G, Bainton BG, Summer WR. The effects of acute and chronic alcoholism on tumor necrosis factor and the inflammatory response. *J Infect Dis* 1989;160:422–429
180. Maher JJ. Rat hepatocytes and Kupffer cells interact to produce interleukin-8 (CINC) in the setting of ethanol. *Am J Physiol* 1995;269:G518–G523
181. Spitzer JA, Zheng M, Kolls JK, Vande SC, Spitzer JJ. Ethanol and LPS modulate NF-kappaB activation, inducible NO synthase and COX-2 gene expression in rat liver cells in vivo. *Front Biosci* 2002;7:a99–a108
182. Bautista AP. Chronic alcohol intoxication primes Kupffer cells and endothelial cells for enhanced CC-chemokine production and concomitantly suppresses phagocytosis and chemotaxis. *Front Biosci* 2002;7:a117–a125
183. Paik YH, Schwabe RF, Bataller R, Russo MP, Jobin C, Brenner DA. Toll-like receptor 4 mediates inflammatory signaling by bacterial lipopolysaccharide in human hepatic stellate cells. *Hepatology* 2003;37:1043–1055
184. Roman J, Colell A, Blasco C, et al. Differential role of ethanol and acetaldehyde in the induction of oxidative stress in HEP G2 cells: effect on transcription factors AP-1 and NF-kappaB. *Hepatology* 1999;30:1473–1480
185. Aroor AR, Shukla SD. MAP kinase signaling in diverse effects of ethanol. *Life Sci* 2004;74:2339–2364
186. Cao Q, Mak KM, Lieber CS. Cytochrome P4502E1 primes macrophages to increase TNF-alpha production in response to lipopolysaccharide. *Am J Physiol Gastrointest Liver Physiol* 2005;289:G95–G107
187. Wheeler MD. Endotoxin and Kupffer cell activation in alcoholic liver disease. *Alcohol Res Health* 2003;27:300–306
188. Yamashina S, Takei Y, Ikejima K, Enomoto N, Kitamura T, Sato N. Ethanol-induced sensitization to endotoxin in Kupffer cells is dependent upon oxidative stress. *Alcohol Clin Exp Res* 2005;29:246S–250S
189. Jokelainen K, Thomas P, Lindros K, Nanji AA. Acetaldehyde inhibits NF-kappaB activation through IkappaBalpha preservation in rat Kupffer cells. *Biochem Biophys Res Commun* 1998;253:834–836
190. Roman J, Colell A, Blasco C, et al. Differential role of ethanol and acetaldehyde in the induction of oxidative stress in HEP G2 cells: effect on transcription factors AP-1 and NF-kappaB. *Hepatology* 1999;30:1473–1480

191. Koteish A, Yang S, Lin H, Huang X, Diehl AM. Chronic ethanol exposure potentiates lipopolysaccharide liver injury despite inhibiting Jun N-terminal kinase and caspase 3 activation. *J Biol Chem* 2002;277:13037–13044
 192. Altura BM, Gebrewold A. Pyrrolidine dithiocarbamate attenuates alcohol-induced leukocyte-endothelial cell interaction and cerebral vascular damage in rats: possible role of activation of transcription factor NF-kappaB in alcohol brain pathology. *Alcohol* 1998;16:25–28
 193. Nanji AA, Jokelainen K, Fotouhinia M, et al. Increased severity of alcoholic liver injury in female rats: role of oxidative stress, endotoxin, and chemokines. *Am J Physiol Gastrointest Liver Physiol* 2001;281:G1348–G1356
 194. Rot A, von Andrian U. Chemokines in innate and adaptive host defense: basic chemokinese grammar for immune cells. *Annu Rev Immunol* 2004;22:891–928
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