

补体与脂肪肝研究进展

王燕, 杨耀娴

王燕, 杨耀娴, 内蒙古科技大学包头医学院第二附属医院消化病研究所 内蒙古自治区包头市 014030

作者贡献分布: 本文由王燕综述, 杨耀娴审校。

通讯作者: 杨耀娴, 教授, 014030, 内蒙古自治区包头市, 内蒙古科技大学包头医学院第二附属医院消化病研究所。

wina7335831@sina.com

电话: 0472-3169716

收稿日期: 2010-01-24 修回日期: 2010-04-20

接受日期: 2010-04-27 在线出版日期: 2010-05-28

Advances in understanding the role of complement in the pathogenesis of fatty liver disease

Yan Wang, Yao-Xian Yang

Yan Wang, Yao-Xian Yang, Institute of Digestive Diseases, the Second Affiliated Hospital of Baotou Medical College, Baotou 014030, Inner Mongolia Autonomous Region, China

Correspondence to: Professor Yao-Xian Yang, Institute of Digestive Diseases, the Second Affiliated Hospital of Baotou Medical College, Baotou 014030, Inner Mongolia Autonomous Region, China. wina7335831@sina.com

Received: 2010-01-24 Revised: 2010-04-20

Accepted: 2010-04-27 Published online: 2010-05-28

Abstract

Patients with fatty liver disease (FLD) exhibit various immunologic abnormalities in the adipose tissue and the liver. Complement plays an important role in the development of FLD. Innate immune dysfunction in the adipose tissue can lead to abnormal production of adipose-derived factors, some of which can activate complement. Complement can not only amplify the inflammatory response and lead to mitochondrial damage, but also inhibit hepatic fat disposal and promote lipid accumulation in hepatocytes. An exploration of the relationship between complement and the liver can help us have a deep understanding of the mechanisms underlying the pathogenesis of FLD. The antagonists of the C5L2 receptor provide us potential new medicines for FLD. A further study of the role of complement in stress-induced liver remodeling can help clarify the role of complement in the development and progression of FLD.

Key Words: Fatty liver disease; Complement; In-

flammation

Wang Y, Yang YX. Advances in understanding the role of complement in the pathogenesis of fatty liver disease. *Shijie Huaren Xiaohua Zazhi* 2010; 18(15): 1577-1581

摘要

脂肪肝(fatty liver disease, FLD)存在脂肪组织和肝脏等的免疫功能紊乱, 补体参与了肝脏脂质沉积发生发展的全过程。肝脂肪变性时过多的脂肪细胞分泌的炎症因子可激活补体, 促进脂质沉积并使炎症反应级联放大, 继而激发肝细胞线粒体损伤, 加重脂质在肝细胞内积存。补体与脂肪肝关系的研究有助于我们对脂肪肝的发病机制进行更深入的认识, C5L2受体拮抗剂的研究有助于研制开发新一代治疗药物。因此需要进一步了解补体在肝脏代谢性应激状态下的免疫机制, 从而进一步澄清其在FLD发生发展中的作用, 并采取措施预防病变发展。

关键词: 脂肪肝; 补体; 炎症

王燕, 杨耀娴. 补体与脂肪肝研究进展. 世界华人消化杂志 2010; 18(15): 1577-1581

<http://www.wjgnet.com/1009-3079/18/1577.asp>

0 引言

脂肪肝(fatty liver disease, FLD)是指弥漫性肝实质细胞大泡性脂肪变性和脂肪(主要是三酰甘油)蓄积为特征的临床病理综合征。脂肪肝可以演变为脂肪性肝炎(nonalcoholic steatohepatitis, NASH)、肝纤维化和肝硬化^[1]。近来研究发现FLD呈慢性炎症状态, 与免疫系统密切相关, 存在脂肪组织和肝脏的天然免疫功能紊乱^[2,3], 补体系统是自身免疫系统的一部分, 参与了肝脏脂质沉积的发生^[4]。研究显示肝脂肪变性时过多的脂肪细胞可分泌多种炎症因子^[5], 炎症因子可激活补体并介导一系列的炎症反应^[6], 补体又可抑制炎症细胞凋亡^[7], 引起上述炎症反应级联放大, 继而引起肝细胞线粒体损伤, 加重脂质在肝细胞内积存^[8]。补体在FLD的形成与演变中发挥重要作用, 本文就其在FLD发病机制中的作用作一综述。

■背景资料

脂肪肝(FLD)的发病机制尚未完全明确, 近来研究发现, FLD存在脂肪组织和肝脏等的天然免疫紊乱, 与补体密切相关, 来源于脂肪组织和肝脏的补体可能对FLD的发生发展起重要作用。

■同行评议者

黄晓东, 副主任医师, 武汉市中心医院消化内科

■研究前沿

补体参与FLD疾病的发生发展,但其具体作用机制错综复杂,如何进一步澄清其作用机制并采取措施预防疾病发生、发展是当前亟待解决的问题。

1 肝脏是补体产生的主要器官

FLD与免疫系统密切相关,存在脂肪组织和肝脏等的免疫功能紊乱。补体系统是获得性免疫系统重要的组成部分,参与了肝脏脂质沉积发生发展的全过程^[9]。自19世纪末发现补体以来,已明确多数补体分子属 β 球蛋白,少数属 α 球蛋白及 γ 球蛋白,补体组分中含量最高的成分是C3,正常人体血清中达1 200 mg/L, C3含量的高低与总补体含量平行,其水平是衡量体液免疫的重要指标。虽然机体不同组织细胞均能合成补体,但血浆中大部分补体组分由肝细胞合成分泌。

2 补体在脂质代谢中起重要作用

脂肪组织由成熟的脂肪细胞和间质细胞构成,后者包括与免疫相关的巨噬细胞、淋巴细胞、内皮细胞和未成熟的脂肪细胞(如前脂肪细胞)^[10]。近来研究发现,脂肪组织作为体内最大的能量贮库,并不是被动贮存脂肪的惰性组织,还可能是体内最大的内分泌器官^[11,12],肝脏细胞是产生脂质的主要细胞,而脂肪组织是储存三酰甘油的主要场所。脂肪代谢依赖于机体对能量的需要,并受营养成分、神经及内分泌激素的调节^[13]。近期的研究发现,脂肪组织不仅能储存能量,而且还可以分泌产生一些激素和细胞因子,积极参与能量平衡、神经内分泌及自身免疫的调节^[14]。有研究表明,脂肪细胞能分泌C3,表达C3a受体,其中补体C3加工转化生成促酰化蛋白(C3a desArg77, acylation stimulating protein, ASP)^[15-17], ASP进一步刺激脂肪细胞摄取血液中自由脂肪酸(free fatty acid, FFA)促进脂肪细胞合成三酰甘油(triacylglycerol, TG)^[18]。此外, Cianflone等报道在血液游离脂肪酸的刺激下,促使C3的 α 链氨基末端上的精氨酸-丝氨酸键断裂,在补体B参与下生成一分子C3a和一分子C3b。C3a羧基末端上的精氨酸(Arg)迅速被羧基肽酶B(carboxypeptidase B, CPB)移去,从而生成76个氨基酸肽链的酰化刺激蛋白,而C3裂解产生的C3b重新进入循环,从而不断扩大循环^[19]。C3a与ASP可结合受体C5L2,并促进TG的合成^[20-22]。血清ASP浓度随进食不断上升,并促进三酰甘油的合成与储存^[23]。脂肪萎缩小鼠ASP缺乏,餐后脂肪酸升高,三酰甘油合成减少^[17]。提示补体C3是促进脂质沉积的起始因素,其分解代谢产物促使脂肪细胞摄取脂质^[24]。

3 补体激活是脂肪肝形成的重要原因

肝脏是脂质合成和代谢的主要器官,脂质在脂

肪细胞中以TG的形式储存。当肝脏的脂质输入或生物合成远大于脂质氧化或输出时,脂质在肝细胞内蓄积,产生脂肪变性。

3.1 补体可以促进肝细胞脂质沉积 酒精性脂肪肝中乙醇可致磷酸甘油增多而促进三酰甘油的合成。且乙醇在代谢过程中,促进氧化型辅酶I转变为还原型辅酶I,故使依赖于NADH的生化反应加强,依赖NAD的反应如三羧酸循环、脂肪酸 β 氧化和氧化磷酸化、糖异生抑制。患者出现高乳酸血症、高尿酸血症、低血糖、高脂血症、FLD等^[25,26]。Pritchard等研究显示,在用酒精喂养的天然小鼠血清中补体C3、C5均升高,敲除C5基因小鼠与天然小鼠出现高TG血症,而敲除C3基因小鼠没有出现高TG血症,肝脏没有明显的脂质沉积,提示补体C3促进肝细胞内脂质的沉积,参与脂肪肝的发生与发展^[4,9,27]。

3.2 补体是参与脂肪肝炎性损害的重要因子 目前已证实脂肪肝存在氧化应激、脂质过氧化、线粒体功能失调、呼吸链复合物活性降低、活性氧簇(reactive oxygen species, ROS)及肿瘤坏死因子生成增加,而TNF- α 和脂质过氧化物使电子在呼吸链中传递氧的能力降低,影响ATP的生成。大量ROS使体内抗氧化剂耗竭,导致体内氧自由基增多,进一步形成恶性循环^[3,28-29]。脂肪肝变性时过多的脂肪细胞可分泌多种炎性因子,导致肝细胞发生炎症浸润坏死,甚至进展为肝纤维化及肝硬化。炎症、坏死和凋亡激活补体,补体又通过多种途径激发炎症反应,导致肝脏促炎症(Th-1)和抗炎(Th-2)细胞因子的失调^[2,30]。炎症反应也可降低脂肪组织缓冲(nonesterified fatty acids, NEFA)的能力,尽管肥胖时机体的脂肪组织增加,但血液中游离脂肪酸水平仍很高。网膜释放出的NEFA通过门静脉沉积到肝脏内,导致脂质产生增多^[31,32]。

补体促进各种炎性因子的激活。有研究报道C5a、C5a desArg74、C4a、C4a desArg77结合其受体后,无TG的合成^[4]。Pritchard等研究报道用乙醇喂养后,去除C5基因的小鼠血清中ALT与TNF- α 不升高^[4],提示C5是重要的炎症介质,与脂肪肝脂质沉积无相关性,而与脂肪肝炎症反应的发生有关。相关机制有(1)C5a是炎症反应的重要介质和趋化因子,其受体广泛表达于肥大细胞、嗜酸性粒细胞、嗜碱性粒细胞、中性粒细胞、单核巨噬细胞和内皮细胞等炎性细胞表面。C5a与相应受体结合,可介导肥大细胞和单核细胞释放炎性介质^[33]。(2)有研究报道C5a

通过其受体-CD88和C5L2(C5a like receptor-2)来实现生物学活性^[34,35]。C5a与CD88通过两点模型相互作用后,介导一系列的炎症反应,如激发细胞脱颗粒,释放组胺,增强血管通透性,诱导白细胞表达分泌IL-6、TNF- α 等细胞因子^[36]。有研究报道抗C5a单克隆抗体能够改善组织氧摄取并且降低IL-6和乳酸水平^[37]。(3)C5a还能激活花生四烯酸代谢的脂氧合酶途径,促进中性粒细胞和单核细胞进一步释放炎症介质。(4)补体C5对中性粒细胞有趋化作用,并且抑制中性粒细胞凋亡^[38]。C5a可直接作用于血管内皮细胞,导致血管渗透性增加并表达P-选择素,促进中性粒细胞黏着于血管内皮细胞^[39]。并且中性粒细胞和单核细胞的趋化因子、中性粒细胞所释放的溶酶体及炎症渗出物中的蛋白水解酶又能激活补体^[40],从而形成驱动中性粒细胞游走的反馈性环路,引起上述反应逐级发达,继而引起肝细胞线粒体损伤,脂蛋白形成减少^[34,41-42],减少脂质外运,加重脂质在肝细胞内存积^[43]。

4 补体在脂肪肝形成中起清除内毒素与自身抗原的重要作用

乙醇在小肠上段吸收的同时可使肠腔内毒素异位到门脉系统,肝脏的库普弗细胞通过表达CD14或TLR诱发CD14表达,促使其与异位内毒素成分脂多糖(LPS)结合,并释放TNF- α 激活一系列炎症反应。内毒素是所有革兰阴性菌的细胞壁成分,补体可清除内毒素。有报道1993年,英国Zenaide等对受脂多糖攻击的先天性C3缺陷狗进行观察,提示补体C3可保护机体免受细菌毒素(内毒素)的损伤。国内有实验证实,通过静脉注射纯化人重组iC3b片段,可以明显降低由大肠杆菌导致的小鼠内毒素休克的死亡率^[44]。提示补体参与了可以引发脂肪肝形成的内毒素的清除。

Th2辅助B细胞增殖,产生抗体,参与体液免疫应答。其中C3处于三种补体激活途径的中间环节,三途径最终形成C5转化酶,裂解C5,若此激活发生在脂质双层上,则形成C5b-9,即膜攻击复合物(MAC),清除抗原抗体免疫复合物。TUNEL法检测发现NASH大鼠的肝细胞凋亡显著高于正常大鼠,而且随着肝组织脂肪变、炎症和坏死的加重,肝细胞的凋亡也越明显^[45]。因此,补体可参与肝细胞坏死、凋亡细胞等自身抗原的清除。

5 结论

FLD是代谢综合征的肝脏组分,存在脂肪组织和肝脏等的天然免疫功能紊乱,补体系统是获得性自身免疫系统的一部分,脂肪因子和肝脏衍生的补体及致炎细胞因子与其受体结合,使肝脏从脂质沉积发展到脂肪肝,甚至脂肪性肝炎。补体与脂肪肝关系的研究有助于我们对脂肪肝的发病机制进行更深入的认识,C5L2受体拮抗剂的研究有助于研发新一代治疗药物。有必要深入了解补体在肝脏代谢性应激状态下的免疫机制,从而进一步澄清其在FLD发生发展中的作用,并采取措施预防病变发展。

6 参考文献

- 1 中华医学会肝病学会脂肪肝和酒精性肝病学组. 非酒精性脂肪性肝病诊疗指南. 中华肝脏病杂志 2006; 14: 161-163
- 2 Li Z, Soloski MJ, Diehl AM. Dietary factors alter hepatic innate immune system in mice with nonalcoholic fatty liver disease. *Hepatology* 2005; 42: 880-885
- 3 Leber B, Mayrhauser U, Rybczynski M, Stadlbauer V. Innate immune dysfunction in acute and chronic liver disease. *Wien Klin Wochenschr* 2009; 121: 732-744
- 4 Pritchard MT, McMullen MR, Stavitsky AB, Cohen JL, Lin F, Medof ME, Nagy LE. Differential contributions of C3, C5, and decay-accelerating factor to ethanol-induced fatty liver in mice. *Gastroenterology* 2007; 132: 1117-1126
- 5 Rector RS, Thyfault JP, Wei Y, Ibdah JA. Non-alcoholic fatty liver disease and the metabolic syndrome: an update. *World J Gastroenterol* 2008; 14: 185-192
- 6 Choi S, Diehl AM. Role of inflammation in nonalcoholic steatohepatitis. *Curr Opin Gastroenterol* 2005; 21: 702-707
- 7 Li Z, Diehl AM. Innate immunity in the liver. *Curr Opin Gastroenterol* 2003; 19: 565-571
- 8 Solís Herruzo JA, García Ruiz I, Pérez Carreras M, Muñoz Yagüe MT. Non-alcoholic fatty liver disease. From insulin resistance to mitochondrial dysfunction. *Rev Esp Enferm Dig* 2006; 98: 844-874
- 9 Bykov I, Junnikkala S, Pekna M, Lindros KO, Meri S. Complement C3 contributes to ethanol-induced liver steatosis in mice. *Ann Med* 2006; 38: 280-286
- 10 Herrero L, Shapiro H, Nayer A, Lee J, Shoelson SE. Inflammation and adipose tissue macrophages in lipodystrophic mice. *Proc Natl Acad Sci U S A* 2010; 107: 240-245
- 11 Meier U, Gressner AM. Endocrine regulation of energy metabolism: review of pathobiochemical and clinical chemical aspects of leptin, ghrelin, adiponectin, and resistin. *Clin Chem* 2004; 50: 1511-1525
- 12 Waki H, Tontonoz P. Endocrine functions of adipose tissue. *Annu Rev Pathol* 2007; 2: 31-56
- 13 Schäffler A, Schölmerich J, Büchler C. Mechanisms of disease: adipocytokines and visceral adipose tissue--emerging role in nonalcoholic fatty liver disease. *Nat Clin Pract Gastroenterol Hepatol* 2005; 2:

■ 相关报道

英国Zenaide等对受脂多糖攻击的先天性C3缺陷狗进行观察,提示补体C3可保护机体免受细菌毒素(内毒素)的损伤。国内有实验证实,通过静脉注射纯化人重组iC3b片段,可以明显降低由大肠杆菌导致的小鼠内毒素休克的死亡率。

■应用要点

本文通过FLD早期预警因子进行测定, 提高对其早期诊断。补体的分解产物ASP与受体C5L2结合后, 可促进脂肪细胞内三酰甘油的合成, 并调控肝脏成脂作用。可通过阻断其作用受体进行更早期的干预治疗。

- 273-280
- 14 Garruti G, Cotecchia S, Giampetruzzi F, Giorgino F, Giorgino R. Neuroendocrine deregulation of food intake, adipose tissue and the gastrointestinal system in obesity and metabolic syndrome. *J Gastrointest Liver Dis* 2008; 17: 193-198
- 15 Cianflone K, Xia Z, Chen LY. Critical review of acylation-stimulating protein physiology in humans and rodents. *Biochim Biophys Acta* 2003; 1609: 127-143
- 16 Faraj M, Cianflone K. Differential regulation of fatty acid trapping in mouse adipose tissue and muscle by ASP. *Am J Physiol Endocrinol Metab* 2004; 287: E150-E159
- 17 Cianflone K, Maslowska M, Sniderman AD. Acylation stimulating protein (ASP), an adipocyte autocrine: new directions. *Semin Cell Dev Biol* 1999; 10: 31-41
- 18 Yesilova Z, Ozata M, Oktenli C, Bagci S, Ozcan A, Sanisoglu SY, Uygur A, Yaman H, Karaeren N, Dagalp K. Increased acylation stimulating protein concentrations in nonalcoholic fatty liver disease are associated with insulin resistance. *Am J Gastroenterol* 2005; 100: 842-849
- 19 Yu H, Yang Y, Zhang M, Lu H, Zhang J, Wang H, Cianflone K. Thyroid status influence on adiponectin, acylation stimulating protein (ASP) and complement C3 in hyperthyroid and hypothyroid subjects. *Nutr Metab (Lond)* 2006; 3: 13
- 20 Kalant D, Cain SA, Maslowska M, Sniderman AD, Cianflone K, Monk PN. The chemoattractant receptor-like protein C5L2 binds the C3a des-Arg77/acylation-stimulating protein. *J Biol Chem* 2003; 278: 11123-11129
- 21 Pagliarlunga S, Schrauwen P, Roy C, Moonen-Kornips E, Lu H, Hesselink MK, Deshaies Y, Richard D, Cianflone K. Reduced adipose tissue triglyceride synthesis and increased muscle fatty acid oxidation in C5L2 knockout mice. *J Endocrinol* 2007; 194: 293-304
- 22 Okinaga S, Slattery D, Humbles A, Zsengeller Z, Morteau O, Kinrade MB, Brodbeck RM, Krause JE, Choe HR, Gerard NP, Gerard C. C5L2, a nonsignaling C5A binding protein. *Biochemistry* 2003; 42: 9406-9415
- 23 Murray I, Sniderman AD, Cianflone K. Mice lacking acylation stimulating protein (ASP) have delayed postprandial triglyceride clearance. *J Lipid Res* 1999; 40: 1671-1676
- 24 Xia Z, Stanhope KL, Digitale E, Simion OM, Chen L, Havel P, Cianflone K. Acylation-stimulating protein (ASP)/complement C3adesArg deficiency results in increased energy expenditure in mice. *J Biol Chem* 2004; 279: 4051-4057
- 25 Lee YJ, Lee HR, Lee JH, Shin YH, Shim JY. Association between serum uric acid and non-alcoholic fatty liver disease in Korean adults. *Clin Chem Lab Med* 2010; 48: 175-180
- 26 Lee K. Relationship between uric acid and hepatic steatosis among Koreans. *Diabetes Metab* 2009; 35: 447-451
- 27 Bykov I, Jauhiainen M, Olkkonen VM, Saarikoski ST, Ehnholm C, Junnikkala S, Väkevä A, Lindros KO, Meri S. Hepatic gene expression and lipid parameters in complement C3(-/-) mice that do not develop ethanol-induced steatosis. *J Hepatol* 2007; 46: 907-914
- 28 Morino K, Petersen KF, Shulman GI. Molecular mechanisms of insulin resistance in humans and their potential links with mitochondrial dysfunction. *Diabetes* 2006; 55 Suppl 2: S9-S15
- 29 Sariçam T, Kircali B, Köken T. Assessment of lipid peroxidation and antioxidant capacity in non-alcoholic fatty liver disease. *Turk J Gastroenterol* 2005; 16: 65-70
- 30 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
- 31 Charlton M, Viker K, Krishnan A, Sanderson S, Veldt B, Kaalsbeek AJ, Kendrick M, Thompson G, Que F, Swain J, Sarr M. Differential expression of lumican and fatty acid binding protein-1: new insights into the histologic spectrum of nonalcoholic fatty liver disease. *Hepatology* 2009; 49: 1375-1384
- 32 Fabbrini E, deHaseth D, Deivanayagam S, Mohammed BS, Vitola BE, Klein S. Alterations in fatty acid kinetics in obese adolescents with increased intrahepatic triglyceride content. *Obesity (Silver Spring)* 2009; 17: 25-29
- 33 Woodruff TM, Ager RR, Tenner AJ, Noakes PG, Taylor SM. The Role of the Complement System and the Activation Fragment C5a in the Central Nervous System. *Neuromolecular Med* 2009 Sep 11. [Epub ahead of print]
- 34 Hollmann TJ, Mueller-Ortiz SL, Braun MC, Wetsel RA. Disruption of the C5a receptor gene increases resistance to acute Gram-negative bacteremia and endotoxic shock: opposing roles of C3a and C5a. *Mol Immunol* 2008; 45: 1907-1915
- 35 Monk PN, Scola AM, Madala P, Fairlie DP. Function, structure and therapeutic potential of complement C5a receptors. *Br J Pharmacol* 2007; 152: 429-448
- 36 Conroy A, Serghides L, Finney C, Owino SO, Kumar S, Gowda DC, Liles WC, Moore JM, Kain KC. C5a enhances dysregulated inflammatory and angiogenic responses to malaria in vitro: potential implications for placental malaria. *PLoS One* 2009; 4: e4953
- 37 Niederbichler AD, Hoesel LM, Westfall MV, Gao H, Ipaktchi KR, Sun L, Zetoun FS, Su GL, Arbabi S, Sarma JV, Wang SC, Hemmila MR, Ward PA. An essential role for complement C5a in the pathogenesis of septic cardiac dysfunction. *J Exp Med* 2006; 203: 53-61
- 38 Strey CW, Markiewski M, Mastellos D, Tudoran R, Spruce LA, Greenbaum LE, Lambris JD. The proinflammatory mediators C3a and C5a are essential for liver regeneration. *J Exp Med* 2003; 198: 913-923
- 39 Blatteis CM, Li S, Li Z, Perlik V, Feleder C. Signaling the brain in systemic inflammation: the role of complement. *Front Biosci* 2004; 9: 915-931
- 40 Mastroeni P, Clare S, Khan S, Harrison JA, Hormaeche CE, Okamura H, Kurimoto M, Dougan G. Interleukin 18 contributes to host resistance and gamma interferon production in mice infected with virulent *Salmonella typhimurium*. *Infect Immun* 1999; 67: 478-483
- 41 Gentile CL, Pagliassotti MJ. The endoplasmic reticulum as a potential therapeutic target in nonalcoholic fatty liver disease. *Curr Opin Investig Drugs* 2008; 9: 1084-1088
- 42 Solís Herruzo JA, García Ruiz I, Pérez Carreras M, Muñoz Yagüe MT. Non-alcoholic fatty liver

- disease. From insulin resistance to mitochondrial dysfunction. *Rev Esp Enferm Dig* 2006; 98: 844-874
- 43 Ji C. Dissection of endoplasmic reticulum stress signaling in alcoholic and non-alcoholic liver injury. *J Gastroenterol Hepatol* 2008; 23 Suppl 1: S16-S24
- 44 Devlin LA, Nguyen MD, Figueroa E, Gordon LE, Feldhoff PW, Lassiter HA. Effects of endotoxin administration and cerebral hypoxia-ischemia on complement activity and local transcriptional regulation in neonatal rats. *Neurosci Lett* 2005; 390: 109-113
- 45 Wang Y, Ausman LM, Russell RM, Greenberg AS, Wang XD. Increased apoptosis in high-fat diet-induced nonalcoholic steatohepatitis in rats is associated with c-Jun NH2-terminal kinase activation and elevated proapoptotic Bax. *J Nutr* 2008; 138: 1866-1871

■同行评价

本文综述内容较为重要, 提供了有意义的信息。

编辑 李军亮 电编 何基才

ISSN 1009-3079 CN 14-1260/R 2010年版权归世界华人消化杂志

●消息●

2008 年内科学类期刊总被引频次和影响因子排序

| 代码 | 期刊名称 | 总被引频次 | | | 影响因子 | | |
|------|-----------------------------------|-------|------|-------|-------|------|-------|
| | | 数值 | 学科排名 | 离均差率 | 数值 | 学科排名 | 离均差率 |
| 1170 | JOURNAL OF GERIATRIC CARDIOLOGY | 7 | 41 | -0.99 | 0.043 | 41 | -0.92 |
| G275 | WORLD JOURNAL OF GASTROENTEROLOGY | 5432 | 1 | 3.71 | 0.792 | 6 | 0.52 |
| G803 | 肝脏 | 586 | 25 | -0.49 | 0.594 | 11 | 0.14 |
| G938 | 国际呼吸杂志 | 645 | 22 | -0.44 | 0.294 | 34 | -0.43 |
| G415 | 国际内分泌代谢杂志 | 663 | 20 | -0.43 | 0.379 | 28 | -0.27 |
| G501 | 临床肝胆病杂志 | 582 | 27 | -0.50 | 0.441 | 22 | -0.15 |
| G658 | 临床荟萃 | 1709 | 8 | 0.48 | 0.356 | 32 | -0.32 |
| G257 | 临床内科杂志 | 875 | 16 | -0.24 | 0.412 | 24 | -0.21 |
| G855 | 临床消化病杂志 | 314 | 32 | -0.73 | 0.294 | 34 | -0.43 |
| G261 | 临床心血管病杂志 | 836 | 17 | -0.28 | 0.371 | 29 | -0.29 |
| G293 | 临床血液学杂志 | 408 | 31 | -0.65 | 0.329 | 33 | -0.37 |
| G491 | 岭南心血管病杂志 | 161 | 39 | -0.86 | 0.158 | 40 | -0.70 |
| G662 | 内科急危重症杂志 | 308 | 34 | -0.73 | 0.279 | 36 | -0.46 |
| G523 | 内科理论与实践 | 34 | 40 | -0.97 | 0.171 | 39 | -0.67 |
| G746 | 实用肝脏病杂志 | 312 | 33 | -0.73 | 0.562 | 14 | 0.08 |
| G190 | 世界华人消化杂志 | 2480 | 6 | 1.15 | 0.547 | 17 | 0.05 |
| G800 | 胃肠病学 | 619 | 23 | -0.46 | 0.621 | 10 | 0.19 |
| G326 | 胃肠病学和肝病杂志 | 580 | 28 | -0.50 | 0.415 | 23 | -0.20 |
| G083 | 心肺血管病杂志 | 246 | 37 | -0.79 | 0.361 | 31 | -0.31 |
| G419 | 心血管病学进展 | 585 | 26 | -0.49 | 0.410 | 25 | -0.21 |
| G260 | 心脏杂志 | 553 | 29 | -0.52 | 0.406 | 26 | -0.22 |
| G610 | 胰腺病学 | 268 | 35 | -0.77 | 0.366 | 30 | -0.30 |
| G234 | 中国动脉硬化杂志 | 934 | 15 | -0.19 | 0.557 | 16 | 0.07 |
| G267 | 中国实用内科杂志 | 2309 | 7 | 1.00 | 0.487 | 20 | -0.06 |
| G211 | 中国糖尿病杂志 | 1567 | 11 | 0.36 | 0.570 | 13 | 0.10 |
| G380 | 中国心血管杂志 | 256 | 36 | -0.78 | 0.225 | 37 | -0.57 |
| G203 | 中国心脏起搏与心电生理杂志 | 657 | 21 | -0.43 | 0.562 | 14 | 0.08 |
| G633 | 中国血液净化 | 680 | 19 | -0.41 | 0.546 | 18 | 0.05 |
| G119 | 中国循环杂志 | 694 | 18 | -0.40 | 0.406 | 26 | -0.22 |
| G231 | 中华肝脏病杂志 | 3283 | 4 | 1.84 | 1.119 | 2 | 1.15 |
| G235 | 中华高血压杂志 | 1168 | 14 | 0.01 | 0.730 | 8 | 0.40 |
| G639 | 中华老年多器官疾病杂志 | 166 | 38 | -0.86 | 0.207 | 38 | -0.60 |
| G876 | 中华老年心脑血管病杂志 | 588 | 24 | -0.49 | 0.442 | 21 | -0.15 |
| G155 | 中华内分泌代谢杂志 | 1612 | 10 | 0.40 | 0.897 | 5 | 0.73 |
| G156 | 中华内科杂志 | 3484 | 3 | 2.02 | 0.788 | 7 | 0.52 |
| G161 | 中华肾脏病杂志 | 1643 | 9 | 0.42 | 1.068 | 3 | 1.05 |
| G285 | 中华消化内镜杂志 | 1314 | 13 | 0.14 | 0.578 | 12 | 0.11 |
| G168 | 中华消化杂志 | 2571 | 5 | 1.23 | 1.025 | 4 | 0.97 |
| G892 | 中华心率失常学杂志 | 494 | 30 | -0.57 | 0.657 | 9 | 0.26 |
| G170 | 中华心血管病杂志 | 4186 | 2 | 2.63 | 1.375 | 1 | 1.64 |
| G172 | 中华血液学杂志 | 1501 | 12 | 0.30 | 0.489 | 19 | -0.06 |
| | 平均值 | 1154 | | | 0.520 | | |

以上数据摘自2009年版《中国科技期刊引证报告》(核心版). 科学技术文献出版社, 177-178.