

单味中药对膝骨性关节炎软骨细胞凋亡的作用述略

洛佳¹ 关雪峰^{2*}

1. 辽宁中医药大学, 辽宁 沈阳 110032

2. 辽宁中医药大学附属医院, 辽宁 沈阳 110032

中图分类号: R684. 3 文献标识码: A 文章编号: 1006-7108(2015) 10-1282-05

摘要: **目的** 粗略汇总单味中药对膝骨性关节炎软骨细胞凋亡的文献, 探究单味中药其作用机理。 **方法** 检索 1990 年至 2015 年期间 CNKI, 维普, pubmed 数据库上有关单味中药对膝骨性关节炎软骨细胞凋亡的国内外中英文文献, 从中筛选出所发表期刊具有影响力的、所选中药临床常用并具有代表性的、研究量大且具有针对性的文献, 将筛选出的文献进行分类, 总结提炼出核心结论并进行分析。 **结果** 国内外已经存在大量研究单味中药作用于软骨细胞机制的文献。国内文献多根据中医对本病的认识, 辨证虚实, 对应中药性味施治, 集中研究单味中药的临床疗效研究。国外的中医理论知识薄弱, 将中药抽离中医基础, 更关注中药内主要有效成分, 注重有效成分在软骨细胞中的作用靶点, 故对其机理研究较多。其中大部分中药的治疗作用与调节软骨细胞的凋亡密切相关。 **结论** 总体上, 国内外承认中药对本病的有效作用, 大量研究认为中药能够抑制软骨细胞的凋亡, 对软骨细胞的增殖有促进作用, 可以通过不同途径改善软骨损伤。

关键词: 膝骨性关节炎; 中药; 软骨细胞

The effect of single traditional Chinese herb on chondrocyte apoptosis in knee osteoarthritis

LUO Jia¹, GUAN Xuefeng²

1. Liaoning University of Traditional Chinese Medicine, Shenyang 110032

2. The Affiliated Hospital of Liaoning University of Traditional Chinese Medicine, Shenyang 110032, China

Corresponding author: GUAN Xuefeng, Email: lauralu0@163.com

Abstract: Objective To summarize articles about the mechanism of traditional Chinese drug on chondrocyte apoptosis of knee osteoarthritis (KOA) using a single herb. **Methods** All the Chinese and English research articles about the effect of single traditional Chinese herb on chondrocyte apoptosis of knee osteoarthritis from China national knowledge internet (CNKI), Vip Database, and PubMed database from 1990 to 2015 were searched. Articles from influential journals, with Chinese herbs representative in clinic, and typical and with a large amount of targeted research were chosen. The selected articles were classified, summarized, and analyzed. **Results** A lot of articles about mechanism of the use of single Chinese drug on chondrocytes have been published. Most domestic studies based on traditional Chinese medicine (TCM) theory and focused on clinical efficacy. The studies were weak of TCM knowledge. They pulled out herbs from TCM and focused on the main effective components and the targets in chondrocytes. Therefore the studies were more in the mechanism, among which the clinical effect of TCM on KOA was the inhibition of chondrocyte apoptosis. **Conclusion** On the whole, both national and international studies acknowledge the efficacy of traditional Chinese drugs on OA. Most studies show that traditional Chinese drug can inhibit chondrocyte apoptosis, promote chondrocyte proliferation, and repair cartilage injury.

Key words: Knee osteoarthritis; Traditional Chinese drug; Chondrocytes; Briefing

膝骨性关节炎(knee osteoarthritis, KOA)是临床上常见的退行性骨病,为目前导致中老年人畸形

的四大原因之一^[1],严重影响患者生活质量,给个人、家庭乃至社会带来严重负担。KOA的主要临床表现特点有疼痛、晨僵、活动受限和关节畸形。导致KOA的病机不明,大量研究发现不同时期KOA的软骨面形态特点不同,软骨退变的形态学改变与KOA病情严重程度相关^[2]。对膝骨性关节炎的治

基金项目: 辽宁省科技厅中医药治疗骨关节炎医院特色制剂及其临床诊疗标准化研究项目(2013226012)

* 通讯作者: 关雪峰, Email: lauralu0@163.com

疗仍在探寻当中,西医指南推荐运动疗法、药物治疗(如非甾类镇痛药和激素等),但其同时带来的副作用不可忽视,如非甾类药可损伤胃粘膜、引起出血,激素可引起糖、脂肪或钙离子等的代谢紊乱。中医主要用口服中药结合中医外治法或针灸推拿等,但中药的作用机理尚不明确,目前多数人认为软骨细胞凋亡是导致 KOA 的主要原因,很多中药可以抑制软骨细胞的凋亡,通过汇总中药作用机制相关文献,为中药在 KOA 领域的治疗提供理论依据。

1 中医病因病机

KOA 在中医领域属于“骨痹”范畴,有虚实之分。中医认为“骨痹”与筋、骨、经、脉相关,《内经》提到“病在骨,骨重不可举,骨髓酸痛,寒气至,名曰骨痹。”《张氏医通》曰:“膝为筋之府。”肝主筋、肾主骨,虚证多为肝肾阴虚、气血乏源,经筋失养,致不容而痛;实证多为风、寒、湿、瘀闭阻经脉,致不通而痛。临床上虚证多发生于年老体虚的慢性 KOA 患者,实证多见于慢性病急性发作的患者。虚实之证不可完全分开辩证,如虚证患者可能因为某些诱因出现关节积液,则为虚中有实,本痿标痹,实证患者也可能因为病久不愈而耗伤阴血而致实中有虚,治疗上应分清虚实主次,标本缓急,辩证施治。中药治疗 KOA 常从补益肝肾,活血通络入手,补益肝肾常用中药有鹿茸、牛膝、淫羊藿、杜仲、桑寄生、菟丝子、吴茱萸等,活血通络常用中药有川芎、丹参、赤芍、蒲黄、延胡索、乳香、三棱、红花等,因缺乏 KOA 单味中药使用频率研究,从所查文献中筛选临床常用、研究量较多且与软骨细胞凋亡相关的中药,参考临床常见证型,将所选中药简略分类。

2 补益肝肾类中药

2.1 鹿茸

中医认为鹿茸温补肾阳,可用于肾阳不足导致的腰膝酸软,强筋健骨,常与其他中药合用于骨折后期,加速骨质愈合。转化生长因子(transforming growth factor, TGF)超家族的亚家族包括 TGF 和骨形态发生蛋白(Bone morphogenetic protein, BMP),其中 TGF 通过抑制软骨细胞的增生肥大从而使其维持正常功能,而 BMP 能够促进软骨细胞的成熟^[3]。Smad 蛋白是 TGF 超家族的直接底物蛋白,是其传导中的最重要的通路^[4],缺乏 smad2/3 可导致软骨细胞的终末分化^[5],鹿茸可以提高 TGF 的表达,并同时激活 smad2/3,起到保护、修复软骨细胞

的作用^[6]。鹿茸归肝肾二经,其对 TGF/smad 通路的激活作用与中医所说的归经相似^[7]。鹿茸中的主要有效成分鹿茸多肽通过降低关节液中 IL-1、TNF 水平,大大的减少了膝关节内的炎症反应,进而减少软骨细胞的凋亡,延缓软骨退变^[8]。

2.2 牛膝

肾主骨,肝藏血,骨病责肝血、肾精不足,不能濡养骨髓,肝血亏虚,局部经络不荣而痛,经筋失养。牛膝有活血、补肾、强筋骨的功效,是 KOA 的主要引经药,具有引药下行的特质,可直达膝盖患处,其药味平和,为治疗骨痹常用药。牛膝常被分为川牛膝和怀牛膝,川牛膝以活血为主,怀牛膝以补益为主。软骨的主要成分是 II 型胶原,是软骨结构框架的基础,与软骨损伤密切相关。牛膝提取物可通过上调蛋白激酶 A 调节基 I β (Protein Kinase A Regulatory, PKAR I β) 促进软骨细胞增殖,改善骨质密度,稳定骨小梁结构^[9],抑制 NOS 的生成,减少免疫炎症反应,保护软骨细胞^[10]。P38MAPK 信号转导通路为传递细胞内外信息的重要通路,尤其在炎症等反应中时,牛膝可阻断此通路,抑制凋亡,进而保护软骨细胞,其主要成分为甾酮类化合物,可抑制葡萄糖氨基聚糖的降解,维持软骨细胞的增殖分化^[11]。

2.3 淫羊藿

淫羊藿又称仙灵脾,为壮阳要药,常用于肾阳虚衰导致的阳痿、尿频等,同时它还有祛风除湿的作用,与其辛温可散风寒有关,归经上归肝肾二经,中医认为,KOA 虽然病变累及于筋骨,但其病位之本在肝肾,其补肾作用可间接影响骨及软骨。近年来,软骨组织工程学正在兴起,通过直接的方法修复软骨缺损,在实践应用中常会使用一种促进剂,提高软骨的增殖效果。淫羊藿某种程度上可以促进软骨细胞增殖,并调控 iNOS 和 MMPs 来保护胶原和蛋白多糖^[12]。Sox9 在软骨生成过程中起重要作用,参与软骨细胞的增殖和分化和软骨细胞外基质部分成分表达,淫羊藿可以通过上调骨形态发生蛋白 2 促进 Sox9 的表达^[13,14]。

3 活血通络类中药

3.1 川芎

川芎在中医里属于活血止痛药,可治外伤所致的红肿疼痛,也可用于风湿痹痛,其主要成分川芎嗪有抗血小板凝集的作用,临床心脑血管疾病常用。软骨细胞凋亡的主要途径是诱导型一氧化氮合酶

(inducible nitric oxide synthase, iNOS) 途径,这一途径的激活可产生大量一氧化氮,在 IL-1 刺激下的软骨细胞可大量激活 iNOS 途径并表达,川芎嗪可抑制此表达^[15],同时生成的一氧化氮是诱导软骨细胞凋亡的主要原因^[16]。川芎嗪可降低 IL-1 的水平,降低基质金属蛋白酶-13 (MMP-13),从而降低其对细胞外基质的降解,使软骨退变得延缓^[17]。川芎嗪同样可以提高 SOD 活性,通过清除氧自由基而延缓退变进程^[18]。川芎嗪能够降低关节液中一氧化氮和前列腺素 E₂ 的含量,这两种物质均与疼痛有关,考虑川芎嗪改善 KOA 症状的机制与参与抗炎、镇痛过程有关^[19]。川芎独特的活血化瘀作用可降低 KOA 膝关节内高压,修复软骨传导性^[20],促进软骨细胞增殖期,使细胞的静止期和 DNA 合成前期向 DNA 合成期和增殖期转变^[21]。

3.2 丹参

丹参为活血调经药,常应用于心脑血管疾病,活血化瘀、改善微循环,此外,丹参活血祛瘀止痛,药性微寒,入肝经,适于关节红肿疼痛的症状,配伍祛风除湿药可用于风湿痹痛。丹参的主要成分是丹参酮 II A,同其他大部分活血药一样具有抗炎、抗氧化作用,抗炎清除氧自由基,通过提高 IGF-1 和 TGF- β ,促进软骨基质合成,抑制软骨细胞的凋亡^[22]。软骨退变其主要的病理变化为软骨纤维化,这与成纤维样滑膜细胞 (fibroblast-like synoviocytes, FLSs) 的增殖和结构变化有关^[23],丹参可抑制这一过程的进展^[24]。成年后软骨很难自我修复,因为软骨细胞是终末分化细胞,脂肪源性干细胞 (adipose-derived stem cells, ASCs) 可分化为多种细胞,经丹参诱导后增加了向软骨细胞分化的能力^[25],这一作用,为软骨细胞愈合、增殖的困难开辟了新途径。

4 其他类中药

人参是大补元气的要药,临床多用于元气虚脱之重症,而人参亦有补益肾气的作用,常与鹿茸配伍合用,二者相互增益彼此功效,是补益肾精的常用配伍。人参的有效成分为人参皂苷,按化学结构可分为多种亚型,其中人参皂甙 Rb1 可促进软骨细胞增殖,增加 II 型胶原 mRNA 的表达,保护软骨细胞^[26],通过阻滞钙离子通道活性抑制软骨细胞凋亡^[27]。Rg1 与 Rb1 作用相似,可通过抑制 PI3K/Akt 通路,抑制凋亡^[28]。人参皂甙 Rb1 能够降低环氧合酶 2 mRNA 的表达^[29],从而减少前列腺素 E₂,起到抗炎镇痛的效果^[30]。人参多糖能够使软骨细胞内氨基

葡聚糖含量增加,并且人参多糖用量越多,氨基葡聚糖增长的就越多,从而影响了软骨细胞的增殖率^[31]。软骨的组成软骨细胞和细胞外基质都含有较多的蛋白多糖,通过提高蛋白多糖的含量,可延缓 KOA 软骨的退变进程^[32]。

正常的软骨具有弹性,可以缓冲机械震荡,光滑的表面能减小摩擦。软骨中软骨细胞的量很少,大多是胶原和蛋白多糖,早期的软骨中含水量可达 90% 之多,靠蛋白多糖的亲水性而维持水的含量,随着年龄的增长而减少。目前认为,导致膝关节关节炎的主要原因是膝关节软骨细胞的凋亡。影响软骨细胞凋亡因素很多,机制复杂,至今不清。软骨细胞的主要代谢方式为无氧代谢,其能量来源尚不清楚,可能与关节腔滑液有关。细胞外基质是细胞存活的基础,基质减少可导致细胞凋亡^[33]。临床上常见 KOA 患者为高强度关节活动的工作者,机械性软骨磨损是导致软骨损伤的主要因素。反复对软骨施压可导致软骨弹性下降,大于 6MPa 的压力就可使软骨细胞凋亡^[34]。很多因素可以导致软骨细胞的凋亡,这点与 KOA 的形成密切相关,但具体机制尚在研究中。中药对 KOA 的作用是建立在大量临床经验数据的基础上的,主要治疗原则是补益肝肾、活血通络,治疗上因人施治,辨证论治。目前对中药治疗 KOA 机理研究的选药范围仍旧局限在临床常用药上,如青风藤、威灵仙、补骨脂、骨碎补、姜黄等等,因研究量较少,不予赘述。虽然临床上很少选用单味中药进行临床研究亦或治疗,大量的文献研究局限于体外细胞实验或动物实验,但通过对单味药作用机制的研究,可以完善 KOA 形成的病理机制的探究,对中药干预 KOA 机理提供理论依据,指导临床用药,方便规模推广。

【参 考 文 献】

- [1] Cooper CI, Adachi JD, Bardin T, et al. How to define responders in osteoarthritis. [J]. Curr Med Res Opin, 2013, 29 (6): 719-729.
- [2] Penq Z, Baena JC, Wanq M. Investigations of micron and submicron wear features of diseased human cartilage surfaces [J]. Proc Inst Mech Eng H, 2015, 229(2): 164-174.
- [3] 杨冠, 杨晓. TGF- β 超家族在软骨发生、发育和维持中的作用 [J]. 遗传, 2008, 30(8): 953-959.
Yang Guan, Yang Xiao. Roles of TGF- β superfamily in the genesis, development and maintenance of cartilage. [J]. Hereditas, 2008, 30(8): 953-959.
- [4] 黄金珠, 周昕, 黄昕, 等. 通脉大生片对肾虚排卵障碍型不孕大鼠卵巢 TGF- β 1 及 Smad7 表达的影响 [J]. 中华中医药杂

- 志,2015,30(3):833-836.
- Huang Jinzhu, Zhou Xin, Huang Xin, et al. Effects of Tongmai Dasheng tablet on expression of ovary TGF- β 1 and Smad7 in rat with ovulatory obstacle sterility induced by kidney deficiency[J]. China Journal of Traditional Chinese Medicine and Pharmacy, 2015,30(3):833-836.
- [5] Li TF, Darowish M, Zuscik MJ, et al. Smad3-deficient chondrocytes have enhanced BMP signaling and accelerated differentiation [J]. J Bone Miner Res, 2006,21(1):4-16.
- [6] 牛维,孙志涛,曹学伟,等. 单味药鹿茸调控大鼠骨关节炎软骨组织 smad2、3 表达的研究[J]. 中国中西医结合杂志, 2014,34(2):209-213.
- Niu Wei, Sun Zhitao, Cao Xuewei, et al. Regulation of single herb pilose antler on the expression of Smad2 and Smad3 in the cartilage of OA rats: an experimental research [J]. Chinese Journal of Integrated Traditional And Western Medicine, 2014,34(2):209-213.
- [7] 牛维,孙志涛,林定坤,等. 鹿茸归经与早期骨关节炎软骨靶器官 TGF- β 受体的相关性研究[J]. 中华中医药杂志, 2014,29(11):3626-3629.
- Niu Wei, Sun Zhitao, Lin Dingkun, et al. Study on the correlation between channel tropism of pilose antler and TGF- β receptors of cartilage target organs in early osteoarthritis[J]. China Journal of Traditional Chinese Medicine and Pharmacy, 2014,29(11):3626-3629.
- [8] 修忠标,孙磊. 鹿茸多肽对实验性膝骨性关节炎软骨细胞凋亡及相关细胞因子的影响[J]. 中国骨伤, 2012,25(5):418-423.
- Xiu Zhongbiao, Sun Lei. Effect of pilose antler polypeptide on apoptosis of chondrocyte and related cytokines in experimental knee osteoarthritis [J]. China Journal of Orthopaedics and Traumatology, 2012,25(5):418-423.
- [9] 孙奋勇,潘秋辉,洪岸. 牛膝促进成骨细胞增殖的作用与机理研究[J]. 中药材, 2004,27(4):264-266.
- Sun Fenyong, Pan Qiuhui, Hong An. The effect and mechanism research of achyranthes on osteoplast multiplication promotion [J]. Journal of Chinese Medicinal Materials, 2004,27(4):264-266.
- [10] 柯晖,黄宗著. 怀牛膝对 OA 模型兔膝关节液一氧化氮合酶与超氧化物歧化酶活性的影响[J]. 时珍国医国药, 2014,25(12):2889-2890.
- Ke Hui, Huang Zongzhu. Effect of Achyranthes bidentata on nitric oxide OA rabbit model of knee joint fluid synthase and superoxide dismutase activity [J]. Lishizhen Medicine and Materia Medica Research, 2014,25(12):2889-2890.
- [11] 林平冬,翁霞萍,刘发元,等. 牛膝有效成分防治骨关节炎的作用机制探讨[J]. 风湿病与关节炎, 2015,4(2):56-59.
- Lin Pingdong, Weng Xiaping, Liu Fayuan, et al. To explore the mechanism of Achyranthes bidentata effective components of prevention and cure of osteoarthritis [J]. Rheumatism and Arthritis, 2015,4(2):56-59.
- [12] Liu MH, Sun JS, Tsai SW, et al. Icarin protects murine chondrocytes from lipopolysaccharide-induced inflammatory responses and extracellular matrix degradation. Nutr Res, 2010,30(1):57-65.
- [13] Qin L, Zhang G, Hung WY, et al. Phytoestrogen-rich herb formula "XLGB" prevents OVX-induced deterioration of musculoskeletal tissues at the hip in old rats. J Bone Miner Metab, 2005,23 suppl:55-61.
- [14] Tew SR, Li Y, Pothacharoen P, et al. Retroviral transduction with Sox9 enhances re-expression of the chondrocyte phenotype in passaged osteoarthritic human articular chondrocytes. Osteoarthritis Cartilage, 2005,13(1):80-89.
- [15] 黄建花,何英,赖国旗,等. 川芎嗪对 IL-1 β 诱导的兔原代软骨细胞 iNOS 表达和 NO 合成的影响[J]. 第三军医大学学报, 2012,34(16):1642-1645.
- Hang Jianhua, He Ying, Lai Guoqi, et al. Tetramethylpyrazine inhibits interleukin-1 β -induced iNOS expression and NO synthesis in rabbit articular chondrocytes [J]. Journal of Third Military Medical University, 2012,34(16):1642-1645.
- [16] Vuolteenaho K, Moilanen T, Jalonen U, et al. TGF beta inhibits IL-1-induced iNOS expression and NO production in immortalized chondrocytes [J]. Inflamm Res, 2005,54(10):420-427.
- [17] 李应池,王晓霞,邱桐,等. 川芎嗪对鼠骨关节炎软骨组织病理学和 IL-1 β 表达的影响[J]. 中国中医骨伤科杂志, 2011,19(7):7-10.
- Li Yingchi, Wang Xiaoxia, Qiu Tong, et al. Effect of ligustrazine injection on histopathology and expression of IL-1 β in cartilage in rat model of osteoarthritis [J]. Chinese Journal of Traditional Medical Traumatology & Orthopedics, 2011,19(7):7-10.
- [18] 王文瑞,刘宏泽,卫小春,等. 川芎嗪防治膝关节软骨退变的实验研究[J]. 中国骨伤, 2004,17(2):20-22.
- Wang Wenrui, Liu Hongze, Wei Xiaochun, et al. Experimental study of therapeutic and preventive effects of ligustrazine on OA cartilage degeneration of the knee [J]. China Journal of Orthopaedics and Traumatology, 2004,17(2):20-22.
- [19] 梁桂洪,孙赫,黄宇新,等. 川芎嗪对实验性骨关节炎模型大鼠关节液中 NO 和 PGE2 的调节作用[J]. 动物医学进展, 2014,35(9):66-69.
- Liang Guihong, Sun He, Huang Yuxin, et al. Effect of Ligustrazine on NO and PGE2 in synovial fluid of experimental osteoarthritis model in rats [J]. Progress in Veterinary Medicine, 2014,35(9):66-69.
- [20] 岳珍,王嘉芙,吕红兵,等. 川芎嗪注射液对关节软骨传导性损伤的治疗作用实验研究[J]. 中国运动医学杂志, 1993,12(3):176-178.
- Yue Zhen, Wang Jiafu, Lu Hongbing, et al. Experimental study on the effect of Ligustrazine Injection in the treatment of articular cartilage injury conductivity [J]. Chinese Journal of Sports Medicine, 1993,12(3):176-178.
- [21] 李西海,刘伯龄,刘献祥,等. 川芎嗪含药血清干预软骨细胞周期作用机制的研究[J]. 中医正骨, 2009,21(2):1-3.
- Li Ximei, Liu Bailing, Liu Xianxiang, et al. Empirical study on the mechanism of action to blood serum contained with chuanxiongzin in intervening cartilage cell cycle [J]. The Journal of Traditional Chinese Orthopedics and Traumatology, 2009,21(2):1-3.

- [22] 张晓,张国庆,顾伯林,等. 丹参及其有效成分对骨代谢影响的实验研究进展[J]. 中国骨质疏松杂志,2015,21(1):112-116.
Zhang Xiao, Zhang Guoqing, Gu Bailin, et al. Current advance in the effect of salvia miltiorrhiza and its effective components on bone metabolism[J]. Chinese Journal of Osteoporosis, 2015, 21(1):112-116.
- [23] 张鹏,石关桐,郑昱新. 膝骨性关节炎滑膜细胞体外培养及生物学特性观察[J]. 中国骨伤,2006,19(11):656-658.
Zhang Peng, Shi Guantong, Zheng Yuxin. Biologic characteristics of human synoviocytes of gonarthrosis in vitro[J]. China Journal of Orthopaedics and Traumatology, 2006, 19(11):656-658.
- [24] 刘青松,唐中,刑艳,等. 丹参诱导成纤维样滑膜细胞 caspase-1 基因表达研究[J]. 四川医学,2010,31(12):1737-1740.
Liu Qingsong, Tang Zhong, Xing Yan, et al. The expressions of caspase-1 gene in fibroblast-like synoviocytes induced by salvia miltiorrhiza[J]. Sichuan Medical Journal, 2010, 31(12):1737-1740.
- [25] Ahrari I, Purhabibi Zarandi N, Khosravi Maharlooei M, et al. Adipose tissue derived multipotent mesenchymal stromal cells can be isolated using serum-free media[J]. Iran Red Crescent Med J, 2013, 15(4):324-329.
- [26] 王昭佩,杨仁轩,许树柴,等. 人参皂甙 Rb1 对外体软骨细胞 II 型胶原 mRNA 表达的影响[J]. 中国骨伤,2005,18(9):543-545.
Wang Zhaopei, Yang Renxuan, Xu Shuchai, et al. Effects of ginsenoside Rb1 on the expression of collagen II mRNA of chondrocytes in vitro [J] China Journal of Orthopaedics and Traumatology, 2005, 18(9):543-545.
- [27] Schnabel M, Marlovits S, Echkhoff G, et al. Differentiation-associated changes in morphology and gene expression in primary human articular chondrocytes in culture [J]. Osteoarthritis Cartilage, 2002, 10(1):62-70.
- [28] 袁芳,何晓瑾,邱亦江,等. 骨关节炎的软骨细胞凋亡机制[J]. 实用医学杂志,2015,31(4):666-668.
Yuan Fang, He Xiaojin, Qiu Yijiang, et al. Mechanism of chondrocyte apoptosis of osteoarthritis [J]. The Journal of Practical Medicine, 2015, 31(4):666-668.
- [29] 张业勇,程文丹,陈哲峰,等. 人参皂苷 Rg1 对软骨细胞 II 型胶原表达的影响[J]. 中国组织工程研究,2013,17(11):1917-1924.
Zhang Yeyong, Cheng Wendan, Chen Zhefeng, et al. Effect of ginsenoside Rg1 on type II collagen expression in chondrocytes [J]. Chinese Journal of Tissue Engineering Research, 2013, 17(11):1917-1924.
- [30] Alvarez-Soria MA, Largo R, Santillana J, et al. Long term NSAID treatment inhibits COX-2 synthesis in the knee synovial membrane of patients with osteoarthritis: differential proinflammatory cytokine profile between celecoxib and aceclofenac. Ann Rheum Dis. 2006;65(8):998-1005.
- [31] 杨国志,李振武,赵瑞强,等. 人参与多糖、黄芪多糖对大鼠骨关节炎细胞模型葡糖氨基聚糖合成的影响及其可能机制[J]. 中国生化药物杂志,2014,34(8):57-64.
Yang Guozhi, Li Zhenwu, Zhao Ruiqiang, et al. Effect and mechanism of panaxan and astragalus polysaccharides on glycosaminoglycan synthesis of rat osteoarthritic chondrocytes in vitro[J]. Chinese Journal of Biochemical Pharmaceutics, 2014, 34(8):57-64.
- [32] 谭杨,李景,汪晖,等. 人参与多糖抗大鼠骨关节炎及其机制研究[J]. 中药药理与临床,2013,29(3):91-93.
Tan Yang, Li Jing, Wang Hui, et al. Study on ginseng polysaccharide on rat osteoarthritis and its mechanism [J]. Pharmacology and Clinics of Chinese Materia Medica, 2013, 29(3):91-93.
- [33] Zemmyo M, Meharra EJ, Kuhn K, et al. Accelerated, aging-dependent development of osteoarthritis in alpha1 integrin-deficient mice. Arthritis Rheum, 2003, 48(10):2873-2880.
- [34] Clements KM, Bee ZC, Crossingham GV, et al. How severe must repetitive loading be to kill chondrocytes in articular cartilage? Osteoarthritis Cartilage, 2001, 9(5):499-507.
(收稿日期:2015-03-25,修回日期:2015-05-09)

(上接第 1281 页)

- [33] Goldring MB, Goldring SR. Articular cartilage and subchondral bone in the pathogenesis of osteoarthritis[J]. Annals of the New York Academy of Sciences, 2010, 1192(1):230-237.
- [34] Clemmons DR, Busby WH, Garmong A, et al. Inhibition of insulin-like growth factor binding protein 5 proteolysis in articular cartilage and joint fluid results in enhanced concentrations of insulin-like growth factor I and is associated with improved osteoarthritis[J]. Arthritis & Rheumatism, 2002, 46(3):694-703.
- [35] Tardif G, Hum D, Pelletier JP, et al. Regulation of the IGFBP-5 and MMP-13 genes by the microRNAs miR-140 and miR-27a in human osteoarthritic chondrocytes [J]. BMC Musculoskeletal Disorders, 2009, 10(1):148.
- [36] Li X, Wu JF. Recent developments in patent anti-cancer agents targeting the matrix metalloproteinases (MMPs) [J]. Recent Patents on Anti-Cancer Drug Discovery, 2010, 5(2):109-141.
- [37] Tortorella MD, Tomasselli AG, Mathis KJ, et al. Structural and inhibition analysis reveals the mechanism of selectivity of a series of aggrecanase inhibitors[J]. Journal of Biological Chemistry, 2009, 284(36):24185-24191.
- [38] Liang Z, Zhuang H, Wang G, et al. MiRNA-140 is a negative feedback regulator of MMP-13 in IL-1 β -stimulated human articular chondrocyte C28/I2 cells[J]. Inflammation Research, 2012, 61(5):503-509.
(收稿日期:2015-03-02,修回日期:2015-05-12)