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基于中西医理论指导的类风湿关节炎动物模型分析

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【摘要】 类风湿关节炎(rheumatoid arthritis,RA)是一种以关节炎症、滑膜增生、软骨和骨破坏为主要表现的系统性自身免疫性疾病。本文基于中西医理论对 RA 的认识,对常用 RA 动物模型进行梳理,从发病机制、造模方法、模型评价指标、临床症状吻合度以及模型适用研究方面进行分析,以期为建立更好的 RA 动物模型提供参考。

【关键词】 类风湿关节炎;动物模型;评价标准
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Analysis of animal models of rheumatoid arthritis based on theories of traditional Chinese and Western medicine

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【Abstract】 Rheumatoid arthritis (RA) is a complex autoimmune disease characterized by severe joint inflammation, synovial hyperplasia, and cartilage and bone destruction. Based on our understanding of RA and the theories of traditional Chinese and Western medicine, this paper presents the existing RA animal models and analyzes the modeling method, mechanisms, model evaluation indicators, clinical symptom coincidences, advantages and disadvantages, and model applicability to provide a reference for the establishment of better RA animal models.

【Keywords】 rheumatoid arthritis; animal model; evaluation criteria
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类风湿关节炎(rheumatoid arthritis,RA)是一种严重的伴有关节炎症、滑膜增生、软骨和骨破坏的系统性自身免疫性疾病[1]。RA 的一系列病症和并发症表现复杂繁多[2],但目前尚未有特效治疗药物,给患者和家庭带来沉重负担。因此,构建与人类疾病模拟度和吻合度高的动物模型,对更好地推

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动 RA 的基础研究和探索临床诊疗手段具有至关重要的作用。本文以相关文献研究为基础，选取广泛使用的模型，从中医和西医对 RA 病因病机和临床诊疗的理论指导角度，对现有 RA 实验动物模型进行评价分析和归纳总结，以期为 RA 的研究提供更多参考。

1　中医对类风湿关节炎的认识

1.1　RA 的中医病因病机

中医文献中没有记载与 RA 相应的病名，但根据 RA 的临床表现，其应当归属于中医“痹证”范畴。《黄帝内经》记载：“风寒湿三气杂至，合而为痹。”指出风寒湿邪侵袭机体而致痹；《金匮要略》曰：“少阴脉浮而弱……风血相搏，即疼痛如掣”认为营卫不足，邪气侵袭筋骨，闭阻血脉而致痹，指出素体虚弱在本病中的作用；后世医家提出“痹久必有淤血”、“淤血致痹”，指出了淤血在痹证中的作用；朱良春、王为兰指出“痰湿”、“痰瘀”在痹证中的重要作用，丰富了痹证的病因病机理论[3-4]。

经过历代医家的认识补充，痹证病因可概括为正气不足，卫外不固；风寒湿热，外邪入侵。痹证的病机根本为邪气痹阻经脉，即风、寒、湿、热、痰、瘀等邪气滞留于肢体筋脉、关节、肌肉，气血痹阻不通，不通则痛。

1.2　RA 的中医诊断标准、临床表现及证治分型

诊断标准参照《中医病证诊断疗效标准》[5]，临床表现可概括为：(1)关节疼痛肿胀、屈伸不利，甚则僵硬变形；(2)痛随寒重，局部紫暗；(3)关节触之热感，局部红热；(4)关节刺痛，局部紫暗，肌肤甲错；(5)发病与季节、气候、饮食有关。参照此标准，RA 的证治分型为：风湿痹阻证、寒湿痹阻证、湿热痹阻证、痰瘀痹阻证、瘀血阻络证、气血两虚证、肝肾不足证、气阴两虚证。

2　现代医学对类风湿关节炎的认识

2.1　RA 的现代病理机制

类风湿性关节炎是一种自身免疫性慢性炎症疾病，以关节肿痛、滑膜增生、炎性浸润、血管翳形、软骨和骨破坏为特征表现[6-7]。遗传因素、环境因素、免疫因素、炎症反应等在 RA 发病中发挥重要作用[8-11]。RA 的发病机制尚不十分明确，目前相关机制研究成果主要包括：(1)B 细胞分泌自身抗体、自身反应性 T 细胞激活、炎症细胞因子异常分泌等途径诱发 RA[12-14]，B 细胞通过抑制成骨细胞分化抑制 RA 的骨形成[15]；(2)外源性刺激如软骨寡聚体基质蛋白(cartilage oligomer matrix protein, COMP)激活 T 细胞免疫，产生细胞因子，诱导炎症反应和骨破坏导致 RA[16-17]；T 细胞异常免疫激活促进 B 细胞分泌自身抗体，促进 RA 进程[18]；T 细胞还与 MHC-Ⅱ类分子共同调控 RA 的进程[19]；(3)细胞因子失衡在 RA 中起着重要作用，如肿瘤坏死因子(tumor necrosis factor, TNF)通过 NF-κB 和 MAPK 信号通路调控一系列炎症反应，刺激滑膜细胞产生前列腺素和胶原酶[20-21]；TNF 信号传导还可促进谷胱甘肽的胱氨酸摄取和生物合成，以保护成纤维细胞免受铁凋亡的影响[22]；其他细胞因子如 IL-1、IL-6、IL-17 等也参与调控 RA[23]；(4)肠道菌群及其代谢物对 RA 发病起着重要作用[24-25]，如丁酸代谢物促进 RA 自身抗体的产生和骨破坏[26]，肠道菌群可通过促进抗坏血酸降解来促进早期 RA 进展[27]。

2.2　RA 的西医诊断标准与临床表现

诊断标准参照 2010 年美国风湿病协会/欧洲抗风湿联盟制定的类风湿关节炎分类诊断标准，即 ACR/EULAR2010 标准[28]。临床表现概括为：(1)关节受累；(2)血清学检测类风湿因子(rheumatoid factor, RF)或抗环瓜氨酸肽(cyclic citrullinated peptide, CCP)抗体阳性；(3)滑膜炎持续时间大于 6 周；(4)C 反应蛋白(C-reactive protein, CRP)或红细胞沉降率(erythrocyte sedimentation rate, ESR)升高；(5)炎症因子升高。

3　常用类风湿关节炎动物模型分析

3.1　RA 造模依据

根据 RA 病症特点，其造模依据可概括为：(1)外源性抗原诱导自身免疫反应，活化 B 细胞，产生免疫复合物；(2)外源刺激活化 T 细胞免疫，引起强烈炎症和抗体反应；(3)外源性抗原激活免疫与补体系统，产生免疫复合物诱发关节炎症；(4)细胞因子失衡引起炎症反应；(5)风寒湿热等外邪留滞经脉，痹阻气血；(6)脾肾亏虚，湿邪内生，痹阻经脉；(7)寒瘀互结，留滞肌肤，痹阻筋脉。

3.2　RA 模型评价指标

综合 RA 动物模型，其评价指标可概括为：(1)关节肿胀、炎症；(2)血清炎症因子升高；(3)滑膜组织增生，炎性浸润；(4)软骨和骨破坏；(5)$CD4^+$、

$CD8^+$ T 细胞数量上升;(6)神倦毛枯,活动受限。

3.3 常用 RA 动物模型

目前用于 RA 模型制备的动物主要包括啮齿类、兔、非人灵长类动物、犬类、小型猪等,其中啮齿类较为常用[29]。基于西医理论指导的 RA 模型主要根据 RA 的临床特征或致病机制构建而成,包括用外源刺激如牛 II 型胶原(collagen II, CII)、弗氏佐剂(complete Freund's adjuvant, CFA)、或血清等诱导的炎症模型及相关转基因动物模型。基于西医理论指导的常用的 RA 动物模型见表 1。中医药研究所用的 RA 模型,主要在西医构建的动物模型基础上,依据中医理论对 RA 的认识增加了环境因素等的影响,进而构建不同证型的模型。基于中医理论指导的常用的 RA 动物模型见表 2。

表 1 基于西医理论指导的类风湿关节炎动物模型分析

Table 1 Animal models for RA based on Western medicine

模型 Models	造模方法 Modeling method	造模依据 Basis	评价指标 Index	疾病症状 Disease symptom	适用研究 Application
胶原诱导性 RA 模型 Collagen induced RA model	间隔 6 d 或 21 d 于大鼠足跖或尾部注射 0.3 mL CII 与弗氏佐剂混合液[30-31] Inject 0.3 mL of a mixture of CII and Freund's adjuvant into the soles or tails of rats at intervals of 6 or 21 days[30-31]	(1)	(1) (2)	符合西医(1)(3)(5) Meet with the Western medicine criteria (1) (3) (5)	RA 的炎症、免疫机制 Inflammation and immune response of RA
弗氏佐剂诱导性 RA 模型 Freund's adjuvant induced RA model	大鼠尾部及足趾多点注射 0.2 mL CFA 乳剂[32];或只于大鼠后肢注射 0.1 mL CFA[33] Inject 0.2 mL of CFA emulsion into the tail and toes of rats at multiple points[32] or 0.1 mL of CFA into the hind limbs of rats only[33]	(2)	(1) (2) (3)	符合西医(1)(2)(3)(5) Meet with the Western medicine criteria (1) (2)(3) (5)	RA 的炎症、免疫机制,炎性药物筛选 Inflammation and immune mechanisms of RA, and drug discovery
卵蛋白诱导的 RA 模型 Ovalbumin induced RA model	前 3 周以 10 g/L 卵蛋白乳化液注射于家兔背部,第 4 周末将 5 mg 卵蛋白注射到家兔膝关节腔内[34] Inject 10 g/L ovalbumin emulsion into the back of the rabbit for 3 weeks, and 5 mg ovalbumin into the knee joint cavity of the rabbit at the end of the fourth week[34]	(3)	(1) (2) (3) (4)	符合西医(1)(3)(5) Meet with the Western medicine criteria (1) (3) (5)	RA 软骨和骨破坏的机制、治疗 RA cartilage and bone destruct
降植烷诱导的 RA 模型 Norphytane induced RA model	在第 0、9、18 周于小鼠腹腔注射 0.5 mL 降植烷[35];或于大鼠尾部注射 150 μL 降植烷[36] Inject 0.5 mL pristine into mice at 0, 9, and 18 weeks, intraperitoneally[35]; or inject 150 μL pristane into tail of rats[36]	(2)	(1) (4) (5)	符合西医(1)(5) Meet with the Western medicine criteria (1) (5)	T 细胞免疫在 RA 的机制研究 T cell in RA
COMP 诱导的 RA 模型 RA model induced by cartilage oligomer matrix protein	在第 1、35 天分别于小鼠尾部注射 CFA 和 COMP 的等量混合乳剂[17] Inject the equal volume mixed emulsion of CFA and COMP into the tail of mice respectively on the 1st and 35th days[17]	(2)	(1) (5)	符合西医(1)(5) Meet with the Western medicine criteria (1) (5)	补体系统激活在 RA 的作用 Complement activation in RA
K/BxN 血清转移性 RA 模型 K/BxN serum metastatic RA model	第 0、2 天于小鼠尾静脉注射 150 μL K/BxN 小鼠血清[37]或 100 μL 血清和 50 μL PBS 混合液[38] 150 μL K/BxN mouse serum[37] or 100 μL serum and 50 μL PBS mixture[38] was injected into mice on day 0 and 2	(1) (2)	(1) (2) (3)	符合西医(1)(3)(5) Meet with the Western medicine criteria (1) (3) (5)	神经、免疫系统及肠道菌群在 RA 的作用 The role of nervous system, immune system and gut microbiota in RA
人 TNF 转基因(Tgtc)小鼠 RA 模型 Human TNF transgenic (Tgtc) mouse RA model	运用转基因技术整合 3'端修饰的 human TNF-α 基因序列获得具有 FVB 背景的转基因小鼠品系[39] Transgenic mouse strains with FVB background obtained by integrating the 3'-end modified human TNF-α gene sequence using transgenic technology[39]	(4)	(1) (2) (3) (4)	符合西医(1)(3)(5) Meet with the Western medicine criteria (1) (3) (5)	TNF-α 在 RA 的作用 The role of TNF-α in RA

注:表中造模依据见"3.1 RA 造模依据",评价指标见"3.2 RA 模型评价指标",疾病症状见"2.2 RA 的西医诊断标准与临床表现"。

Note. See "3.1 RA modeling basis" for basis, "3.2 RA model evaluation indexes" for indexes, and "2.2 Western medical diagnostic criteria and clinical manifestations of RA" for the disease symptoms.

表 2　基于中医理论指导的类风湿关节炎动物模型分析

Table 2　Animal models for RA based on the traditional Chinese medicine

模型 Models	造模方法 Modeling method	造模依据 Basis	评价指标 Index	疾病症状 Disease symptom	适用研究 Application
风寒湿痹证 RA 模型 Wind cold dampness arthralgia syndrome RA model	将大鼠置于风速 5 m/s，温度 0 ~ 2℃，湿度 90% ~ 95%的气候箱 4 h，持续 45 d，并在第 15 天于大鼠尾部注射 0.1 mL CFA[40-41] Put the rats in a climate box with wind speed of 5 m/s, temperature of 0 ~ 2℃, and humidity of 90% ~ 95%, 4 h/d for 45 days, and inject 0.1 mL of CFA into the tail on the 15th day[40-41]	(2) (5)	(1) (4) (5)	符合中医(1)(5) Meet with Chinese medicine (1) (5)	祛风除湿药对 RA 的作用 The effect of "Qufeng Chushi" medicine for RA
风湿热痹证 RA 模型 Rheumatism heat arthralgia syndrome RA model	在第 1、13 天于大鼠注射 0.3 mL、0.1 mL CII 乳剂，并将其置于温度 36 ~ 38℃，风速 5 m/s，相对湿度≥95%的气候箱 30 min/d，持续 18 d[42-43] Inject 0.3 mL and 0.1 mL CII emulsion into the rats respectively on the 1st and 13th days, and place in a climate box with temperature of 36 ~ 38℃, wind speed of 5 m/s, and humidity of ≥95%, 30 min/d for 18 days[42-43]	(1) (5)	(1) (2)	符合中医(1)(5) Meet with Chinese medicine (1) (5)	治疗湿热痹证药物的研究 The effect of "Qingre Chushi" medicine for RA
寒证 RA 模型 Cold syndrome RA model	于家兔注射卵蛋白 21 d 后将后腿置于(-20) ~ (-25)℃环境中冷冻 1.5 h[44]；或将 Tgtc 小鼠置于 8℃、90%湿度的气候箱，每次 2 h，每天 2 次，连续 14 d[45] Inject ovalbumin into rabbit , and place its hind legs in the environment of -20~25℃ and freeze them for 1.5 h[44] or place Tgtc mice in a climate box at 8℃ and 90% humidity for 2 hous per time, twice per day, and for 14 d[45]	(3) (5)	(1) (3) (4)	符合中医(1)(2)(4)(5) Meet with Chinese medicine (1) (2) (4) (5)	乌头等药物改善 RA 关节和骨破坏 Aconitum treatment for RA joint and bone destruction
脾虚证 RA 模型 Spleen deficiency syndrome RA model	大鼠以 0.5 mg/kg 利血平腹腔注射 14 d，并于第 15、21 天尾部注射 0.2 mL 和 0.1 mL CII 乳剂[46] Inject 0.5 mg/kg reserpine into rat for 14 d, and 0.2 mL and 0.1 mL of CII emulsion on the 15th and 21st days[46]	(1) (6)	(1) (2) (5)	符合中医(1)(5) Meet with Chinese medicine (1) (5)	脾虚与免疫在 RA 中的研究 Spleen deficiency and immunity in RA
肾虚证 RA 模型 Kidney deficiency syndrome RA model	切除大鼠双侧卵巢后分别以 200 μg、100 μg 的 CII 乳剂尾部注射[47-48] Inject 200 μg and 100 μg CII emulsion into the rat after bilateral ovariectomy[47-48]	(1) (6)	(1) (3) (4)	符合中医(1)(5) Meet with Chinese medicine (1) (5)	补肾固元药改善 RA 骨破坏 "Bushen Guyuan" medicine improves bone destruction in RA
淤血痹阻证 RA 模型 Congestion and obstruction syndrome RA model	在第 1、15 天于大鼠注射 CII 乳剂，并以 0.1 mg/kg 盐酸肾上腺皮下注射，2 h 后置于 4℃冷水中游泳 5 min，连续 14 d[49] Inject CII emulsion and 0.1 mg/kg adrenal hydrochloride into rat, on the 1st and 15th days and place in cold water at 4℃ for 5 minutes for 14 consecutive day[49]	(1) (5) (7)	(1) (2) (5)	符合中医(1)(4)(5) Meet with Chinese medicine (1) (4) (5)	祛瘀生新药物对 RA 血液流变的研究 Study on blood rheology of RA with "Quyu Shengxin" medicine

注：表中造模依据见"3.1 RA 造模依据"，评价指标见"3.2 RA 模型评价指标"，疾病症状见"1.2 RA 的中医诊断标准、临床表现及证治分型"。
Note. See "3.1 RA modeling basis for basis", "3.2 RA model evaluation indexes" for indexes, and "1.2 traditional Chinese medicine diagnostic criteria, clinical manifestations and evidence-based classification of RA" for the disease symptoms.

4　讨论

目前常用的基于西医理论指导制备的 RA 动物模型可基本满足 RA 研究需求，但存在的主要问题在于所构建的动物模型尚不能完全模拟人类 RA 的临床症状，只能表现部分症状，这是由于 RA 是系统性自身免疫性疾病，涉及多系统、多器官、多组织的病变。中医药研究常用 RA 模型，即病证结合模型，其制备方法是在西医理论构建的模型基础上，再根据中医理论对 RA"风寒湿三气杂至，合而为痹"的基本认识，通过气候模拟等环境因素对动物的影响而构建不同证型的模型；该类模型存在的主要问题在于：(1)中医"证型"是根据患者自身的机体表现而辨别寒热阴阳，而非像现有 RA 病证结合模型依靠环境气候偏驳来辩证；(2)动物模型的四诊合参尚未建立一个可行的标准，且现有的病证结合模

型,病和证实际上是独立开来的。

不论是中医还是西医理论认识的 RA,都是复杂、多因素且具有一系列病理表现的疾病。临床上 RA 在不同的病理阶段都有占主导的病机和病理表现,若依据其不同时空的主要症状,将病程规范划分为不同阶段,结合基因编辑技术、外源性刺激和环境影响等因素,精准构建既满足西医机制探讨,也符合中医理论的 RA 动物模型,将有利于推动 RA 研究进程。

参 考 文 献(References)

[1] Zhang W, Chen Y, Liu Q, et al. Emerging nanotherapeutics alleviating rheumatoid arthritis by readjusting the seeds and soils [J]. J Control Release, 2022, 345: 851-879.

[2] Sapart E, Sokolova T, de Montjoye S, et al. Should we use glucocorticoids in early rheumatoid arthritis? Results at 5 years from the early RA UCLouvain Brussels cohort [J]. Rheumatology (Oxford), 2021, 60(12): 5576-5582.

[3] 高红勤, 朱良春, 朱婉华, 等. 朱良春治疗痛风经验应用体会 [J]. 中国中医药信息杂志, 2014, 21(8): 114-115.
Gao HQ, Zhu LC, Zhu WH, et al. Zhu Liangchun's experience in treating gout [J]. Chin J Inf Tradit Chin Med, 2014, 21(8): 114-115.

[4] 邵培培, 王北. 王为兰治疗类风湿关节炎临证经验 [J]. 北京中医药, 2017, 36(3): 242-244.
Shao PP, Wang B. Clinical experience of treating rheumatoid arthritis in Wang Weilan [J]. Beijing J Tradit Chin Med, 2017, 36(3): 242-244.

[5] 姜泉, 王海隆, 巩勋, 等. 类风湿关节炎病证结合诊疗指南 [J]. 中医杂志, 2018, 59(20): 1794-1800.
Jiang Q, Wang HL, Gong X, et al. Guidelines of diagnosis and treatment of rheumatoid arthritis disease and syndrome combination [J]. J Tradit Chin Med, 2018, 59(20): 1794-1800.

[6] Maijer KI, Gudmann NS, Karsdal MA, et al. Neo-epitopes-fragments of cartilage and connective tissue degradation in early rheumatoid arthritis and unclassified arthritis [J]. PLoS One, 2016, 11(3): e0149329.

[7] Smith MH, Berman JR. What is rheumatoid arthritis? [J]. JAMA, 2022, 327(12): 1194.

[8] Tsuchiya H, Ota M, Sumitomo S, et al. Parsing multiomics landscape of activated synovial fibroblasts highlights drug targets linked to genetic risk of rheumatoid arthritis [J]. Ann Rheum Dis, 2021, 80(4): 440-450.

[9] Rosetti F, Madera-Salcedo IK, Rodríguez-Rodríguez N, et al. Regulation of activated T cell survival in rheumatic autoimmune diseases [J]. Nat Rev Rheumatol, 2022, 18(4): 232-244.

[10] Ge X, Frank-Bertoncelj M, Klein K, et al. Functional genomics atlas of synovial fibroblasts defining rheumatoid arthritis heritability [J]. Genome Biol, 2021, 22(1): 247.

[11] Nayak RR, Alexander M, Deshpande I, et al. Methotrexate impacts conserved pathways in diverse human gut bacteria leading to decreased host immune activation [J]. Cell Host Microbe, 2021, 29(3): 362-377.

[12] Moura RA, Fonseca JE. B cells on the stage of inflammation in juvenile idiopathic arthritis: leading or supporting actors in disease pathogenesis? [J]. Front Med (Lausanne), 2022, 9: 851532.

[13] He J, Ju J, Wang X. The Current status of anti-citrullinated protein antibodies and citrullinated protein-reactive B cells in the pathogenesis of rheumatoid arthritis [J]. Mol Biol Rep, 2022, 49(3): 2475-2485.

[14] Kristyanto H, Blomberg NJ, Slot LM, et al. Persistently activated, proliferative memory autoreactive B cells promote inflammation in rheumatoid arthritis [J]. Sci Transl Med, 2020, 12(570): eaaz5327.

[15] Sun W, Meednu N, Rosenberg A, et al. B cells inhibit bone formation in rheumatoid arthritis by suppressing osteoblast differentiation [J]. Nat Commun, 2018, 9(1): 5127.

[16] Giwa R, Brestoff JR. Mitochondria transfer to $CD4^+$ T cells may alleviate rheumatoid arthritis by suppressing pro-inflammatory cytokine production [J]. Immunometabolism, 2022, 4(2): e220009.

[17] Zhao Y, Urbonaviciute V, Xu B, et al. Cartilage oligomeric matrix protein induced arthritis-a new model for rheumatoid arthritis in the C57BL/6 mouse [J]. Front Immunol, 2021, 12: 631249.

[18] Tahamoli-Roudsari A, Tabatabaei R, Alvandpur N, et al. Peripheral distributions of IL-4-producing CD4 + T cells and CD4 + CD25 + FoxP3 + T cells (Tregs) in rheumatoid arthritis patients with poor response to therapy are associated with HLA shared epitope alleles and ACPA status [J]. Immunol Res, 2022, 70(4): 481-492.

[19] Ge C, Weisse S, Xu B, et al. Key interactions in the trimolecular complex consisting of the rheumatoid arthritis-associated DRB1* 04: 01 molecule, the major glycosylated collagen II peptide and the T-cell receptor [J]. Ann Rheum Dis, 2022, 81(4): 480-489.

[20] Zhao B, Grimes SN, Li S, et al. TNF-induced osteoclastogenesis and inflammatory bone resorption are inhibited by transcription factor RBP-J [J]. J Exp Med, 2012, 209(2): 319-334.

[21] Wright HL, Chikura B, Bucknall RC, et al. Changes in expression of membrane TNF, NF-κB activation and neutrophil apoptosis during active and resolved inflammation [J]. Ann Rheum Dis, 2011, 70(3): 537-543.

[22] Wu J, Feng Z, Chen L, et al. TNF antagonist sensitizes synovial fibroblasts to ferroptotic cell death in collagen-induced arthritis mouse models [J]. Nat Commun, 2022, 13(1): 676.

[23] 罗帅, 李小枫, 黄成, 等. 炎症因子在类风湿关节炎中的研究进展 [J]. 中国药理学通报, 2022, 38(3): 330-338.
Luo S, Li XF, Huang C, et al. Research progress of inflammatory cytokines in rheumatoid arthritis [J]. Chin

Pharmacol Bull, 2022, 38(3): 330-338.

[24] Gupta VK, Cunningham KY, Hur B, et al. Gut microbial determinants of clinically important improvement in patients with rheumatoid arthritis [J]. Genome Med, 2021, 13(1): 149.

[25] Kishikawa T, Maeda Y, Nii T, et al. Metagenome-wide association study of gut microbiome revealed novel aetiology of rheumatoid arthritis in the Japanese population [J]. Ann Rheum Dis, 2020, 79(1): 103-111.

[26] He J, Chu Y, Li J, et al. Intestinal butyrate-metabolizing species contribute to autoantibody production and bone erosion in rheumatoid arthritis [J]. Sci Adv, 2022, 8(6): eabm1511.

[27] Zhao Y, Cheng M, Zou L, et al. Hidden link in gut-joint axis: gut microbes promote rheumatoid arthritis at early stage by enhancing ascorbate degradation [J]. Gut, 2022, 71(5): 1041-1043.

[28] Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative [J]. Ann Rheum Dis, 2010, 69(9): 1580-1588.

[29] 惠香香, 白明, 苗明三. 基于数据挖掘的 274 例类风湿关节炎动物模型应用分析 [J]. 中国比较医学杂志, 2021, 31(1): 79-86.
Hui XX, Bai M, Miao MS. Analysis of 274 rheumatoid arthritis animal models by data mining [J]. Chin J Comp Med, 2021, 31(1): 79-86.

[30] 陈彩娥, 崔向军, 郑可, 等. 胶原诱导型大鼠类风湿关节炎模型的制备 [J]. 泰山医学院学报, 2012, 33(12): 821-823.
Chen CE, Cui XJ, Zheng K, et al. Preparation of collagen-induced rat rheumatoid arthritis model [J]. J Taishan Med Coll, 2012, 33(12): 821-823.

[31] 裴冰. IL-38 通过 SIRT1/HIF-1α 信号通路调节 Th17/Treg 平衡抑制胶原诱导性关节炎大鼠炎性反应 [D]. 沈阳: 中国医科大学; 2021.
Pei B. IL-38 regulates Th17/treg balance through SIRT1/HIF-1αsignaling pathway and inhibits inflammatory response in collagen-induced arthritis rats [D]. Shenyang: China Medical University; 2021.

[32] 张瑶, 屠莹, 胡占嵩, 等. 祛风舒筋丸对佐剂关节炎大鼠免疫调节及血管内皮生长因子、细胞黏附分子-1 表达的影响 [J]. 安徽医药, 2019, 23(3): 454-458.
Zhang Y, Tu Y, Hu ZS, et al. The effect of Qufengshujin pills on immunoregulation and expression of VEGF and ICAM-1 in rats with adjuvant arthritis [J]. Anhui Med Pharm J, 2019, 23(3): 454-458.

[33] 刘佳钰, 李锐, 周威, 等. 薯蓣皂苷对弗氏佐剂诱导类风湿关节炎大鼠的影响 [J]. 中医学报, 2021, 36(10): 2173-2177.
Liu JY, Li R, Zhou W, et al. Effect of protodioscin on rheumatoid arthritis rats induced by freund's adjuvant [J]. J Chin Med, 2021, 36(10): 2173-2177.

[34] 曹庆勇, 王培源, 王巧云, 等. 通痹胶囊对类风湿性关节炎模型兔关节病变的影响 [J]. 中国中药杂志, 2018, 43(5): 1034-1041.
Cao QY, Wang PY, Wang QY, et al. Effects of Tongbi capsule on joint lesions in rabbits with rheumatoid arthritis [J]. Chin J Chin Mater Med, 2018, 43(5): 1034-1041.

[35] 陶云霞, 蔡磊, 沈辉, 等. 降植烷诱导小鼠类风湿关节炎的模型 [J]. 中国免疫学杂志, 2015, 31(11): 1498-1500.
Tao YX, Cai L, Shen H, et al. Pristine-induced rheumatoid arthritis model in mice [J]. Chin J Immunol, 2015, 31(11): 1498-1500.

[36] Tanner MR, Huq R, Sikkema WKA, et al. Antioxidant carbon nanoparticles inhibit fibroblast-like synoviocyte invasiveness and reduce disease severity in a rat model of rheumatoid arthritis [J]. Antioxidants (Basel), 2020, 9(10): 1005.

[37] 闫梦真, 余婕, 董甜甜, 等. 由肠道菌群变化研究资木瓜总苷对 K/BxN 小鼠血清转移性关节炎的治疗作用 [J]. 现代免疫学, 2020, 40(4): 265-271.
Yan MZ, Yu J, Dong TT, et al. Therapeutic effect of TSCS on K/BxN mouse serum-transfer arthritis via gut microbiota disturbance [J]. Curr Immunol, 2020, 40(4): 265-271.

[38] Liao YC, Wu SY, Huang YF, et al. NOX2-deficient neutrophils facilitate joint inflammation through higher pro-inflammatory and weakened immune checkpoint activities [J]. Front Immunol, 2021, 12: 743030.

[39] 朱兴旺, 赵文婷, 陈永, 等. 三水白虎汤对类风湿关节炎人 TNF-α 转基因小鼠模型的作用研究 [J]. 中国中西医结合杂志, 2020, 40(4): 480-484.
Zhu XW, Zhao WT, Chen Y, et al. Effect of Sanshui Baihu Decoction on the human TNF-α alpha transgenic mice with rheumatoid arthritis [J]. Chin J Integr Tradit West Med, 2020, 40(4): 480-484.

[40] 林也, 戴宗顺, 张婷, 等. 基于"以方测证"的类风湿关节炎风寒湿痹证动物模型的构建研究 [J]. 湖南中医药大学学报, 2021, 41(5): 668-672.
Lin Y, Dai ZS, Zhang T, et al. Construction of animal model of rheumatoid arthritis with wind cold dampness arthralgia syndrome based on the theory of "testing syndrome by formula" [J]. J Hunan Univ Chin Med, 2021, 41(5): 668-672.

[41] 李鑫, 魏艳霞, 林也, 等. 风寒湿外邪对痹证(佐剂性关节炎)发生发展的影响 [J]. 中国中西医结合杂志, 2017, 37(12): 1496-1501.
Li X, Wei YX, Lin Y, et al. Effect of exogenous evils of wind-cold-damp on the occurrence and development of Bi syndrome (adjuvant-induced arthritis) [J]. Chin J Integr Tradit West Med, 2017, 37(12): 1496-1501.

[42] 马腾茂, 刘飞, 王蓉, 等. 基于主成分分析和聚类分析的秦艽不同配伍药对对风湿热痹类风湿关节炎大鼠的作用研究 [J]. 中草药, 2017, 48(11): 2255-2260.
Ma TM, Liu F, Wang R, et al. Based on principal component analysis and cluster analysis to study effects of gentianae *Macrophyllae radix* in cold and heat compatibility in rheumatic

fever arthralgia rheumatoid arthritis model rats [J]. Chin Tradit Herb Drugs, 2017, 48(11): 2255-2260.

[43] 马腾茂, 刘飞, 王蓉, 等. 秦艽寒热不同配伍药对对风湿热痹类风湿关节炎大鼠 MMP-3、TIMP-1 表达及踝关节病理学改变的影响 [J]. 中草药, 2017, 48(9): 1812-1819.
Ma TM, Liu F, Wang R, et al. Effect of Gentianae *Macrophyllae radix* in different combinations on expression of MMP-3, TIMP-1, and ankle pathological changes in wind-damp-heat arthralgia rheumatoid arthritis model rats [J]. Chin Tradit Herb Drugs, 2017, 48(9): 1812-1819.

[44] 袁博, 王金海, 方晓丽, 等. 家兔类风湿关节炎寒证模型的建立与病理学研究 [J]. 中华中医药杂志, 2017, 32(7): 3117-3120.
Yuan B, Wang JH, Fang XL, et al. Establishment and pathological study of cold syndrome animal model of rheumatoid arthritis in rabbits [J]. China J Tradit Chin Med Pharm, 2017, 32(7): 3117-3120.

[45] 朱兴旺, 赵文婷, 赵晓峰, 等. 基于人 TNF-α 转基因关节炎小鼠建立寒痹模型及评价 [J]. 中国免疫学杂志, 2022, 38(4): 448-452, 461.
Zhu XW, Zhao WT, Zhao XF, et al. Establishment and evaluation of cold arthralgia model based on human TNF-α transgenic arthritis mice [J]. Chin J Immunol, 2022, 38(4): 448-452, 461.

[46] 杜中平, 赵宏艳, 肖诚, 等. 类风湿性关节炎脾虚证病证结合动物模型的建立 [J]. 世界科学技术(中医药现代化), 2012, 14(2): 1384-1392.
Du ZP, Zhao HY, Xiao C, et al. Establishment of disease-syndrome combination rat model of rheumatoid arthritis with spleen deficiency [J]. World Sci Technol Mod Tradit Chin Med Mater Med, 2012, 14(2): 1384-1392.

[47] 艾景录, 吕爱平, 徐世杰, 等. 性腺功能异常型肾虚痹证发生机理的实验研究 [J]. 中国中医基础医学杂志, 1995, 1(1): 42-44.
Ai JL, Lyu AP, Xu SJ, et al. Experimental study on pathogenesis of kidney deficiency arthralgia syndrome with gonadal dysfunction [J]. Chin J Basic Med Tradit Chin Med, 1995, 1(1): 42-44.

[48] 陶黎, 刘梅洁, 薛欣, 等. 益肾蠲痹丸对肾虚胶原诱导性关节炎大鼠踝关节骨质破坏的影响 [J]. 中医杂志, 2018, 59(5): 420-426.
Tao L, Liu MJ, Xue X, et al. Impact of yishen juanbi wan on ankle bone destruction of kidney deficiency collagen-induced arthritis rats [J]. J Tradit Chin Med, 2018, 59(5): 420-426.

[49] 李茜, 梁晓东, 曹永仓, 等. 类风湿关节炎血瘀证大鼠模型的制备及评价 [J]. 山东中医药大学学报, 2017, 41(5): 476-481.
Li Q, Liang XD, Cao YC, et al. Preparation and evaluation about rat models with blood stasis syndrome of rheumatoid arthritis [J]. J Shandong Univ Tradit Chin Med, 2017, 41(5): 476-481.

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