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基于中西医临床病证特点的强直性脊柱炎动物模型分析

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【摘要】 强直性脊柱炎(ankylosing spondylitis,AS)是一种以骶髂关节炎、脊柱关节炎为主要表现的自身免疫性疾病。该病好发于青壮年男性,致残率高,严重威胁患者生命健康。临床常用的治疗药物中生物制剂价格昂贵,激素、非甾体抗炎药、抗风湿药不良反应多。中医药可调节免疫、抗炎,临床疗效佳。为了深入研究强直性脊柱炎的发病机理和治疗药物、方法的研发及筛选,本文总结了现有强直性脊柱炎动物模型造模方法、机制及分析模型优缺点,对动物模型的中西医病证特点进行对比,评价中西医病证吻合度。构建中西医病证吻合度更高的强直性脊柱炎动物模型是中医药治疗强直性脊柱炎的关键。本文分析动物模型中西医病证吻合度,以期为强直性脊柱炎的中药研发、针灸治疗等中医疗法奠定基础。

【关键词】 强直性脊柱;动物模型;临床病症特点
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Analysis of ankylosing spondylitis animal model based on clinical characteristics of traditional Chinese and Western medicine

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【Abstract】 Ankylosing spondylitis is an autoimmune disease with sacroiliac arthritis and spinal arthritis as the main manifestations. The disease mainly occurs in young men, has a high disability rate, and is a serious threat to the life and health of patients. Biological agents are expensive, and many adverse reactions to hormones, non-steroidal anti-inflammatory drugs, and anti-rheumatic drugs have been recorded. Traditional Chinese medicine can regulate the immunity and anti-inflammatory effects of the disease, and has good clinical effects. To promote the further study of the pathogenesis of ankylosing spondylitis and the development and screening of therapeutic drugs and therapies, in this paper, we summarize the method and mechanisms of modeling of the existing animal model of ankylosing spondylitis and analyze the advantages and disadvantages of the model. To evaluate the agreements between Chinese and Western medicine clinical characteristics, we compare the characteristics of Chinese and Western medical syndromes of the animal model. Building an

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animal model of ankylosing spondylitis with a higher degree of consistency between traditional Chinese and Western medicine is the key to innovative research into traditional Chinese medicine method of treating ankylosing spondylitis. To lay the foundation for research into traditional Chinese medicines and acupuncture for ankylosing spondylitis, this paper analyzes the degree of concurrence between the Chinese and Western medicine clinical characteristics of animal models.

【**Keywords**】 ankylosing spondylitis; animal model; clinical syndrome characteristics

Conflicts of Interest: The authors declare no conflict of interest.

强直性脊柱炎(ankylosing spondylitis,AS)是一种严重的慢性炎症性疾病,主要累及中轴骨骼,影响脊柱和骶髂关节,常伴有关节外器官症状,如炎性肠病、葡萄膜炎、AS 相关心血管疾病等。据统计表明,AS 全球患病率约为 0.2%~1.4%[1]。该病好发于青壮年男性,致残率高,严重威胁患者生命健康。目前西医治疗 AS 多采用激素、非甾体抗炎药、抗风湿药、生物制剂等。药物治疗 AS 疗效尚可,但不良反应多,如耐药性、胃肠道反应、肝肾毒性等,且价格昂贵,需长期用药,停药易复发。中药复方治疗 AS 疗效确切,可调节机体免疫,控制炎症,发展前景广阔[2-3]。因此 AS 的中药创新研发意义重大。与中医证型相似度高的动物模型是中药研发的关键因素。目前 AS 模型众多,造模方法各异,不同模型症状有一定差异。临床研究主要以构建西医疾病模型为主,鲜见中医证候模型。本文通过分析 AS 动物模型的中西医病证吻合度,为构建完善的中医证候动物模型提出建议,推进中药新药研发及针灸治疗等中医疗法的发展。

1 AS 病因病机

1.1 AS 西医病因病机

AS 的发病机制复杂,病因不清。现代医学认为 AS 的致病因素有遗传因素、免疫因素、微生物感染、内分泌因素等[4-5]。AS 的发病关键是炎症反应和后期的病理性新骨生成。炎症导致了组织最初的损伤,随后出现愈合和修复,最后通过机械因素等独立机制导致骨骼再造,新骨生成,导致强直[6]。AS 是一种由多种致病途径和细胞类型介导的疾病,近来研究强调了局部免疫代谢环境、肠道免疫轴和 T 细胞可塑性在疾病发病机制中的重要性[7]。

1.2 AS 中医病因病机

中医将 AS 归属于“大偻”“肾痹”“督痹”“竹节风”“龟背风”等范畴,认为其病位在筋骨,病因病机为本虚标实。“大偻”首次见于《黄帝内经》,“阳气者,精则养神,柔则养筋。开阖不得,寒气从之,乃生大偻”,表述了大偻的病因病机。《素问·痹论篇》谓:“肾痹者,善胀,尻以代踵,脊以代头”,指出“肾痹”的症状是脊背屈曲。中医辨证将其分为湿热痹阻、寒湿痹阻、瘀血痹阻、肾阳亏虚、肝肾不足等[8]。中医认为肾主骨,肝主筋,肾精亏虚不能充髓,则骨骼失去濡养,肝血亏虚,则不能荣养筋骨。肝肾不足,正虚则外邪侵袭,风寒湿邪乘虚而入,邪滞经脉,不通则痛。如《素问》指出:“风寒湿三气杂至合而为痹也”。《诸病源候论》亦谓:“肝主筋而藏血。血为阴,气为阳。阳气,精则养神,柔则养筋。阴阳和同,则气血调适,共相荣养也,邪不能伤。若虚则受风,风寒搏于脊膂之筋,冷则挛急,故令背偻。”兼之久病多虚、多瘀,寒湿之邪日久化痰化瘀,痰瘀互结,胶着筋脉,发为背偻。

2 AS 中西医诊断标准

2.1 AS 西医诊断标准

西医诊断标准根据国际脊柱关节炎协会(ASAS)公布的 2009 年 ASAS 标准[9]拟订。脊柱关节炎的分类和诊断标准:(1)临床表现:①炎性腰背痛≥3 个月,发病年龄<45 岁;②X 线或 MRI 提示骶髂关节炎兼 1 个及以上 SpA 特征;③HLA-B27 阳性兼 2 个及以上 SpA 特征。(2)SpA 特征:①炎性腰背痛;②起止点炎;③关节炎;④指(趾)炎;⑤葡萄膜炎;⑥炎症性肠病;⑦银屑病;⑧SpA 家族史;⑨非甾体类抗炎药疗效好;⑩HLA-B27 阳性;⑪CRP 升高。临床表现中符合①、②或①、③者均可诊断为中轴型脊柱关节病,中轴型脊柱关节病中放射学阳性者可诊断为强直性脊柱炎。根据动物可出现的症状总结如下:①中轴关节炎;②炎性腰背痛;③HLA-B27 阳性;④起止点炎;⑤外周关节炎;⑥指(趾)炎;⑦葡萄膜炎;⑧炎症性肠病;⑨牛皮癣样皮肤或指甲病变;在判断与西医临床症状匹配度时符合①则赋值 20%,其余每一项赋值 10%。

2.2 AS 中医诊断标准

中医诊断标准根据《中药新药临床研究指导原则 试行》[8]拟订。每个证型主症总赋值 70%,次症总赋值 30%,总分 100%,主症、次症每一小项赋值具体见表 1。

表 1 强直性脊柱炎中医辨证分型

Table 1 Traditional Chinese medicine syndrome differentiation and typing of ankylosing spondylitis

辨证分型 Syndrome differentiation and classification	主症 Main symptoms	次症 Secondary symptoms	舌脉 Tongue and pulse	赋值 Assignment
湿热痹阻证 Damp heat obstruction syndrome	①晨僵;②发热;③脊背、腰骶疼痛;④脊柱活动度受限;⑤目赤肿痛;⑥四肢关节红肿热痛 ① Morning stiffness; ② fever; ③ pain in the back and lower back; ④ limited spinal mobility; ⑤ swelling and pain in the eyes; ⑥ redness, swelling, heat and pain in the joints of the limbs	①口干不欲饮或口渴;②肢体困重;③大便干;④小便黄 ① Dry mouth, no desire to drink or thirst; ② limb fatigue and heaviness;; ③ dry stool; ④ yellow urine	舌质红,苔黄厚腻或黄,脉滑数 Red tongue yellow, thick and greasy or yellowish moss, slippery pulse	符合 1 项主症时赋值 11.7%,符合 1 项次症赋值 7.5% 11.7% when 1 main symptom is met, 7.5% when 1 secondary symptom is met
寒湿痹阻证 Cold dampness obstruction syndrome	①腰骶、脊背疼痛;②脊柱活动度受限;③遇寒晨僵加重,遇热晨僵减轻 ①Lumbosacral and back pain; ② limited spinal mobility; ③ aggravated morning stiffness when encountering cold, and reduced morning stiffness when encountering heat	①肢体困重;②四肢冷痛 ①Limb fatigue and heaviness; ② cold pain in limbs	舌质淡,苔水滑或白,脉弦滑 Pale tongue, watery or white moss, stringy and slippery pulse	符合 1 项主症时赋值 23.3%,符合 1 项次症赋值 15% 23.3% when 1 main symptom is met, 15% when 1 secondary symptom is met
瘀血痹阻证 Stagnation of blood stasis and obstruction syndrome	①晨僵;②腰骶、脊背疼痛;③疼痛夜间加重,或刺痛;④脊柱活动度受限 ①Morning stiffness; ② lumbosacral and back pain; ③ pain worsens at night, or stings; ④ limited spinal mobility	①肌肤干燥少泽 ① Dry and dull skin	舌质暗或见瘀斑,脉涩或沉细 Dark tongue or petechiae, astringent or fine pulse	符合 1 项主症时赋值 17.5%,符合 1 项次症赋值 30% 17.5% when 1 main symptom is met, 30% when 1 secondary symptom is met
肾阳亏虚证 Kidney Yang deficiency syndrome	①晨僵;②腰、脊背、足跟疼痛;③脊柱活动度受限;④手足不温,畏寒喜暖,局部冷痛 ①Morning stiffness; ② pain in the waist, back and heels; ③ limited spinal mobility; ④ lukewarm hands and feet, aversion to cold and warmth, and local cold pain	①面色不华;②精神不振;③腰膝酸软;④遗精;⑤阳痿 ①Poor complexion; ② low spirits; ③ sore waist and knees; ④ nocturnal emission; ⑤ impotence	舌质淡,苔白,脉沉细 Tongue pale, moss white, veins sunken and fine	符合 1 项主症时赋值 17.5%,符合 1 项次症赋值 6% 17.5% when 1 main symptom is met, 6% when 1 secondary symptom is met
肝肾不足证 Syndrome of liver and kidney deficiency	①晨僵;②腰膝酸软;③腰骶、脊背、足跟疼痛;④脊柱活动度受限;⑤眩晕耳鸣;⑥局部酸痛 ①Morning stiffness; ② soreness and weakness in the waist and knees; ③ pain in the lumbosacral, spinal, and heel regions; ④ limited spinal mobility; ⑤ dizziness and tinnitus; ⑥ local soreness and pain	①盗汗;②手足心热;③肌肉瘦削 ①Night sweats; ② hot palms and feet; ③ thin muscles	舌质红,苔少或见剥脱,脉细数或沉细 Red tongue, scanty or flaking moss, fine or subtle pulse	符合 1 项主症时赋值 11.7%,符合 1 项次症赋值 10% 11.7% when 1 main symptom is met, 10% when 1 secondary symptom is met

3 AS 动物模型研究现状分析

AS 动物模型造模方式大致可分为 4 类,分别是附着点炎动物模型、HLAB27 转基因动物模型、炎症诱导的动物模型和其他动物模型。目前多以大鼠和小鼠为建模对象。鼠类价格低、饲养方便、生命周期短、操作简单,是良好的模型对象。AS 动物模型也有犬科、熊科及灵长类动物[10],但因其影响因素多、价格昂贵、饲养难度高,很少研究。文中对 AS 常见动物模型的造模方法和特点进行对比分析,参照中医证型诊断标准,进行中西医病证吻合度分析,见表 2。HLA-B27 转基因大鼠模型与西医吻合度高,临床表现相似度高,与中医吻合度在所有模型中较高,符合中医肾阳亏虚证,但其操作复杂,技术难度高、价格昂贵,难以广泛运用。HLA-B27 转基因小鼠模型中医吻合度在所有模型中较高,但因

其发病未涉及中轴关节，不合适进行研究。SKG 小鼠模型西医吻合度一般，中医吻合度在所有模型中最高，符合中医湿热痹阻证，有利于研究 AS 的中医致病机制。BALB/c 小鼠模型西医吻合度一般，中医吻合度低，符合中医湿热痹阻证，其操作简单，成模率高，疾病进程与人类相似，是较有价值的动物模型。TNF$^{\triangle ARE}$ 小鼠模型操作复杂，周期长，西医吻合度一般，中医吻合度低，符合中医肝肾不足证，该法利用基因工程技术，特异性敲除 TNF 中的 ARE 序列，与人类 AS 相似度尚可，适合研究人类肠道关节轴疾病相关机制。但此造模方法价格昂贵，技术难度高，不易推广。tmTNF 小鼠模型中医、西医吻合度低，符合中医肝肾不足证。tmTNF 小鼠的病理学与脊柱关节病患者的病理学相似度高，早期炎症阶段表现为受影响关节的附着点炎和滑膜炎，特征是嗜中性粒细胞浸润和间充质细胞积聚；随后，炎症的消退伴随异位骨形成，导致关节强直[11]。该模型利于评估针对疾病不同阶段的人类疗法的疗效。不足之处为利用转基因技术造模，周期长，技术要求严格。DBA/1 小鼠为自发性关节炎模型，操作简单，中西医吻合度低，符合中医肝肾不足证，是研究性别、压力、炎症和与人类关节炎之间关系的重要工具。(BXSB×NZB) F1 小鼠模型中西医吻合度均低，发病未涉及中轴关节，但适用于识别在疾病发病机制中多重易感性等位基因的相互作用和阐明环境因素和遗传在不同疾病表型(如强直性附着点

表 2　强直性脊柱炎动物模型中西医病证评价

Table 2　Evaluation of traditional Chinese and Western medicine syndrome in ankylosing spondylitis animal models

分类 Classification	模型 Model	造模方法 Modeling method	模型特点 Model characteristics	机制 Mechanism	临床符合度 Clinical compliance
HLA-B27 转基因动物模型 HLA-B27 transgenic animal model	Lewis 大鼠、Fisher 大鼠[14-17] Lewis rats, Fisher rats[14-17]	将 6.5 kb EcoR I 片段(含 HLA-B * 2705 基因)和 15 kb Sall-PvuI 片段(含人 β2-微球蛋白基因)显微注射入大鼠受精卵，构建双转基因大鼠模型 A double transgenic rat model was constructed by microinjecting a 6.5 kb EcoR I fragment (containing the HLA-B * 2705 gene) and a 15 kb Sall-PvuI fragment (containing the human β2-microglobulin gene) into the fertilized eggs of rats	优点：与人类脊柱关节病的临床和组织学相似度高 缺点：操作复杂，价格昂贵，技术要求高 Advantages: high clinical and histologic similarity to human spondyloarthropathies Disadvantages: complex, expensive and technically demanding operation	发病机制不明确，可能与同源二聚体形成[18-20]、HLA-B27 错误折叠[21]、肠道生态失调相关[22-25] Pathogenesis is unclear and may be associated with homodimer formation[18-20], HLA-B27 misfolding[21], and intestinal ecological dysregulation[22-25]	符合西医临床表现：①中轴关节炎；②炎性腰背痛；③HLA-B27 阳性；⑤外周关节炎；⑥指(趾)炎；⑦葡萄膜炎；⑧炎症性肠病；⑨牛皮癣样皮肤或指甲病变；吻合度 90%；符合中医肾阳亏虚证，主症：①晨僵；②腰、脊背、足跟疼痛；次症：②精神不振；⑤阳痿；吻合度 47% Consistent with clinical manifestations in western medicine: ① axial arthritis; ② inflammatory low back pain; ③ HLA-B27 positive; ⑤ peripheral arthritis; ⑥ finger (toe) inflammation; ⑦ uveitis; ⑧ inflammatory bowel disease; ⑨ psoriasis like skin or nail lesions, with a 90% degree of anastomosis; In line with the traditional Chinese medicine kidney yang deficiency syndrome, the main symptoms are: ① morning stiffness; ② pain in the waist, spine, and heel; Secondary symptoms: ② mental depression; ⑤ erectile dysfunction; consistency 47%
小鼠[26] Mice[26]	(β2m$^{-/-}$ · HLA-B27) F1 产生的 B27+后代互相杂交以获得 B27 + β2m$^{-/-}$ 动物模型 B27 + progeny from (β2m$^{-/-}$ · HLA-B27) F1 were crossed with each other to obtain a B27 + β2m$^{-/-}$ animal model	优点：与人类疾病部分临床表现类似 缺点：耗时长，有性别差异，雄性较雌性症状更严重，发病未涉及中轴关节， 不合适进行研究 Advantages: similar to some of the clinical manifestations of the disease in humans Disadvantages: time-consuming, gender differences, males have more severe symptoms than females, onset does not involve the mid-axial joints, unsuitable for studies		符合西医临床表现：⑤外周关节炎；⑥指(趾)炎；⑨牛皮癣样皮肤或指甲病变；吻合度 30%；符合中医瘀血痹阻，主症：①晨僵；次症：①肌肤干燥少泽；吻合度 47.5% Matches the clinical manifestations of Western medicine: ⑤ peripheral arthritis; ⑥ finger (toe) inflammation; ⑨ psoriasis-like skin or nail lesions; the degree of match is 30%; matches the Chinese medicine blood stasis obstruction, the main symptom: ① morning stiffness; the secondary symptom: ① skin dryness and lack of luster; the degree of match is 47.5%

续表2

分类 Classification	模型 Model	造模方法 Modeling method	模型特点 Model characteristics	机制 Mechanism	临床符合度 Clinical compliance
炎症诱导的动物模型 Animal models of inflammation induction	SKG 小鼠[27-32] SKG mice [27-32]	在 ZAP70 的 SH2 结构域上具有缺陷的 SKG 小鼠腹腔注射 β-葡聚糖或酵母多糖或通过阴道拭子将鼠衣原体接种到小鼠生殖道可诱导 SpA 疾病 SpA disease is induced in SKG mice with defects in the SH2 structural domain of ZAP70 by intraperitoneal injection of β-glucan or yeast polysaccharides or by inoculation of Chlamydia muridarum into the reproductive tract of mice by vaginal swabbing	优点:周期短,操作简单,无性别差异 缺点:注意饲养环境,环境菌群变化会影响疾病严重程度[33] Advantages: short cycle time, simple operation, no gender differences Disadvantages: pay attention to the rearing environment, changes in the environmental flora can affect the severity of the disease [33]	ZAP-70 是 T 细胞中关键的信号转导分子,编码 ZAP-70 SH2 结构域的基因突变,使胸腺中 T 细胞的阳性和阴性选择配对,导致胸腺产生致关节炎自身免疫性 $CD4^+$ T 细胞[27] Mutations in the gene encoding the structural domain of ZAP-70 SH2, a key signaling molecule in T cells, pair positive and negative selection of T cells in the thymus, leading to the production of arthritogenic autoimmune $CD4^+$ T cells in the thymus [27]	符合西医临床表现:①中轴关节炎;②炎性腰背痛;⑤外周关节炎;⑥指(趾)炎;⑧炎症性肠病;⑨牛皮癣样皮肤或指甲病变;吻合度 70%;符合中医湿热痹阻证,主症:①晨僵;③脊背、腰骶疼痛;⑤目赤肿痛;⑥四肢关节红肿热痛;次症:②肢体困重;吻合度 54.3% In line with the clinical manifestations of Western medicine: ① axial arthritis; ② inflammatory lower back pain; ⑤ peripheral arthritis; ⑥ finger (toe) inflammation; ⑧ inflammatory bowel disease; ⑨ psoriasis-like skin or nail lesions; with a degree of match of 70%; in line with the Chinese medicine of the damp-heat paralysis syndrome, the main symptom: ① morning stiffness; ③ spine, lumbar-sacral pain; ⑤ redness of the eyes and swelling pain; ⑥ redness, swelling, heat and pain of the joints of the limbs; the secondary symptom: ② heavy limb sleepyness; with a degree of match of 54.3%
	BALB/c 小[34-35] BALB/c mice [34-35]	BALB/c 小鼠腹膜内注射溶解于 100 μL PBS(0.14 mol/L 氯化钠溶于 0.01 mol/L 磷酸钠缓冲液,pH 7.2)中的蛋白多糖和弗氏完全佐剂,1 周和 4 周后,给小鼠重新注射 PBS 中的抗原和弗氏不完全佐剂 BALB/c mice were injected intraperitoneally with proteoglycans dissolved in 100 μL of PBS (0.14 mol/L NaCl dissolved in 0.01 mol/L sodium phosphate buffer, pH 7.2) and Fuchs' complete adjuvant, and the mice were re-injected with antigens in PBS and Fuchs' incomplete adjuvant after 1 and 4 weeks	优点:操作简单,成模率高 缺点:具有性别差异,雌性小鼠患病率高 Advantages: easy to use, high modeling rate Disadvantages: gender differences, high prevalence of disease in female mice	蛋白聚糖的一些 T 细胞表位已被表征为显性/致关节炎,由于人和小鼠蛋白聚糖之间的序列高度同源性,用人蛋白聚糖对易感 BALB/c 小鼠进行免疫会引发对小鼠的自身免疫反应,诱发关节炎和脊椎炎[35] Some T-cell epitopes of proteoglycans have been characterized as dominant/arthritogenic, and immunization of susceptible BALB/c mice with human proteoglycans triggers an autoimmune response against the mice, inducing arthritis and spondylitis, due to a high degree of sequence homology between human and mouse proteoglycans [35]	符合西医临床表现:①中轴关节炎;②炎性腰背痛;④起止点炎;⑤外周关节炎;⑥指(趾)炎;⑨牛皮癣样皮肤或指甲病变;吻合度 70%;符合中医湿热痹阻证,主症:③腰骶、脊背疼痛;④脊柱活动度受限;次症:②肢体困重;吻合度 30.9% Clinical manifestations of Western medicine: ① mid-axis arthritis; ② inflammatory low back pain; ④ origin and destination inflammation; ⑤ peripheral arthritis; ⑥ dactylitis; ⑨ psoriasis-like skin or nail lesions, with a degree of match of 70%; in line with the Chinese medicine of the damp-heat paralysis syndrome: ③ lumbosacral, spinal and dorsal pain; ④ spinal mobility restriction; the secondary symptom: ② heavy limb sleepyness; with a degree of match of 30.9%

续表2

分类 Classification	模型 Model	造模方法 Modeling method	模型特点 Model characteristics	机制 Mechanism	临床符合度 Clinical compliance
	TNF$^{\triangle ARE}$小[36-37] TNF$^{\Delta ARE}$ mice[36-37]	TNF$^{\triangle ARE}$ 模型造模方法为靶向敲除鼠 TNF 中 ARE 序列 TNF$^{\Delta ARE}$ model modeling method for targeted knockdown of ARE sequence in murine TNF	优点:成模率高; 缺点:操作复杂,技术难度高,价格昂贵 Advantages: high mold formation rate; Disadvantages: complex operation, technically difficult and expensive	TNF 调节因子 ARE 的缺失导致 TNF 过度表达,诱导肠道炎症和 SpA[36] Deletion of the TNF regulator ARE leads to TNF overexpression, inducing intestinal inflammation and SpA[36]	符合西医临床表现:①中轴关节炎;②炎性腰背痛;④起止点炎;⑤外周关节炎;⑧炎症性肠病;吻合度 60%;符合中医肝肾不足证,主症:③腰骶、脊背、足跟疼痛;④脊柱活动度受限;次症:③肌肉瘦削;吻合度 33.4% In line with the clinical manifestations of Western medicine: ① axial arthritis; ② inflammatory low back pain; ④ origin and destination inflammation; ⑤ peripheral arthritis, ⑧ inflammatory bowel disease; with a degree of match of 60%; in line with the Chinese medicine liver and kidney deficiency syndrome, the main symptom: ③ lumbosacral, spine, heel pain; ④ spinal mobility limitation; the secondary symptom: ③ thin muscles; with a degree of match of 33.4%
	TgA86 小鼠[38,11] TgA86 mice[38,11]	将含有 muTNF$_{\triangle 1-12}$珠蛋白杂交基因的 BamHI-Sal I 片段显微注射到(CBA X C57BL/6)F2 杂交小鼠的受精卵中 BamHI-Sal I fragment containing the muTNF$_{\triangle 1-12}$ bead protein hybrid gene was microinjected into fertilized eggs of (CBA X C57BL/6) F2 hybrid mice	优点:与人类病理表现相似度高,成模率高; 缺点:操作复杂,周期长 Advantages: high similarity to human pathological manifestations, high mold-forming rate; Disadvantages: complex operation, long cycle time	该转基因小鼠过度表达鼠 TNF 的突变跨膜蛋白(muTNF$_{\triangle 1-12}$),跨膜 TNF 通过协同 p55/p75 TNFR 信号传导介导其致关节炎活性[38] This transgenic mouse overexpresses a mutant transmembrane protein of murine TNF (muTNF$_{\triangle 1-12}$), and transmembrane TNF mediates its arthritogenic activity through synergistic p55/p75 TNFR signaling mediates its arthritogenic activity[38]	符合西医临床表现:①中轴关节炎;②炎性腰背痛;④起止点炎;⑤外周关节炎;吻合度 50%;符合中医肝肾不足证,主症:③腰骶、脊背、足跟疼痛;④脊柱活动度受限;次症:③肌肉瘦削;吻合度 33.4% In line with the clinical manifestations of Western medicine: ① central axis arthritis; ② inflammatory low back pain; ④ origin and destination inflammation; ⑤ peripheral arthritis, with a degree of match of 50%; in line with the Chinese medicine liver and kidney deficiency syndrome, the main symptom: ③ pain in the lumbosacral region, spine, and heel; ④ limitation of spinal mobility; the secondary symptom: ③thin muscles; with a degree of match of 33.4%
附着点炎的动物模型 Animal models of adhesion pitting	DBA/1 小鼠[39-40] DBA/1 mice[39-40]	衰老雄性 DBA/1 小鼠 Senescent male DBA/1 mice	优点:与人类病理表现相似度高,成模率高,操作简单; 缺点:具有性别差异、环境差异,周期长 Advantages: high similarity to human pathological manifestations, high modeling rate, simple operation; Disadvantages: gender differences, environmental differences, long lead times	激素、衰老、环境、行为、压力等因素参与了 DBA/1 小鼠附着点炎、关节炎和关节强直的自发发展过程[39-41] Hormonal, aging, environmental, behavioral, and stress factors are involved in the spontaneous development of attachment point inflammation, arthritis, and joint ankylosis in DBA/1 mice[39-41]	符合西医临床表现:④起止点炎;⑤外周关节炎;⑥指(趾)炎;⑨牛皮癣样皮肤或指甲病变;吻合度 40%;符合中医肝肾不足证,主症:①晨僵;⑥局部酸痛;次症:②手足心热;吻合度 33.4% In line with the clinical manifestations of Western medicine: ④ starting and ending point inflammation; ⑤ peripheral arthritis; ⑥ finger (toe) inflammation; ⑨ psoriasis like skin or nail lesions; 40% fit; in line with the Chinese medicine liver and kidney deficiency syndrome, the main symptoms: ① morning stiffness; ⑥ local soreness; the secondary symptom: ② hand, foot, and heart heat; with a fit rate of 33.4%

续表2

分类 Classification	模型 Model	造模方法 Modeling method	模型特点 Model characteristics	机制 Mechanism	临床符合度 Clinical compliance
	(BXSB×NZB)F1 小鼠[12] (BXSB×NZB)F1 mice[12]	(BXSB×NZB)F1 小鼠 (BXSB×NZB)F1 mice	优点:操作简单,成模率高; 缺点:具有性别差异,雄性出现强直性附着点炎,雌性出现系统性红斑狼疮,发病未涉及中轴关节 Advantages: easy to perform, high rate of mold formation; Disadvantages: gender-specific, males present with ankylosing adhesion pemphigoid, females present with systemic lupus erythematosus, onset of disease does not involve the midshaft joints	源自 BXSB 和 NZB 的易感性等位基因的联合作用参与了关节病的发病机制,可能与 IFN-γ 和 IL-17 上调介导 BMP 信号通路相关[12] Combined action of susceptibility alleles derived from BXSB and NZB is involved in the pathogenesis of arthropathy and may be associated with the upregulation of IFN-γ and IL-17 mediating the BMP signaling pathway[12]	符合西医临床表现:④起止点炎;⑤外周关节炎;吻合度 20%;符合中医肝肾不足证,主症:①晨僵;⑥局部酸痛;吻合度 23.4% In line with the clinical manifestations of Western medicine: ④ inflammation at the starting and ending points; ⑤ peripheral arthritis; 20% fit; In line with the traditional Chinese medicine liver and kidney deficiency syndrome, the main symptoms are: ① morning stiffness; ⑥ local soreness; fit 23.4%
	ANK/ANK 小鼠[42-43] ANK/ANK mice[42-43]	ANK 突变小鼠的杂合子雄性后代与(C3HeB/FeJ×C57BL/6J-A^{W-J})F1 杂交,杂交后代继续重复杂交以维持 ANK 基因 Heterozygous male progeny of ANK mutant mice were crossed with (C3HeB/FeJ×C57BL/6J-A^{W-J}) F1, and the cross progeny continued to repeat the cross to maintain the ANK gene	优点:无性别差异,与人类 SpA 疾病相似度高; 缺点:周期长,操作复杂,小鼠进行性强直为非炎症介导 Advantages: no sex differences, high similarity to human SpA disease; Disadvantages: long cycle time, complex operation, progressive tonus in mice is non-inflammatory mediated	ANK 编码一种转运无机焦磷酸盐的跨膜蛋白,ANK 功能丧失使焦磷酸盐沉积于细胞内,导致过量羟基磷灰石钙沉积,椎间盘或软骨钙化引起关节或脊柱强直[42] ANK encodes a transmembrane protein that transports inorganic pyrophosphate, and loss of ANK function allows pyrophosphate to be deposited intracellularly, leading to excess calcium hydroxyapatite deposition and calcification of the intervertebral discs or cartilage resulting in ankylosis of the joint or spine[42]	符合西医临床表现:①中轴关节炎;②炎性腰背痛;⑤外周关节炎;⑥指(趾)炎;吻合度 50%;符合中医肝肾不足证,主症:①晨僵;③腰骶、脊背、足跟疼痛;④脊柱活动度受限;次症:③肌肉瘦削;吻合度 45.1% Consistent with clinical manifestations in Western medicine: ① axial arthritis; ② inflammatory lower back pain; ⑤ peripheral arthritis; ⑥ finger (toe) inflammation; 50% fit; In line with the traditional Chinese medicine liver and kidney deficiency syndrome, the main symptoms are: ① morning stiffness; ③ pain in the lumbosacral; spinal, and heel regions; ④ limited spinal mobility; and the secondary symptoms are: ③ thin muscles; fit 45.1%
其他动物模型 Other animal models	(MRL/rpl×C3H/lpr;MC)F1 小鼠[44] (MRL/rpl×C3H/lpr;MC)F1 mice[44]	由两种 Fas 缺陷型小鼠进行杂交,(MRL/rpl×C3H/lpr;MC)F1 Hybridization by two Fas-deficient mice, (MRL/rpl × C3H/lpr; MC) F1	优点:操作简单,成模率高; 缺点:具有性别差异,雄性发病率高,发病未涉及中轴关节 Advantages: easy to perform, high rate of mold formation Disadvantages: gender differences, high incidence in males, onset of disease not involving the mid-axial joints	与 7 号染色体显性基因座和 Y 连锁基因座的共同作用相关 Associated with the co-occurrence of dominant and Y-linked loci on chromosome 7	符合西医临床表现:④起止点炎;⑤外周关节炎;吻合度 20%;符合中医肝肾不足证,主症:①晨僵;⑥局部酸痛;吻合度 23.4% It is consistent with the clinical manifestations of Western medicine: ④ origin and destination inflammation; ⑤ peripheral arthritis; the degree of coincidence is 20%; it is consistent with the evidence of insufficiency of liver and kidney in Chinese medicine, and the main symptoms are: ① morning stiffness; ⑥ localized aching pain; the degree of coincidence is 23.4%

续表2

分类 Classification	模型 Model	造模方法 Modeling method	模型特点 Model characteristics	机制 Mechanism	临床符合度 Clinical compliance
	A20 缺陷小鼠[45-46] A20-deficient mice[45-46]	$A20^{fl/fl}$ Cd11c-Cre 小鼠 $A20^{fl/fl}$ Cd11c-Cre mice	优点:成模率高;缺点:小鼠易死亡 Advantages: high rate of mold formation; Disadvantages: mice die easily	A20 可维持免疫稳态,抑制 NF-κB 活化,控制炎症反应。DC 中缺乏 A20 的小鼠会出现自发的 DC 激活、T 细胞激活和 T 细胞扩增导致免疫紊乱[45] A20 maintains immune homeostasis, inhibits NF-κB activation, and controls inflammatory responses. Mice lacking A20 in DC develop spontaneous DC activation, T-cell activation, and T-cell expansion leading to immune disorders[45]	符合西医临床表现:①中轴关节炎;②炎性腰背痛;④起止点炎;⑤外周关节炎;⑧炎症性肠病;吻合度 60%;符合中医肝肾不足证,主症:①晨僵;③腰骶、脊背、足跟疼痛;④脊柱活动度受限;⑥局部酸痛;吻合度 46.8% Consistent with clinical manifestations in Western medicine: ① axial arthritis; ② inflammatory lower back pain; ④ starting and ending point inflammation; ⑤ peripheral arthritis; ⑧ inflammatory bowel disease; 60% fit; In line with the traditional Chinese medicine liver and kidney deficiency syndrome, the main symptoms are: ① morning stiffness; ③ pain in the lumbar, sacral, spinal, and heel regions; ④ limited spinal mobility; ⑥ local soreness; fit 46.8%

注:高吻合度,中医≥70%,西医≥75%;一般吻合度,50%≤中医<70%,55%≤西医<75%;低吻合度,中医<50%,西医<55%。
Note. High degree of anastomosis, traditional Chinese medicine ≥ 70%, Western medicine ≥ 75%. General fit, 50% ≤ traditional Chinese medicine < 70%, 55% ≤ Western medicine < 75%. Low degree of anastomosis, traditional Chinese medicine < 50%, Western medicine < 55%.

炎和系统性红斑狼疮)发展中的关系机制[12]。ANK/ANK 小鼠模型中西医吻合度低,符合中医肝肾不足证,ANK/ANK 小鼠与人类 AS 影像学改变相似度高,但这种强直是非免疫介导的疾病[13]。(MRL/rpl×C3H/lpr;MC)F1 小鼠模型中西医吻合度低,符合中医肝肾不足证。此模型适合研究 AS 附着点炎,但价格昂贵,耗时长,不易获得。$A20^{fl/fl}$ Cd11c-Cre 小鼠模型西医吻合度一般,中医吻合度在所有动物模型中较高,符合中医肝肾不足证,此模型操作技术要求高,周期长,有待完善。表中动物模型西医吻合度较高,中医证型吻合度较低,在 AS 动物模型中难以体现中医诊断标准。

4 讨论

西医的非甾体药、抗风湿药、生物制剂均无法治愈 AS[47]。中药有良好的抗炎作用,是治疗多种炎症和炎症相关疾病的有效方法[48]。中医临床吻合度高的动物模型对中药研发具有重要意义。因此,建立高吻合度的 AS 中医动物模型势在必行。由于西医不同造模方法形成的动物模型倾向于不同的中医证型,笔者认为,可先规范验证各类西医造模方法与不同中医证型吻合度,在此基础上,根据所倾向的中医证型再进行二次造模,以提高中医证型临床吻合度。湿热痹阻证可通过将鼠置于人工气箱模拟的湿热环境,同时予高糖饲料、猪油、蜂蜜水、二锅头等饲养[49]造模;通过湿热评分[50],临床关节炎分级[51]评估模型。AS 寒湿痹阻证模型将鼠置于人工气候箱模拟的寒湿环境造模;通过行皮肤、毛发、大便等评分验证模型[52]。AS 瘀血痹阻证模型通过游泳结合注射 10% 高分子右旋糖酐生理盐水液[53]造模;模型验证通过观察鼠尾部皮肤状态,如是否出现鳞屑、脱皮进行评估。还可采集大鼠舌图像和测量大鼠耳廓血流灌注量验证模型[54]。AS 肾阳亏虚证模型采用灌胃羟基脲[55]二次造模,大鼠出现精神差、四肢温低、体重减轻、毛发杂乱、反应迟钝等表现,提示肾阳虚证型造模成功。肝肾亏虚证型的重要表现是骨质疏松[56]。雌激素对维持骨稳态具有重要作用[57]。有文献采取切除卵巢的方式进行肝肾不足型骨质疏松模型造模[58]。此种造模方法值得参照。模型验证通过主证中的足跟疼痛评估,观察鼠是否跛行、舔舐足跟和附着点炎评分[59]评估足跟疼痛。

表中动物模型西医吻合度较高,中医证型吻合度较低,在 AS 动物模型中难以体现中医诊断标准。目前尚无一致的动物中医证型评估方法,在探索中医药治疗 AS 时,后续应进一步构造吻合度更高的中西医病证模型,以期为中医药治疗 AS 提供科学基础。

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