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基于中西医临床病证特点的银屑病性关节炎动物模型分析

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【摘要】 近年来,随着银屑病性关节炎在我国的发病率逐渐升高且其无法治愈,已经成为了医学事业上的一大难题。本研究基于中西医临床病证特点,积极探讨银屑病性关节炎的发病病机,总结目前现有的动物模型并进行分析评价。对当前所查询到符合本题的文献进行整理归纳总结,通过银屑病性关节炎的中西医病因病机研究、中西医的诊断标准和动物模型的特点及与临床吻合度的分析,给予现有动物模型吻合度评分。本论述发现人白细胞抗原转基因鼠模型、多重杂交转基因小鼠模型以及甘露聚糖诱导的小鼠模型吻合度评分最高。由于银屑病性关节炎多见于欧洲,目前动物模型的制备方法多由国外传来,中医病证特点制备的动物模型极少,因此,西医诊断的模型吻合度评分整体高于中医诊断的吻合度评分。希望未来可以结合中医的独特诊疗方法,进一步完善银屑病性关节炎的动物模型种类,为中西医结合治疗银屑病性关节炎构建更理想的动物模型提供基础。

【关键词】 银屑病性关节炎;临床病证特点;动物模型;吻合度
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Analysis of animal model of psoriatic arthritis based on Chinese and Western medicine characteristics

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【Abstract】 In recent years, psoriatic arthritis has become a major problem in the medical field, with cases gradually increasing in China, and it is still incurable. Here, we summarize the pathogenesis and clinical characteristics of currently available animal models of psoriatic arthritis based on Chinese and Western medical evidence. Literature in line with this topic was collated and summarized. The etiology and pathogenesis according to Chinese and Western medicine of existing psoriatic arthritis models were given agreement scores; the diagnostic criteria of Chinese and Western medicine were compared; and the models' characteristics and degree of agreement with clinical observations were assessed. This study found that the human leukocyte antigen transgenic mouse model, the multiple hybridization transgenic mouse model, and the mannan-induced mouse model had the highest agreement scores. As psoriatic arthritis is more common in Europe, methods for the preparation of animal models have been mostly imported from abroad, and very few animal models have the

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characteristics of Chinese medicine; therefore, the model fitness scores of Western diagnoses were higher than those of Chinese diagnoses as a whole. We hope to leverage the unique diagnosis and treatment method of Chinese medicine further to improve the types of psoriatic arthritis animal models available. This study provides a basis for the construction of improved animal models of psoriatic arthritis with combined traditional Chinese and Western medicine characteristics.

【**Keywords**】 psoriatic arthritis; clinical characteristics; animal model; coincidence degree

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银屑病性关节炎(psoriatic arthritis,PsA)是银屑病的延伸性疾病,发病率较高,约占银屑病患者的20%,属于自身免疫性疾病的一种慢性疾病,以指趾肿胀、关节受损、软组织僵硬、活动受限等为主要症状[1]。大部分患者伴有银屑性皮损的临床表现,严重者可能导致残疾或引发心血管疾病,与类风湿关节炎的症状极为相似,常以附着点炎症的骨骼超声和风湿因子的测定等作为区分[2-3]。PsA 现代医学不可治愈,严重影响了患者的正常生活,目前无法确定银屑病及 PsA 的具体发病机制,也没有合适的治疗药物且容易反复发作,因此,适宜的动物模型是探讨发病机制和寻找治疗药物的关键。目前 PsA 动物模型主要包括自发性模型、基因工程模型、诱导性模型以及关节炎相关模型[4]。随着近年来 PsA 发病率的上升,临床样本量得到有效的积累,为我们评价动物模型的临床吻合度提供了有效参考。本文通过查阅多个中外文献数据库并结合相关资料分别从中西医角度探讨 PsA 的病因病机、辩证诊断标准、动物模型的吻合度 3 个方面对现有 PsA 动物模型进行分析,以期建立完善的评价体系,为后期 PsA 动物实验模型的建立提供新的思路和参考。

1 PsA 的病因病机

1.1 西医病因病机

目前 PsA 现代医学的具体发病机制还不确定,一般多因炎症反应、免疫介导、家族遗传、环境因素、饮食习惯、其他疾病并发等原因导致[5]。IL-23/IL-17 轴失调是当下较为认可的 PsA 发病机制,IL-23/IL-17 轴被认为与机体的炎症反应和免疫功能密切相关[6]。IL-23/IL-17 轴被激活时,末端驻留细胞被活化从而诱导大量炎症细胞的聚集,进而导致关节的退化、破坏以及滑膜炎症,同时,这种改变会进一步促进免疫细胞的聚集,加重此类反应[7]。有研究表明,B 细胞、T 细胞($CD4^+$和 $CD8^+$)以及 TNF-α 因子也是参与该过程的重要一环[8]。

1.2 中医病因病机

PsA 在中医中没有具体的范畴,一般是指多由银屑皮损受累后所出现的痹症。PsA 中银屑病的皮损属于中医中的“白疕”,皮损形状如同松皮,表层银白皮屑下搔之有似红斑的鳞屑,俗称“牛皮癣”[9]。PsA 的关节性病变在中医中属于“顽痹”“尪痹”“历节病”“骨痹”的范畴[10]。明《医林绳墨.痹》记载:“久风入中,肌肉不仁”;《素问.长刺节论》中曰:“病在骨,骨重不可举,骨髓酸痛,寒气至其次”,皆是古人对 PsA 的早期认识。中医认为,风寒、风湿、热邪、血瘀、肝肾亏虚皆可成为 PsA 的发病病因,病邪侵入肌表,伤及经络、骨节,体内血行不通,气血瘀滞,不得上行肌肤失养,不得下行痹阻经络,以致肌肤不荣,筋脉不得通利[11-12]。

2 PsA 的中西医诊断标准

2.1 西医诊断标准

PsA 现代医学的临床诊断并没有确切的“黄金标准”,根据目前国际银屑病和银屑病性关节炎研究和评估组的建议 CASPAR 分类标准[13]为主,以 PsA 的疾病活动度(DAPSA)和银屑病性关节炎诊治指南[14-15]为辅,归纳 PsA 的临床症状、一般检查、病理改变和实验室检查 4 部分作为 PsA 诊断标准,总结西医临床诊断标准结果,见表 1。

由于临床症状最易观察,将其作为评估动物模型赋值的主要参考(①、②、③、⑤、⑦),动物实验中常见的一般检查(⑥、⑦)和实验室检查(④、⑧)作为辅助参考,汇总赋值项如下:①炎症性关节病(关节、脊柱或附着点);②银屑病症状(确诊银屑病、银屑病家族史、银屑病个人史);③甲营养不良;④类风湿因子阴性;⑤指(趾)炎(病史);⑥影像学显示大关节有边界不清的骨化;⑦关节压痛、肿胀;⑧C 反应蛋白(CRP)等炎症因子升高;临床上 PsA 的典型表现为关节炎和银屑样病变,即①、②归为核心指标,其余赋值项归为相关指标,根据文献[16],符合主要症状①、②吻合度每项分别赋值为 30%,符合其余六项吻合度每项分别赋值为 6.67%,总分值为 100%。

表 1 PsA 西医诊断标准

Table 1 Diagnostic criteria of PsA Western medicine

分类 Classification	表现 Presentation
临床症状 Clinical symptoms	①关节发热、疼痛、肿胀、有压痛;②在头皮、躯干、四肢处出现银白色皮屑,皮屑易脱落,有红色肿块;③指甲可能会形成小凹痕(凹面)、碎裂或从甲床上脱落;④手指和脚趾肿胀;⑤并发视觉减退、脊椎炎、心脑血管疾病等。 ①Heat, pain, swelling, and tenderness in the joints; ②Silver-white flakes on the scalp, trunk, and limbs, which are easy to peel off, and red bumps; ③Nails may form small indentations (concave surfaces), chip, or fall off from the nail beds; ④Swelling of the fingers and toes; ⑤Complications such as visual loss, spondylitis, and cardiovascular disease.
一般检查 General inspection	①与类风湿关节炎(RA)比,银屑病性关节炎的关节压痛可能较轻;②患者有家族史或银屑病的既往史;③影像学检查:射线和 CT 扫描显示软骨消失,关节面凹凸不平,有关节炎症而形成新骨的迹象。 ①Psoriatic arthritis may have less joint tenderness than rheumatoid arthritis (RA); ②Patient has a family history or a past history of psoriasis; ③Imaging tests: radiographs and CT scans show loss of cartilage, unevenness of the articular surfaces, and signs of new bone formation due to joint inflammation.
病理改变 Pathological changes	病变早期滑膜细胞轻度增生和肥大,伴少量纤维素样物渗出;病变中期滑膜细胞下轻度水肿和纤维组织增生,小血管明显增生、充血,伴少量淋巴细胞、浆细胞浸润;病变晚期滑膜纤维组织明显增多,残留小血管增厚、管腔狭窄。 Early lesions of synovial cells mild proliferation and hypertrophy, with a small amount of fibrin-like material exudation; middle lesions of synovial cells under the mild edema and fibrous tissue hyperplasia, small blood vessels obvious hyperplasia, congestion, with a small number of lymphocytes, plasma cells infiltration; lesions of advanced synovial fibrous tissue increased significantly, residual small blood vessel thickening, lumen narrowing.
实验室检查 Laboratory examination	①血沉加快、炎症因子增加、补体水平增高;②炎症标志物 C 反应蛋白(CRP)升高;③滑膜液中中性粒细胞和白细胞数增多;④类风湿因子阴性。 ①Accelerated blood sedimentation, increased inflammatory factors, and increased complement levels; ②Elevated C-reactive protein (CRP), a marker of inflammation; ③Increased neutrophil and leukocyte counts in synovial fluid; ④Negative rheumatoid factor.

2.2 中医诊断标准

以中国中西医结合学会第十六届风湿学术年会总结的《银屑病性关节炎的中医辨证用药治疗分析》[17]及各位名医大家治疗 PsA 经验要谈[18-22]为依据,归纳 PsA 的中医辩证分型如下:湿热痹阻证、热毒蕴结证、肝肾阴虚证、寒湿阻络证、阴虚血燥证和血热风燥证。根据文献[16,23]及上述依据汇总的诊断标准对 PsA 模型相应分型赋值,将中医临床诊断标准分为主证和次证,分别计算主证吻合数及次证吻合数,符合主证两项(关节异常、鳞屑样病变)吻合度每项分别赋值 30%,符合次证六项(瘙痒、活动度、寒热、毛发、大小便等)吻合度每项分别赋值 6.67%,总分值 100%,中医各证型的模型具体诊断标准结果见表 2。

3 PsA 动物模型的吻合度分析和模型的选择

3.1 PsA 模型动物的选择

目前用于 PsA 动物实验的模型较多,包括 PsA 大小鼠模型、PsA 兔模型、PsA 狗模型等,它们都具有关节数量多且复杂、皮毛丰富的特点。在野生环境中,研究已发现部分食肉动物及灵长类动物有类似 PsA 的症状发生,但考虑到造模成本和实验的可行性,一般选用 PsA 大、小鼠模型作为主要的实验对象[24]。

3.2 PsA 动物模型中西医吻合度的评价分析

PsA 是在银屑病的基础上所诱导的一种关节炎性疾病,通过 CNKI、万方、PubMed 等多个数据库搜索“psoriasis arthropathica”“psoriatic arthritis”等关键词,得知 PsA 动物模型大多由银屑病动物模型和多种关节炎性动物模型发展而来,以转基因、杂交、诱导的手段造模最为常见[25]。分析发现,西医临床症状吻合度在 43.4%~93.5%,中医临床症状吻合度在 30%~80%,其中以 HLA-B27 转基因大小鼠模型、K5. Stat3C:F759 转基因小鼠以及甘露聚糖诱导的小鼠模型中西医综合评分较高,吻合度约在 83%~87%,症状符合度高,但有造模的成功率偏低、造价偏高的缺点。PsA 动物模型的动物名称、具体构建方法、模型优缺点以及中西医模型临床吻合度分析见表 3。

3.3 中西医吻合度评价 PsA 动物模型的观测标准

本研究参考相关文献[26-27]根据 2.1、2.2 诊断标准的赋值情况评估 PsA 动物模型中西医临床吻

表 2 PsA 中医证候诊断标准

Table 2 Diagnostic criteria for TCM syndromes of PsA

分型 Typing	主证 Main symptom	次证 Secondary symptom	舌脉 Pulse and tongue
湿热痹阻证 Damp-heat paralysis syndrome	①疹多色鲜红,多厚重鳞屑,伴点状出血明显;②手指、足趾关节红肿疼痛、压痛, 活动不利 ① Rash color bright red, thick scales, with pitting hemorrhage obvious; ② Fingers, toes joints red, swollen, pain, pressure pain, adverse activities	①瘙痒;②毛发掉落;③口渴;④大便干;⑤小便短赤;⑥心烦易怒 ① Itching; ② Hair loss; ③ Thirst; ④ Dry stools; ⑤ Short and red urine; ⑥ Upset and irritable	舌质红, 苔黄腻, 脉弦滑 Red tongue, yellow fur, slippery pulse
热毒蕴结证 Heat-toxin amassment pattern	①反复大片红斑鳞屑;②关节处屈伸不利,蹲起困难 ①Repeated large erythematous scales; ② Unfavorable flexion and extension of the joints, squatting difficulties	①双手晨僵;②握力减退;③腕膝关节疼痛;④纳差;⑤寐欠安;⑥大便干 ①Morning stiffness of hands; ②Loss of grip strength; ③Pain in wrist and knee joints; ④ Poor appetite; ⑤ Poor sleep; ⑥Dry stools	舌质黯,苔黄腻,脉弦滑 Dull tongue, yellowish greasy moss, stringy and slippery pulse
肝肾阴虚证 Liver-kidney Yin deficiency	①病程日久,症见皮损色暗或淡红;②关节僵硬疼痛,或变形 ①Disease for a long time, see the skin lesions dark or reddish; ②Joints stiff and painful, or deformed	①筋肉拘急;②潮热盗汗;③心烦失眠;④形寒肢冷;⑤腰背酸痛;⑥小便清长 ①Muscle constriction; ②Hot flashes and night sweats; ③ Heartburn and insomnia; ④ Coldness; ⑤ Lumbar and back pain; ⑥ Prolonged urination	舌质淡红,苔少白,脉沉细 Tongue pale red, moss less white, pulse sunken and fine
寒湿阻络证 Syndrome of cold-dampness blocking collaterals	①皮损颜色暗红并伴有鳞屑,呈蛎壳状关节;②关节红肿疼痛,痛有定处,遇冷加重 ①Skin lesions dark red color with scales, oyster shell joints; ② Joints red, swollen and painful, the pain has a fixed place, aggravated by the cold	①畏寒肢冷;②筋肉拘急;③活动受限;④口渴欲饮;⑤腹胀;⑥便溏 ①Cold feet and limbs; ② Muscle and flesh constriction; ③ Restriction of movement; ④ Thirst and desire to drink; ⑤ Abdominal distension; ⑥Loose stools	舌质淡,苔白,脉沉缓 Tongue pale, moss white, pulse dull and slow
痰瘀互结证 Accumulation of phlegm stasis	①皮损为暗红色斑块,鳞屑肥厚且附着较紧;②关节处剧烈刺痛而位置相对固定不移 ①Lesions are dark red plaques with thick and tightly attached scales; ② Severe tingling in the joints with a relatively fixed location	①瘙痒;②面色晦暗;③唇色青紫;④体倦乏力;⑤食欲减退;⑥饮不解渴 ① Itching; ② Dullness of the face; ③ Blue lips; ④ Tiredness; ⑤ Loss of appetite; ⑥ Drinking does not quench thirst	舌质紫暗并伴有瘀斑,苔白腻,脉沉涩 Purple and dark tongue with petechiae, white greasy moss, dull and astringent pulse
血热风燥证 Signs of heat in the blood and dryness in the wind	①淡红色斑块,上覆银白色鳞屑肥厚干燥;②关节红肿热痛,遇热痛剧,触之温度升高 ① Reddish plaque, covered with silver-white scales, hypertrophy and dryness; ② Joints red, swollen, hot and painful, when the heat pain is sharp, the temperature rises when touched	①皮肤瘙痒;②指甲甲下增厚且有皱襞;③夜寐不安,烦躁易醒;④皮肤干燥;⑤小便色黄,排尿时有灼热感;⑥大便干结 ①Itchy skin; ②Thickening and folds under the fingernails; ③ Sleeplessness at night, restlessness and easy to wake up; ④Dry skin; ⑤ Yellow urine, burning sensation when urinating; ⑥Dry and knotty stools	舌质红,苔黄,脉弦数 Red tongue, yellow moss, stringy pulse

合度,所总结的 PsA 模型中西医观测标准如下:(1)西医:①关节炎症状(脊柱关节炎、踝腕关节炎、指趾关节炎、关节肿痛、软骨破坏等);②银屑病症状(银屑病样皮损、脱皮退毛、表皮增厚、真皮炎症伴有渗出物等);③甲病变(甲凹陷、趾甲碎裂脱落等);④生化指标(C 反应蛋白、炎症因子、血沉、类风湿因子);⑤影像学检查(X 光、CT、核磁);(2)中医:①皮肤斑块鳞屑(鳞屑厚度、皮疹颜色、温度、干燥程度);②关节损伤(活动度、疼痛类型、肿胀程度、寒热);③伴随症状(瘙痒、寒热、筋肉活动度、指甲病变、腹胀、睡眠、大小便等)。现阶段关于 PsA 的研究以临床病例分析以及动物实验为主要方法,由于人类与实验动物临床表现的差异,可能还需要进一步完善。

表 3 PsA 动物模型的特点及与临床吻合度的分析

Table 3 Characteristics of animal models of PsA and analysis of the degree of agreement with the clinic

模型类型 Model type	动物名称 Animal name	制备方式 Preparation method	模型评价 Model evaluation	模型临床吻合度 Consistency with clinical symptoms
自发/遗传基因突变模型[28-29] Spontaneous/genetic mutation models	自发性模型 Spontaneity model	DBA/1 小鼠 DBA/1 mice	通过 DBA/1 品系小鼠的近亲繁殖而来 Inbred through inbreeding in the DBA/1 strain of mice	优点:发病率高;操作简单 Advantages: high morbidity; easy to operate 缺点:无大关节损伤;皮肤病变出现较少 Disadvantages: no major joint damage; fewer skin lesions present	(1)表征:后爪周围关节的强直附着点炎(AE),并伴有脚趾骨炎和甲受累;可自发出现银屑病样皮损;(2)西医临床吻合①②③⑤⑦,综合赋值 80%;(3)中医临床吻合:湿热痹阻型,主证①②,次证①②③,综合赋值 80%。(1) Characteristics: ankylosing attachment point inflammation (AE) of the joints around the hind claws, accompanied by osteitis of the toes and nail involvement; psoriasiform skin lesions may appear spontaneously; (2) Clinical match in Western medicine ①② ③⑤⑦, with a combined value of 80%; (3) Clinical match in Chinese medicine (CM): Damp-heat paralysis type, with the primary symptom①②, and the secondary symptom①②③, with a combined value of 80%.
	基因突变模型[30] Gene mutation model	C57BL/10 小鼠 C57BL/10 mice	老年雄性 C57BL/10 小鼠中出现的 B10. BR (H-2k)小鼠 B10. BR (H-2k) mice arising in aged male C57BL/10 mice	优点:关节炎症表现明显;有肠道菌群紊乱 Advantages: joint inflammation is evident; there are disorders of intestinal flora 缺点:SPF 环境发病率低;无皮肤病变 Disadvantages: low environmental incidence of SPF; no skin lesions	(1)表征:强直性附着点病症状明显,关节僵硬,可观察到炎症细胞浸润及关节处骨质侵蚀;(2)西医临床吻合①③⑥⑦⑧,综合赋值 56. 68%;(3)中医临床吻合:热毒蕴结型,主证②,次证①②③,综合赋值 50%。(1) Characterization: Ankylosing attachment point disease symptoms, joint stiffness, inflammatory cell infiltration and bone erosion at the joints can be observed; (2) Western clinical match ①③⑥⑦⑧ with a combined value of 56. 68%; (3) Chinese medicine clinical match: heat-toxin accumulation type, primary ②, secondary ① ② ③, with a combined value of 50%.
转基因模型 Transgenic model		HLA-DR4 转基因小鼠[31] HLA-DR4 transgenic mice	敲除内源性 MHC Ⅱ类基因,并转移 HLA-DR4 基因 Knockdown of endogenous MHC class II genes and transfer of the HLA-DR4 gene	优点:发病率较高;关节组织病理学和影像学表现与人类相似 Advantages: high prevalence; joint histopathology and imaging similar to humans 缺点:无皮损和关节炎症等典型变现;作用机制不明确 Disadvantages: no typical manifestations such as skin lesions and joint inflammation; mechanism of action unclear	(1)表征:指(趾)炎及指甲病变显著,有严重的骨受损,周围表皮增厚,出现"香肠样"脚趾,雌性多发;(2)西医临床吻合,①③⑥⑦⑧综合赋值 56. 68%;(3)中医临床吻合:血热风燥型,主证①,次证①②,综合赋值 43. 34%。(1) Characteristics: significant finger (toe) inflammation and nail lesions, severe bone damage, thickening of the surrounding epidermis, and the appearance of "sausage-like" toes, which are more frequent in females; (2) Clinical match in Western medicine, ①③⑥⑦⑧, with a combined value of 56. 68%; (3) Clinical match in Chinese medicine: blood-heat-wind-dryness type, primary symptom ①, secondary symptom ①②, with a combined value of 43. 34%.
		HLA-B27 转基因大小鼠模型[32] HLA-B27 transgenic rat mouse model	将 HLA-B27 和人类 β2 微球蛋白基因导入大小鼠体内 Introduction of HLA-B27 and human β2 microglobulin genes into large mice	优点:起病迅速,与人类发病症状相似 Advantages: rapid onset of disease, similar to human onset symptoms 缺点:发病率较低,造模时间较长 Disadvantages: lower incidence, longer molding time	(1)表征:关节炎症状明显并伴有银屑样皮损,同时出现了炎性肠病和甲病变,雄性多发,具有遗传特性;(2)西医临床吻合,①②③④⑤⑦⑧综合赋值 93. 35%;(3)中医临床吻合:湿热痹阻型,主证①②,次证①②④,综合赋值 80%。(1) Characteristics: arthritis with psoriasiform lesions, inflammatory bowel disease and nail lesions, androgenic, with genetic characteristics; (2) Clinical match in Western medicine, ①②③④⑤⑦⑧, 93. 35% of the total value; (3) Clinical match in Traditional Chinese Medicine (TCM): Damp-heat paralysis type, the main symptom ①②, the secondary symptom ①②④, with a combined value of 80%.

续表3

模型类型 Model type	动物名称 Animal name	制备方式 Preparation method	模型评价 Model evaluation	模型临床吻合度 Consistency with clinical symptoms
	JunB/c-Jun 转基因型小鼠模型[33] JunB/c-Jun transgenic mouse model	敲除 JunB 和 c-Jun 双基因或是将携带 JunB 和 c-Jun 基因的小鼠与 K5-Cre-ERT 转基因小鼠杂交并注射他莫昔芬 Knockout of JunB and c-Jun dual genes or crossing of mice carrying JunB and c-Jun genes with K5-Cre-ERT transgenic mice and injection of tamoxifen	优点：起病迅速，皮损明显 Advantages: rapid onset, visible skin lesions 缺点：价格昂贵，无大关节炎症 Disadvantages: expensive, no major joint inflammation	(1)表征：银屑性皮损较为典型，小关节炎症明显，影像学可观察到骨侵蚀；(2)西医临床吻合，①②③④⑤⑥综合赋值 86.68%；(3)中医临床吻合：血热风燥型，主证①②，次证①②，综合赋值 73.34%。 (1) Characterization: psoriasis lesions are typical, inflammation of small joints is obvious, and bone erosion can be observed on imaging; (2) Clinical match in Western medicine, ①②③④⑤⑥, with a combined value of 86.68%; (3) Clinical match in Traditional Chinese Medicine (TCM): blood-heat and wind-drying type, primary symptom ①②, secondary symptom ①②, with a combined value of 73.34%.
	K14-AREG 转基因模型小鼠[34] K14-AREG transgenic model mice	将 K14 启动子和鼠编码基因 AREG 插入到鼠基因组内，控制其过表达 Insertion of the K14 promoter and the murine coding gene AREG into the murine genome to control its overexpression	优点：皮损症状明显，无性别差异 Advantages: obvious symptoms of skin lesions, no gender differences 缺点：操作困难，价格较高，存活率低 Disadvantages: difficult to operate, more expensive, low survival rate	(1)表征：皮肤脱毛，有红色斑块且覆有鳞屑，关节处出现炎性浸润及滑膜炎，是 PsA 的前期表现；(2)西医临床吻合①②④，综合赋值 66.7%；(3)中医临床吻合：湿热痹阻型，主证①②，次证②，综合赋值 66.7%。 (1) Symptoms: skin hair loss, red plaques with scales, inflammatory infiltration and synovitis in joints, which is a pre-presentation of PsA; (2) Clinical match in Western medicine ① ② ④, with a combined value of 66.7%; (3) Clinical match in Chinese medicine: Damp-heat paralysis obstruction type, primary symptom ① ②, secondary symptom ②, with a combined value of 66.7%.
	BMPs-6 基因过表达小鼠[35] BMPs-6 gene overexpressing mice	将表达 BMP 的 cDNA 引入质粒中，以角蛋白 10 为表达载体，构建具有高 BMPs 表达的转基因小鼠 Transgenic mice with high expression of BMPs were constructed by introducing BMP-expressing cDNA into the plasmid and using keratin 10 as the expression vector	优点：起病迅速，无性别差异 Advantages: rapid onset, no gender differences 缺点：价格昂贵，无大关节炎症及银屑样皮损 Disadvantages: expensive, no major joint inflammation or psoriasiform lesions	(1)表征：指(趾)肿胀及甲受累，表皮炎性浸润增厚并伴随脱皮褪毛的表现；(2)西医临床吻合，①③⑤综合赋值 43.4%；(3)中医临床吻合：湿热痹阻型，主证①，次证①②，综合赋值 43.4%。 (1) Symptoms: finger (toe) swelling and nail involvement, epidermal inflammatory infiltration and thickening accompanied by desquamation and hair loss; (2) Clinical match in Western medicine, ①③⑤, with a combined value of 43.4%; (3) Clinical match in Traditional Chinese Medicine (TCM): Damp-heat paralysis type, primary symptom ①, secondary symptom ① ②, with a combined value of 43.4%.
	K5.Stat3C：F759 转基因小鼠[36] K5.Stat3C：F759 transgenic mice	Gp130F759 转基因小鼠与 K5.Stat3C 转基因小鼠杂交而来 Gp130F759 transgenic mice were crossed with K5.Stat3C transgenic mice	优点：组织病理学与人类相似，发作迅速 Advantages: histopathology similar to humans, rapid onset of symptoms 缺点：操作复杂，无大关节炎症 Disadvantages: complex operation, no major joint inflammation	(1)表征：出现皮肤银屑样鳞屑厚重(牡蛎壳样)，指甲畸形以及附着点炎症和关节弯曲、变形；(2)西医临床吻合，①②③④⑤⑦⑧综合赋值 93.35%；(3)中医临床吻合：寒湿阻络型，主证①②，次证②③，综合赋值 73.34%。 (1) Symptoms: thick psoriasis-like scales on the skin (oyster shell-like), deformed nails, inflammation of the attachment points, and flexion and deformation of the joints; (2) Clinical match in Western medicine, ①②③④⑤⑦⑧, 93.35% of the total value; (3) Clinical match in Chinese medicine: cold and dampness blocking the collaterals, the main symptom ①②, and the secondary symptom ②③, with a combined value of 73.34%.
	R26STAT3 Cstopfl/flCD4Cre 转基因小鼠[37] R26STAT3 Cstopfl/flCD4Cre transgenic mice	R26STAT3C 转基因小鼠与 C57BL/6J 小鼠回交，随后与 CD4Cre 小鼠杂交得来 R26STAT3C transgenic mice were backcrossed to C57BL/6J mice and subsequently crossed to CD4Cre mice	优点：起病迅速，无性别差异 Advantages: rapid onset, no gender differences 缺点：价格昂贵，无大关节炎症及银屑样皮损 Advantages: expensive, no major joint inflammation or psoriasiform lesions	表征：皮肤干燥且蜕皮严重，表面有厚重银屑样病变，模型鼠自发出现滑膜炎、附着点炎以及不明显的关节炎症病变；(2)西医临床吻合，①②⑤⑥⑦⑧综合赋值 86.68%；(3)中医临床吻合：血热风燥型，主证①②，次证①②，综合赋值 73.34%。 (1) Characteristics: dry skin with severe molting, thick psoriasis-like lesions on the surface, spontaneous synovitis, adhesion point inflammation and inconspicuous inflammatory lesions in the joints of the model rats; (2) Clinical match in Western medicine, ①②⑤⑥⑦⑧, with a combined value of 86.65%; (3) Clinical match in Chinese medicine: blood-heat and wind-dryness type, primary symptom ①②, secondary symptom ①②, with a combined value of 73.74%.

续表3

模型类型 Model type	动物名称 Animal name	制备方式 Preparation method	模型评价 Model evaluation	模型临床吻合度 Consistency with clinical symptoms
诱导性模型 Induced model	IL-23 过表达小鼠[38] IL-23 overexpressing mice	将编码 IL-23 的微环 DNA 导入小鼠,在小鼠体内过表达 IL-23 基因 Introduction of microcircular DNA encoding IL-23 into mice and overexpression of the IL-23 gene in mice	优点:可靠性较强,发病率高 advantages: greater reliability, high morbidity 缺点:银屑样皮损发生率低 Disadvantages: Low incidence of psoriasiform lesions	(1)表征:骨骼、关节、爪甲被破坏,发生滑膜炎及附着点炎,部分小鼠出现银屑病样皮肤病变;(2)西医临床吻合,①②③⑥⑦⑧综合赋值 86.68%;(3)中医临床吻合:湿热痹阻型,主证①②,次证①,综合赋值 66.67%。 (1) Characterization: bones, joints, paw nails were destroyed, synovitis and attachment point inflammation occurred, and psoriasis-like skin lesions appeared in some mice; (2) Clinical match in Western medicine ① ② ③ ⑥ ⑦ ⑧, with a combined value of 86.68% of the total value; (3) Clinical match in Chinese medicine: Damp-heat paralytic blockage, the main symptom ①②, and the secondary symptom ①, with a combined value of 66.67%.
	I 型/II 型胶原诱导 DBA/1 小鼠模型(CIA)[39] Type I/II collagen-induced DBA/1 mouse model (CIA)	将 DBA/1 小鼠皮内注射溶解在 CFA/ICFA 中的 I 型/II 型胶原蛋白,三周后腹膜内注射同型胶原蛋白 DBA/1 mice were injected intradermally with type I/II collagen dissolved in CFA/ICFA, and homogeneous collagen was injected intraperitoneally three weeks later	优点:造模成功率高,成本较低 Advantages: high molding success rate, lower costs 缺点:无银屑样皮损,发病晚 Disadvantages: no psoriasiform lesions, late onset of disease	(1)表征:爪子发红肿胀,有滑膜炎症和骨侵蚀的表现,多见于雄性;(2)西医临床吻合,①③⑦⑧综合赋值 50%;(3)中医临床吻合:湿热痹阻型,主证①,次证①,综合赋值 36.67%。 (1) Characterization: red and swollen paws with synovial inflammation and bone erosion, mostly seen in males; (2) Clinical match in Western medicine ①③⑦⑧, with a combined value of 50%; (3) Clinical match in Chinese medicine: Damp-heat paralysis obstruction type, primary symptom ①, secondary symptom ①, with a combined value of 36.67%.
	β-葡聚糖诱导 SKG 小鼠模型[40] β-glucan induced SKG mouse model	将 SKG 小鼠腹膜内注射 Zymosan SKG mice were injected intraperitoneally with Zymosan	优点:模型构建简单,无性别差异 Advantages: simple model construction, no gender differences 缺点:银屑样皮损症状发病晚 Disadvantages: late onset of psoriasiform lesion symptoms	(1)表征:有脊柱关节炎,指趾炎,回肠炎和银屑病皮肤病变(表皮增厚),多见于雌性;(2)西医临床吻合,①④⑤⑦综合赋值 50%;(3)中医临床吻合:湿热痹阻型,主证①,次证无,综合赋值 30%。 (1) Characteristics: spondyloarthritis, dactylitis, ileitis and psoriasis skin lesions (thickening of the epidermis), mostly in females; (2) Clinical match in Western medicine ① ④⑤⑦, with a combined value of 50%; (3) Clinical match in Traditional Chinese Medicine (TCM): Damp-heat paralysis, primary symptom ①, secondary symptom none, with a combined value of 30%.
	甘露聚糖诱导的小鼠模型[41] Mouse models of mannan-induced	给易感小鼠腹腔注射酿酒酵母产生的甘露聚糖 Intraperitoneal injection of mannan produced by brewer's yeast in susceptible mice	优点:症状全面,成熟的炎症模型 Advantages: comprehensive symptoms, proven inflammatory modeling 缺点:发病率较低 Disadvantages: low prevalence	(1)表征:皮肤出现炎症性银屑样皮损,有轻度蜕皮脱毛,多关节出现红肿胀痛;(2)西医临床吻合,①②③④⑤⑦⑧综合赋值 93.35%;(3)中医临床吻合:湿热痹阻型,主证①②,次证①②,综合赋值 73.34%。 (1) Characteristics: inflammatory psoriasis-like skin lesions, mild moulting hair loss, redness, swelling and pain in many joints; (2) Clinical match in Western medicine ①②③④⑤⑧, with a combined value of 93.35%; (3) Clinical match in Traditional Chinese Medicine: Damp-heat paralysis type, the main symptom ①②, the secondary symptom ①②, with a combined value of 73.34%.
	IL-23 腺病毒诱导小鼠模型[42] IL-23 adenovirus-induced mouse model	将 IL-23 的腺病毒载体通过尾静脉注射到 NOD/shijl 雌性小鼠体内 Adenoviral vectors for IL-23 were injected into NOD/shijl female mice through the tail vein	优点:起病迅速,症状明显 Advantages: rapid onset of symptoms 缺点:造价高,重复性低 Disadvantages: High cost and low repeatability	(1)表征:全身性皮肤出现银屑样病变,腰膝关节骨被破坏,多见于雌性;(2)西医临床吻合,①③⑦⑧综合赋值 50%;(3)中医临床吻合:湿热痹阻型,主证①,次证①,综合赋值 36.67%。 (1) Symptoms: generalized psoriasis-like skin lesions, destruction of the bones of the lumbar and knee joints, mostly in females; (2) Western clinical match ①③⑦⑧, with a combined value of 50%; (3) Chinese medicine clinical match: damp-heat paralysis blockage type, the main symptom ①, the secondary symptom ①, with a combined value of 36.67%.

4 讨论

PsA 是银屑病后关节受累导致的一种炎性病变,对关节有着不可逆的损伤,与脊柱性关节炎、类风湿关节炎的关节症状相似,但由于部分病人鳞屑样皮肤表征不明显,甚至没有皮肤症状,误诊的情况时有发生[43]。目前现代医学对 PsA 的研究虽然很多,但仍未确定其发病机制和诊断标准,能用于临床的研究也是少之又少,目前尚未寻找到适宜的药物。临床上常以非甾体抗炎药、糖皮质激素注射,口服环孢素、来氟米特等药物治疗,但复发率极高、副作用大[44]。因此,通过结合中医的特色诊疗方法,深入研究 PsA 的作用机理,开发相关新药物迫在眉睫。

考虑到病理学相似度、操作难度和经济情况,多选用啮齿类动物用于 PsA 模型构造,但考虑到与人类临床症状表达的差异性,研究后期可采用将与人类身体机能、病理表现较为相似的灵长类动物。现阶段吻合度较高的 PsA 动物模型大多为银屑病转基因动物模型和关节炎转基因动物模型杂交而来(HLA-B27、K5. Stat3C:F759),虽然造模成本增高,但 PsA 发病率和临床症状的完整度都较高。部分 PsA 动物模型有性别差异,不利于药物的综合开发,如 CIA 诱导的小鼠模型、自发关节炎小鼠、基因突变 C57BL/10 小鼠的雄性发病率高,而 HLA-B27 转基因小鼠雌性发病率高。大多 PsA 动物模型虽两大主要症状(银屑样皮肤病变、多类型关节炎)皆能具备,但程度往往一高一低,且发病率较低,如 HLA-DR4 转基因小鼠、CIA 诱导的小鼠模型无典型的鳞屑样皮肤变化,BMPs-6 基因过表达小鼠、JunB/c-Jun 转基因型小鼠模型、IL-23 腺病毒诱导小鼠模型等无大关节的炎性病变,只有小关节的破坏和附着点炎症的发生。除此之外,个别动物模型还受到环境因素的影响,病情也并不稳定。因此,现有的 PsA 模型局限性较大,但未来可针对性地探究不同病因导致的 PsA,“不求全,但求精”,以方便研究者可根据不同病症表现实验的需求来选择合适的动物模型方式。

对现阶段 PsA 动物模型进行吻合度评价,发现中医临床吻合综合赋值低于西医临床吻合综合赋值,其中的原因可能是:(1)几乎没有关于 PsA 的中医药造模方式,探讨中药对于 PsA 的作用大多也是选用的西医的诊断标准;(2)PsA 中医的临床表现是根据“望闻问切”理论得到准确判断,这在动物模型中无法通过问诊达到症状补充,如筋肉挛急、心烦易怒、皮肤刺痛等;(3)实验过程中对于中医诊断指标的部分次证容易忽视,如寒热、二便、是否腹胀等;(4)现如今中医关于 PsA 的诊断标准未有明确,且中医病机中的先天因素、环境因素和情志因素无法把控;(5)动物与人类症状表达的差异。以上原因使得中医临床吻合度得出的结论难度增大,也存在一定的差异性[45]。通过观察和指标转换,仅可反映部分中医证候。观察到模型动物搔痒次数增多,能够反映模型动物皮肤的瘙痒程度;改变模型动物生活条件,例如温度,判断其证型是属于寒证还是热证;给予模型动物运动刺激,观察其运动后状态,观察其证型是属于实证还是虚证等。因此,本研究建议将中医临床特点结合现有的 PsA 动物模型,体现“四诊”的中医特点,构建更适合中西医诊疗的动物模型。

综上所述,为给予中西医结合治疗 PsA 提供更有效的支撑,本文对现有的 PsA 动物模型吻合度分析并完善,考虑在中西医吻合度较高的 HLA-B27 转基因大小鼠模型、K5. Stat3C:F759 转基因小鼠模型以及甘露聚糖诱导的小鼠模型基础上,叠加中医患病因素,如造模过程中增加冰水刺激诱导寒湿阻络型 PsA 模型[46]、增加高脂高糖饮食诱导湿热体质形成湿热痹阻型 PsA 模型[47]或对模型动物灌服肾上腺皮质激素加夹尾激怒致肝肾阴虚型 PsA 模型[48],以提高中医临床吻合度。此外,也可以考虑对现有 PsA 动物模型施加患病因素,通过模仿人患病的日常致病因素,模拟相关环境,达到破坏免疫力而完善动物模型的患病表现。如大小鼠的饲养过程中减少更换垫料或多只(超出正常容纳范围)共同饲养模拟个人卫生情况;模型动物的饲养环境中加入香烟烟雾模拟吸烟环境;通过击打、单笼饲养、夹尾等方式刺激模型动物的情绪模拟人类日常生活中的情感波动等[49]。根据疾病的个性化自由组合造模方法,模拟病情变化,更符合中医理论中“辩证施治”的概念。由于病情的发展多变且因人而异,多种疾病的经典造模方法都是数个造模手段共同作用形成的,这使得动物模型更贴近临床证候,更好地评价药物疗效。

而今西医对于 PsA 的治愈率极低,且临床患者日益增多,我们迫切在中西医结合疗法中找寻新的出路,通过上述中西医的临床诊断标准,本研究将模型符合度进行量化评分,对现阶段用于实验的 PsA

模型进行吻合度评价分析,以期寻找更适宜的 PsA 模型用于病理机制研究和药物的开发。

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