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特应性皮炎的中西医病证动物模型研究进展

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【摘要】 近年来随着对中医药在治疗免疫系统疾病的研究不断深入, 越来越多的中医药显示出对免疫系统疾病有良好的治疗作用。而特应性皮炎 (atopic dermatitis, AD) 是一种以 2 型免疫为特征的炎症性疾病, 对其发病机制和针对其治疗的免疫药物研究也不断增加, 从而产生了多种不同类型的动物模型。本文旨在对现有的 AD 动物模型及其免疫相关特点进行综述, 希望为未来 AD 的相关研究模型的选择提供相应的参考。

【关键词】 特应性皮炎; 动物模型; 中医病证; 免疫

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Progress in animal models of atopic dermatitis in relation to Chinese and western medicine

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【Abstract】 Recent research progress into the use of Chinese medicine has demonstrated good therapeutic effects for increasing numbers of Chinese medicines for immune system diseases. Atopic dermatitis (AD) is an inflammatory disease characterized by type 2 immunity, and research into its pathogenesis and therapeutic

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immunopharmaceuticals has resulted in various different types of animal models. This review summarizes the existing animal models of AD and their immune-related characteristics, with the aim of providing appropriate references for the selection of future research models related to AD.

【Keywords】 atopic dermatitis; animal models; traditional Chinese medicine(TCM) syndrome types; immunity
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特应性皮炎(atopic dermatitis, AD)是一种以皮肤瘙痒为特征的慢性非感染性皮肤病,其发病高峰期常见于婴幼儿时期^[1],尽管成人期和老年期也存在一定的发病比率,但大多数 AD 会随着年龄的增长发病率逐渐下降。其发病率在地区和种族上存在差异,考虑近年来一些非洲地区出现 AD 发病率增长情况^[2],现对 AD 的研究开始逐步增加。同时 AD 所伴随出现的瘙痒、皮肤疼痛和睡眠问题等症状,会导致患者生活质量受损^[3],尽管成人 AD 与儿童 AD 会存在表型分型不同的情况^[4],但 AD 所伴随的合并症在两者中都存在。结合对临床病例统计分析,AD 患者中,鼻炎、哮喘的总体患病率可分别达 40.5%、25.7%;并且儿童的患病率总体较成人患病率高^[5-6]。除此之外,AD 患者还会出现过敏性结膜炎、白癜风、过敏性接触性皮炎、焦虑抑郁等合并症,更甚者其骨质疏松、心血管风险、皮肤癌症风险可成倍数增加^[7],危害人们的健康生活。

由于不同人群在 AD 临床表现、免疫发病机制和基因相关遗传易感性上存在差异^[8],因此,在临床上所采取的治疗方式会有所差异,但皆不外乎于局部皮质类固醇、光疗、免疫抑制剂、JAK 抑制剂或靶向生物制剂^[9],但以上治疗皆有相应副作用,而近年随着我国中医药事业的不断创新,中医药对于 AD 在临床上的疗效也得到不断重视,由此不同类型的 AD 动物模型在针对研究 AD 的病理机制及后续中西医相关治疗策略创新或新型药物开发上扮演着关键角色,基于此现象本文将综述近年 AD 模型在中西医研究的类型及其特点,为后续研究者能供应参考便利。

1 AD 研究概况

AD 皮肤免疫失衡和屏障功能障碍的病理生理特征,是遗传和环境因素共同作用的结果^[10-11],随着近年对菌群研究的不断深入,有研究发现皮肤微生物组的异常可以影响 AD 病程的

发展^[12-13],皮肤微生物如金黄色葡萄球菌^[14-15]和外源定植于皮肤的酵母马拉色菌^[16]会刺激皮肤免疫并促进 AD 的发展^[17]。

1.1 AD 免疫研究

AD 通常主要以 2 型免疫反应为主^[17],与多种特应性过敏症及其并发症相关,包括食物过敏、过敏性鼻炎和哮喘^[18]。在遗传、环境和微生物等因素影响下,表皮主要结构蛋白——丝聚蛋白(filaggrin, Flg)缺乏,造成皮肤屏障受损。皮肤驻留真皮树突状细胞、朗格汉斯细胞被激活,产生呈递抗原,角质形成细胞释放促炎因子和趋化因子^[19],引起 CD4 表达为主要特征的 T 细胞浸润^[20-22]。以 Th2 轴(IL-4、IL-13、IL-31)为核心,对不同人群及其表型会产生不同程度的其他 T 细胞轴(Th1/IFN- γ 、Th17/IL-22 和 IL-23、Th22)刺激^[23-24],产生复杂多样的炎症类型。被激活的 Th2 细胞释放 IL-4、IL-5、IL-13,促进嗜酸性粒细胞增多和 B 细胞中的 IgE 类别转换产生抗原特异性 IgE^[25],介导局部皮肤及其自身机体的免疫炎症发生。

1.2 AD 中医症候研究

传统中医典籍并未有“特异性皮炎”病名的记载,而“乳癣”“奶癣”“胎敛疮”“四弯风”等病名在古籍中所描述症状的与现在 AD 的临床症状多为相似。《诸病源候论》便初记载有“小儿面上癣,皮如甲错起,干燥,谓之乳癣”;《医宗金鉴》所载“胎敛疮,此证生婴儿头顶,或生眉端,又名奶癣”,上述古籍所记载的描述症状与现代临床儿童 AD 相吻合^[26]。而《医宗金鉴·外科心法要诀》中则记载:“四弯风,生于两腿弯、脚弯,每月一发……其痒无度,搔破津水,形如湿癣”,其描述症状又与现代临床对 AD 最为贴近^[27]。

随着现代中医对 AD 的不断探索,各个医家对其有不同的见解。AD 病机多样,为禀赋不耐、胎毒遗热以致胎儿心脾受损所致^[28];或脾虚水湿运化失健,泛溢肌肤;或心火致郁热,疮生痒

甚^[29];或热气怫郁、玄府闭塞^[30],或肝郁肾虚,气血失合,外加感湿热邪气,搏与肌肤发为本病^[31]。

2 AD 西医动物模型

2.1 AD 临床诊断标准

现临床对 AD 的诊断多是根据国际广泛采用

的 Hanifin 和 Rajka (H&R) 标准^[32-33]、Williams 标准和由其衍生并得到验证的英国工作组 (United Kingdom Working Party, UKWP) 标准来进行诊断^[34-35],同时结合我国 AD 临床诊疗指南^[36-38],现临床诊断标准概括为湿疹性病变、剧烈瘙痒和慢性或复发性病程 (见表 1)。

表 1 AD 临床诊断标准

Table 1 AD clinical diagnostic criteria

国际标准 (在瘙痒为主要标准的基础上符合下边 3 个及以上) International criteria (Compliance on the basis of the major standard about pruritus plus three or more)	国内标准 (以 Williams 标准为基础) Domestic criteria (Based on the Williams criteria)
(1) 2 岁以下发病并孩子在过去 12 个月内必须患有皮肤瘙痒症 (2) 皮肤皱褶受累史,过去 1 年内皮肤普遍干燥 (3) 影响成人屈曲表面和婴儿面部及伸肌的皮炎 (肘窝、腘窝、踝前、颈部,10 岁以下儿童包括颊部皮疹) (4) 慢性或复发性皮炎,有屈侧湿疹 (4 岁以下儿童面颊部/前额和四肢伸侧湿疹) (5) 个人或家族有皮肤或呼吸道特异性病史 (年龄较大的直系亲属有过敏性疾病病史或哮喘或花粉症的个人病史) (1) Children under 2 years of age with onset of pruritus must have had pruritus in the past 12 months (2) History of skin fold involvement and generally dry skin in past year (3) Visible flexural dermatitis in adults and facial, extensor muscles dermatitis in infants (elbow socket, rouge socket, anterior ankle, neck, including children under 10 years of age with cheek rash) (4) Chronic or relapsing dermatitis, with flexural eczema (children under 4 years of age with eczema in facial, forehead and extended extremities) (5) Personal or family history of cutaneous or respiratory atopy (history of atopic disease in 1st degree relative if aged or personal history of asthma or hay fever).	(1) 婴儿期 AD: 婴儿湿疹,多分布于两面颊、额部和头皮,皮疹可干燥或渗出 (2) 儿童 AD: 肘窝、腘窝和小腿伸侧,以亚急性和慢性皮炎为主要表现,皮疹往往干燥肥厚,有明显苔藓样变 (3) 青少年或成人 AD: 皮损与儿童期相似,病程超过 6 个月的对称性湿疹 + 特异性个人史和/或家族史 (包括湿疹、过敏性鼻炎、哮喘、过敏性结膜炎等)/血清总 IgE 升高和 (或) 外周血嗜酸性粒细胞升 (或) 和或过敏原特异性 IgE 阳性 (过敏原特异性 IgE 检测 2 级或 2 级以上阳性) (4) 老年期 AD: 皮疹通常泛发,躯干和四肢伸侧为主。且老年期首次发病,有儿童 AD 病史或老年期复发;青少年期和 (或) 成人期首发 AD 或慢性复发病程直至老年期 ^[38] (1) Infancy AD: infantile eczema, mostly on cheeks, forehead and scalp, the rash may be dry or oozing (2) Child AD: elbow sockets, rouge sockets and calf extensors, subacute and chronic dermatitis as the main symptom, rash tends to be dry, hypertrophic, and distinctly mossy (3) Teen or adults AD: symmetrical eczema with lesions similar to those of childhood and with a duration of more than 6 months + personal or family history of atopic (including eczema, allergic rhinitis, asthma, allergic conjunctivitis, etc)/raised serum IgE, and (or) raised peripheral blood eosinophils and (or) allergen-specific IgE positivity (Positive allergen-specific IgE test grade 2 or higher) (4) Gerontic AD: rash is usually generalized, with a predominance on the trunk and extensor sides of the extremities. The rash is usually present for the first time in gerontic, with a history of child AD or relapse in older age, first AD in teenager and adult or chronic relapsing course into gerontic ^[38]

根据以上国内外的临床表征,现开发了不同类型的动物模型以用于对 AD 发病机制,临床治疗及新药开发上的研究,以下将总结归纳现有的 AD 动物模型。

2.2 AD 西医模型

AD 模型可以根据发病特点分为自发性模型和诱导性模型,自发性模型包括基因工程型和近交系小鼠,近交系多用于研究某种药物对整个疾病的病程进展过程,基因工程型小鼠多为单个特

定基因敲除系,旨在重点研究单个基因对此疾病的影响,侧重点不同,所采用的动物模型也有差别,其中有鳞状尾鼠、NC/Nga 鼠、*Flg*^{-/-} 鼠等。

鳞状尾小鼠 (Flaky tail mice, FT) 是近交系小鼠,特征在于其 *Flg* 表达异常,其病变皮肤可出现 AD 样皮疹及大量 Th2 细胞因子,与人体 AD 发病过程接近。不同的 FT 小鼠其 AD 的发病程度各异,研究中可根据其表型选择不一样的 FT 小鼠 AD 模型^[39]。近交双突变品系 (DM) *ma/ma*

Flg^{fl/fl} 小鼠研究发现在其 *Flg* 基因突变的背景下, 有隐性突变 matted (ma) 的 12 ~ 15 只存在突变, 并且与 *Tmem79* 基因相关, 由此可以在 SPF 条件下自发产生 AD 症状, 因此 DM 品系 *ma/ma Flg^{fl/fl}* 小鼠近年来被常用于皮肤屏障缺陷型 AD 的研究^[40-41]。与上述不同的是, 作为基因工程型的 *Flg^{-/-}* 小鼠特征为 *Flg* 基因的缺乏, 在无致敏原情况下皮肤不会出现过敏症状^[42]; NC/Nga (NC) 小鼠作为另一种近交系 AD 模型, 在非 SPF 级条件下饲养它们才会表现出 AD 症状, 然而这些 AD

症状在 SPF 条件下不会出现^[43], 因此在实验研究中需要外来刺激来诱发疾病。

而外源诱导模型包括半抗原诱导小鼠模型: 二硝基氯苯 (1-chloro-2, 4-dinitrochlorobenzene, DNCB)、二硝基氯苯 (2, 4-dinitrofluorobenzene, DNFB)、恶唑酮 (oxazolone, OX); 过敏原诱导小鼠模型卵清蛋白 (ovalbumin, OVA)、卡泊三醇 (calcipotriol, MC903) 诱导小鼠模型等, 这些模型具有操作性强、时间可控、应用范围广等优点^[44], 以上总结详见表 2。

表 2 基于西医理论 AD 不同动物模型分析

Table 2 Analysis of different animal models of atopic dermatitis based on western medical theories

模型 Model	特点 Characteristic	皮肤炎症特征 Skin inflammation characteristic	皮损表征 Skin lesion characterization	生化特征 Biochemical characteristic
<i>Flg</i> 单缺陷小鼠 纯合 BALB/c 品系 <i>Flg</i> -deficient mice pure BALB/c background	<i>Flg</i> ^{-/-}	T 细胞区室(γδT)略有增加,其他免疫细胞群没有变化 ^[42] Skin shows slight increase in T-cell compartment(γδT) ,but otherwise unchanged immune cell populations ^[42]	(1) 新生小鼠(3 周前)皮肤干燥、鳞状、角化异常;尾部皮肤过度线性和环状收缩、随后皮肤逐步恢复 ^[42, 45] (2) 新生和成年 <i>Flg</i> ^{-/-} 小鼠的经皮水分散失(trans epidermal water loss, TEWL)未见变化 ^[46] (3) 老年期(16 周后)出现皮肤干燥、表皮增厚、TEWL ↑ ^[42, 46] (1) Pups(befor 3 weeks) showed dry and scaly skin, hyperlinearity, and annular constrictions of tail skin phenotype ameliorated after few weeks ^[42, 45] (2) Level of TEWL in neonatal and adult <i>Flg</i> ^{-/-} mice unchanged ^[44] (3) Dry skin and epidermal thickening in old age(after 16 weeks)、TEWL ↑ ^[42, 46]	(1) 角蛋白透明颗粒 ↓ (2) 血清 IgE 无变化 ^[42] (1) Keratohyalin granules ↓ (2) Levels of serum IgE unchanged ^[42]
丝聚蛋白突变小鼠 (<i>Flg</i> ^{fl/fl}) C57BL/6J 品系 Filaggrin mutated mice (<i>Flg</i> ^{fl/fl}) C57BL/6J background	<i>fl</i> 突变 <i>fl</i> mutated	-	(1) SPF 条件下不会出现自发性 AD 症状 ^[41] (2) TEWL 没有变化 (3) 轻度弥漫性角化症和真皮细胞浸润增加 ^[41] (1) No spontaneous AD symptoms in SPF conditions ^[41] (2) TEWL unchanged (3) Mild diffuse keratosis and increased dermal cell infiltration ^[41]	血清 IgE ↑ Serum IgE ↑

续表 2

模型 Model	特点 Characteristic	皮肤炎症特征 Skin inflammation characteristic	皮损表征 Skin lesion characterization	生化特征 Biochemical characteristic
丝聚蛋白突变小鼠 (<i>Flg^{fl/fl}</i>) 亲过敏 BALB/c 品系 Filaggrin mutated mice (<i>Flg^{fl/fl}</i>) Sensitive BALB/c background	<i>fl</i> 突变 <i>fl</i> mutated	(1) 真皮层嗜酸性粒细胞、中性粒细胞、ILC2、肥大细胞、嗜碱性粒细胞 $\uparrow$ ^[47] (2) Th2、Th17 细胞 $\uparrow$ 、Th1 细胞因子 $\uparrow$ ^[48-49] (1) Dermal eosinophils, neutrophils, ILC2, mast cells, basophils ^[47] (2) Th2、Th17 cell $\uparrow$ 、Th1 cytokine $\uparrow$ ^[48-49]	(1) 水肿、红斑、脱屑、苔藓化、表皮增厚 (2) 搔抓、眼睑炎 (3) TEWL $\uparrow$ ^[47] (1) Edema, erythema, desquamation, lichenification, epidermal thickening (2) Scratching, blepharitis (3) TEWL $\uparrow$ ^[47]	(1) 血清 IgE $\uparrow$ (2) Flg $\downarrow$ (1) Serum IgE $\uparrow$ (2) Flg $\downarrow$
鳞片状尾小鼠 (<i>ma/ma Flg^{fl/fl}</i>) Flaky tail mice (<i>ma/ma Flg^{fl/fl}</i>)	(1) <i>fl</i> 突变 (2) <i>Matt</i> 突变 (3) <i>TMEM79</i> 突变 (1) <i>fl</i> mutated (2) <i>Matt</i> mutated (3) <i>TMEM79</i> mutated	(1) 表皮和外周免疫器官 Th17、 $\gamma\delta$ T17 $\uparrow$ ^[50] (2) 病变真皮中嗜酸性粒细胞、中性粒细胞 $\uparrow$ 、IL-17a、IL-23a $\uparrow$ 、FoxP3 ⁺ Treg $\uparrow$ ^[51] (1) Epidermal and peripheral immune organs Th17、 $\gamma\delta$ T17 $\uparrow$ ^[50] (2) Eosinophils, neutrophils in lesion dermis $\uparrow$ 、IL-17a、IL-23a $\uparrow$ 、FoxP3 ⁺ Treg $\uparrow$ ^[51]	(1) 自发性皮肤炎症、搔抓、红斑、皮肤干燥、过敏反应 ^[41, 51] (2) 毛发脆弱、纵向分裂断裂、角质缺陷、毛发形成团块、毛囊形态扭曲 (3) TEWL $\uparrow$ ^[40-41] (1) Spontaneous skin inflammation, scratching, erythema, dry skin, allergic reactions ^[41, 51] (2) Hair fragility, longitudinal splitting and breaking, keratin defects, clumping of hair formation, distorted follicle morphology (3) TEWL $\uparrow$ ^[40-41]	血清 IgE $\uparrow$ Serum IgE $\uparrow$
NC/Nga(NC) 小鼠 NC/Nga(NC) mice	(1) <i>TCR Vβ8⁻</i> (2) iNKT 细胞系统性缺陷 ^[52] (1) <i>TCR Vβ8⁻</i> (2) iNKT cell systemic flaw ^[52]	常规条件(非 SPF 级或粉尘螨刺激)13 周后 CD3 ⁺ $\uparrow$ 、肥大细胞和 T 细胞的浸润 Infiltration of CD3 ⁺ $\uparrow$, mast cells and T cells after 13 week in conventional conditions (non-SPF grade or dust mite stimulation)	(1) SPF 级条件下不会出现 AD 症状 (2) 常规条件下 13 周后可出现搔抓、表皮明显增生、增厚、TEWL $\uparrow$ ^[53] (1) No spontaneous AD symptoms in SPF conditions (2) Scratching, marked epidermal hyperplasia and thickening can occur after 13 week in conventional conditions ^[53]	(1) 常规下或粉尘螨刺激下:血清 IgE、IgG1、IgG2a $\uparrow$ (2) 皮损表皮胸腺基质淋巴细胞生成素(thymic stromal lymphopoietin, TSLP) $\uparrow$ ^[54] (1) Under routine or dust mite irritation: serum IgE、IgG1、IgG2a $\uparrow$ (2) TSLP $\uparrow$ ^[54]

续表 2

模型 Model	特点 Characteristic	皮肤炎症特征 Skin inflammation characteristic	皮损表征 Skin lesion characterization	生化特征 Biochemical characteristic
hlAD 模型 hlAD model	半抗原诱导 DNCB Semi-antigenic induction DNCB	(1)肥大细胞↑ ^[55] (2)IL-4↑ ^[56] (1)Mast cell↑ ^[55] (2)IL-4↑ ^[56]	(1)红斑、干燥、皮肤干裂、搔抓、 TEWL↑ ^[56] (2)表皮增厚(增生)、角化过 度、海绵状水肿 ^[57] (1)Erythema, dryness, chapped skin, scratching, TEWL↑ ^[56] (2)Epidermal thickening (hyperplasia), hyperkeratosis, spongy edema ^[57]	(1)血清 IgG、 IgE↑ ^[57-58] (2)组胺↑ (3)TSLP↑ (4)细胞角蛋白 10 (KRT10)↑ (5)S100A8↑ ^[57] (1)Serum IgG、 IgE↑ ^[57-58] (2)Histamine↑ (3)TSLP↑ (4)Cytokeratin 10 (KRT10)↑ (5)S100A8↑ ^[57]
OX-AD 模型 OX-AD model	半抗原诱导 OX Semi-antigenic induction OX	(1)Th2 型炎症,嗜酸性 粒细胞、肥大细胞↑ (2)IL-4、IL-13↑ ^[59] (1)Th2 type inflammation, eosinophils, mast cells↑ (2)IL-4、IL-13↑ ^[59]	(1)红斑、干燥、脱屑 ^[60] (2)表皮增生、角化不全、真皮水 肿、TEWL↑ ^[59, 61] (1)Erythema, dryness, flaking ^[60] (2)Epidermal hyperplasia, hyperkeratosis, dermal edema, TEWL↑ ^[59, 61]	(1)血清 IgE↑ ^[61] (2)Flg↓、细胞角 蛋白 1 和细胞角蛋 白 10↑ ^[59] (1)Serum IgE↑ ^[61] (2)Flg↓、 cytokeratin 1 and cytokeratin 10↑ ^[59]
OVA-AD 模型 OVA-AD model	过敏原诱导 OVA Allergen induction OVA	(1)皮损组织嗜酸性粒细 胞、肥大细胞、CD4 ⁺ 和 CD8 ⁺ T 细胞↑ ^[62] (2)IL-4、IL-13、 IFN-γ↑ ^[63] (1)Eosinophils, mast cells、CD4 ⁺ and CD8 ⁺ T cell in skin lesion tissue↑ ^[62] (2)IL-4、IL-13、 IFN-γ↑ ^[63]	(1)搔抓、红斑、干燥 (2)表皮增生增厚、脱落 ^[64] (1)Scratching, erythema, dryness (2)Epidermal hyperplasia thickening and peeling ^[64]	(1)血清 IgG1、 IgG2a、IgE↑ ^[62] (2)TSLP↑ ^[65] (1)Serum IgG1、 IgG2a、IgE↑ ^[62] (2)TSLP↑ ^[65]

续表 2

模型 Model	特点 Characteristic	皮肤炎症特征 Skin inflammation characteristic	皮损表征 Skin lesion characterization	生化特征 Biochemical characteristic
MC903-AD 模型 MC903-AD model	MC903 诱导 MC903 induced	(1)Th2 型炎症、嗜酸性 粒细胞、嗜碱性粒细胞、 肥大细胞、巨噬细胞 ↑ (2) IL-33、IL-4、IL-13、 IL-31 ↑ ^[66-69] (1)Th2 type inflammation, eosinophils, basophils, mast cells, macrophages ↑ (2) IL-33、IL-4、IL-13、 IL-31 ↑ ^[66-69]	(1) 红斑、皮肤干燥、抓痕 ^[70] (2) 海绵状水肿、真皮增厚、 角化不全、TEWL ↑ ^[67] (1) Erythema, dry skin, and excoriation ^[70] (2) Spongy edema, dermal thickening and hyperkeratosis, TEWL ↑ ^[67]	(1) 血清 IgE ↑ (2) TSLP ↑ ^[69] (3) 骨膜蛋白 ↑ ^[66] (4) Claudin-1、 Flg ↓ ^[67] (5) 肥大细胞蛋白 酶-1 ^[71] (1) Serum IgE ↑ (2) TSLP ↑ ^[69] (3) Membrane covering bone ↑ ^[66] (4) Claudin-1、 Flg ↓ ^[67] (5) Mast cell protease-1 ^[71]

3 AD 中医证型动物模型

根据中医临床证候分型,AD 主要有心脾积热证、心火脾虚证、脾虚湿蕴证、风湿热蕴证、脾肾阳虚证^[72]。因此基于不同中医证型在临床上存在不同的临床表现,由此也产生了不同种类的证候动物模型,归纳见表 3。

4 AD 模型评价标准

通过对现有模型的总结,AD 模型的评价标准主要基于以下 4 个方面:(1) 皮肤皮炎严重程度评分——一般根据与临床患者症状表现相似程度: 特应性皮炎评分指数 (scoring atopic dermatitis index, SCORAD) ——(清洁:0; 几乎清洁:0.1 ~ 1.0; 轻度:1.1 ~ 7; 中度:7.1 ~ 21; 重度:21.1 ~ 50; 非常严重:50.1 ~ 72)。和湿疹面积与严重程度指数 (eczema and severity index, EASI) ——(清洁:0 ~ 9.9; 轻度:10 ~ 28.9; 中度:29 ~ 48.9; 重度:49.0 ~ 103)。出现不同程度的红斑、脱屑、干燥、丘疹、水疱、水肿、苔藓样变等^[77];(2) 皮损组织病理学改变:淋巴细胞海绵状水肿,伴有表皮增生和过度增殖;皮损皮肤免疫细胞浸润明显,包括活化的 T 细胞(偏向性 Th2 炎症反应)、肥大细胞和嗜酸性粒细胞^[78];(3) 大

部分伴随血清 IgE 水平升高;(4) 分子水平检测: TSLP、骨膜蛋白、Flg、角蛋白、嗜酸细胞活化趋化因子和或特定趋化因子如 趋化因子 CCL17、特定抗菌肽——如 S100A7/S100A8/S100A9^[78-79] 的表达增加,紧密连接蛋白-1 (Claudin-1) 表达降低。Claudin-1 在细胞紧密连接中发挥着骨架蛋白的作用,是维持上皮细胞屏障功能完整重要的蛋白,缺乏 Claudin-1 蛋白会因皮肤屏障缺陷使得 TEWL 增加^[80]。

5 总结与展望

目前 AD 模型的构建方法已经相对成熟,但是每种模型仍存在一定的局限性,尽管提出有 AD 人源化小鼠模型,其表现会更接近与临床病人的症状表现^[81],但由于其技术和使用成本问题无法得到推广,但在未来有可能会成为在针对 AD 临床药物研究的一个新的模型方向。现阶段中医证候模型现研究相对较少,并且大多研究在国内,国外并未有相关研究。尽管中医药在临床治疗和实验研究上显示 AD 有良好的治疗效果^[82-84],但由于中医证候模型缺乏明确的标准评价体系,因此限制了中医证候模型的发展,这可能与国内中医药在科研研究阶段处于探索阶段有关。现有的中医证候模型模式研究更多为“特

表 3 基于中医理论 AD 不同动物模型分析

Table 3 Analysis of different animal models of atopic dermatitis based on traditional Chinese medicine theories

中医证型 Traditional Chinese medicine syndrome types	造模方式 Modeling method	皮损炎症特征 Skin inflammation characteristic	症状 Symptomatic	生化指标 Biochemical characteristic
脾虚证 Spleen deficiency syndrome	(1) 2% 苦基氯 (2,4,6-trinitrochlorobenzene, PCI) 涂擦在 BALB/c 小鼠腹部皮肤表面。4 d 后用 0.8% PCI 每 2 d 涂擦 1 次, 同时每日 25 mL/kg 药量给予 1 g/mL 大黄水灌胃, 共 14 d^[73] (2) FT 小鼠 20 周后用 108 mg/mL 大黄煎煮液 0.3 mL 灌胃给药 1 周^[74] (1) PCI was rubbed on the skin surface of the abdomen of BALB/c mice. 4 days later, 0.8% PCI was rubbed every 2 d, and 1 g/mL of rhubarb water was given by gavage at a dose of 25 mL/kg per day for 14 d (2) FT mice were administered 108 mg/mL rhubarb decoction 0.3 mL by gavage for 1 week after 20 weeks^[74]	IL-4、IL-17、IL-22 ↑ ^[74]	(1) 皮肤明显增厚、红斑、渗出、糜烂、浆痂^[73] (2) 毛发枯槁、疏散、便溏, 体质量、体力和食量下降、畏寒^[73] (3) 红斑、表皮增生增厚、干燥、棘层肥厚、损伤水肿^[74] (1) Marked thickening of the skin, erythema, oozing, vesicles, crusting^[73] (2) Withered and sparse hair, loose stools, loss of body mass, stamina and food intake, cold feeling^[73] (3) Erythema, epidermal hyperplasia and thickening, dryness, hypertrophy of the stratum spinosum, damage edema^[74]	(1) 血清 IgE ↑ (2) TSLP ↑ (3) 血清 IL-4、IL-17、IL-22 ↑^[73-74] (1) Serum IgE ↑ (2) TSLP ↑ (3) Serum IL-4、IL-17、IL-22 ↑^[73-74]
寒湿证病证 Cold dampness syndrome	在比例为 3:1 的丙酮和橄榄油基质溶液中加入 DNCB 配成浓度为 1% (6 d) 或 0.5% (12 d) 的 DNCB 溶液; 小鼠皮肤滴加 200 μL DNCB 溶液, 在人工气候箱中温度 4 ~ 6℃、相对湿度 90% ~ 95%, 6 h/d (10:00 ~ 16:00), 共 18 d 模拟寒湿环境, 用高脂饲料喂养模拟内湿因素^[75] DNCB was added to a 3:1 ratio of acetone and olive oil substrate solution to formulate a 1% (6 d) or 0.5% (12 d) DNCB solution. Mice were dermally dosed with 200 μL of DNCB solution, and fed with high-fat chow to simulate endohydric factors in an artificial climatic chamber at a temperature of 4 ~ 6℃ and a relative humidity of 90% ~ 95% for 6h per day (10:00 ~ 16:00) for 18 d to simulate cold and humid environments^[75]	真皮浅层大量淋巴细胞浸润 ^[75] Massive lymphocytic infiltration of the superficial dermis ^[75]	(1) 搔抓, 表皮增厚, 角化不全、角化过度 (2) 小便颜色清亮透明色。精神萎靡, 反应迟钝, 蜷缩不喜动, 步态不稳 (3) 皮毛污秽, 肛门污秽, 大便软湿甚至便溏^[75] (1) Scratching, epidermal thickening, hyperkeratosis, hyperkeratosis (2) Urine is clear and transparent in color. depressed, unresponsive, hunched over and uninhibited, unsteady gait (3) Soiling of the skin and fur, soiling of the anus, soft and wet stools or even loose stools^[75]	(1) TSLP ↑ (2) Claudin-1、TRPV3 ↓、TRPV4 ↑^[75]
脾虚湿蕴证 Spleen deficiency and dampness stagnation syndrome	在温度 23℃、湿度 95% 的气候箱内进行 10 h/d 的饲养, 单数日喂养高脂饲料; 双数日禁食, 喂高脂饲料的同时以 1 g/mL 番泻叶冷浸液给小鼠灌胃, 每只 10 mL/kg 诱导持续至动物取材^[76] Mice were housed for 10 h/d in a climatic chamber at a temperature of 23℃ and 95% humidity, fed high-fat chow on odd-numbered days; fasted on even-numbered days, and fed high-fat chow while being gavaged with a cold infusion of 1 g/mL senna at 10 mL/kg each. Induction was continued until the animals were retrieved^[76]	—	(1) 皮肤出现严重水肿、红斑、粗糙、溃烂及结痂、TEWL ↑ (2) 精神萎靡、蜷缩聚堆、毛发污秽油腻、腹泻、大便质软或溏薄、肛周清洁度差^[76] (1) Severe edema, erythema, roughness, ulceration and crusting of the skin, TEWL ↑ (2) Depressed, curled up in piles, dirty and greasy fur, diarrhea, soft or loose stools, poor perianal cleanliness^[76]	

应性模型特征 + 中医证型临床表现”,其效果仍与临床病人有较大出入,所产生的模型症状未必会与病人临床表现相似^[85],未来仍需要研究人员深入去研究更适应的中医证候模型。

现阶段成熟的每种 AD 小鼠模型都具有其独特的特性和优势,例如:半抗原诱导模型具有较低成本,适合深入探究 AD 的分子机制和途径,但诱导剂存在安全隐患,且诱导耗时较长;而过敏原诱导模型应用范围广泛,但操作相对复杂;如:MC903 诱导模型建立迅速,然而不适合探究人类 AD 的病理机制;总体而言,没有哪种模型是完美的,即使是自发型模型小鼠,如 NC 小鼠, *Flg*^{-/-} 小鼠,丝聚蛋白-角蛋白 (*FlgHmr*^{-/-}) 双缺陷小鼠^[86]、C57BL/6J 品系 *Flg*^{fl/fl} 小鼠仍需要半抗原或过敏原刺激下才会出现 AD 样反应,然而这些模型对 AD 发病基因相关机制仍然是不错的选择。

无论是关于中医还是西医对 AD 病证的研究,动物模型选择的目的是最大程度适配研究目的及研究内容,针对临床研究其动物模型尽可能选择与临床症状或病理相近的模型;而针对机制研究则更多选择机制贴切的基因工程模型,只有根据特点去适配不同的动物模型才能达到最好的研究效果。

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