

## 常用慢性瘙痒小鼠模型及其行为学评价的研究进展

易婷<sup>1</sup> 米文丽<sup>2,3</sup> 王彦青<sup>1,2,3△</sup>

(<sup>1</sup>广东药科大学中医药研究院 广州 510006; <sup>2</sup>复旦大学基础医学院中西医结合学系 上海 200032;

<sup>3</sup>上海市针灸机制与穴位功能重点实验室 上海 200433)

**【摘要】** 瘙痒是一种可引起抓挠行为的不愉快的躯体感觉。许多皮肤疾病及一些系统性疾病等都存在慢性瘙痒的症状,顽固而剧烈的瘙痒严重影响患者的身心健康和生活质量。稳定可靠且能模拟临床的动物模型是瘙痒机制研究和治疗靶点筛选的基础。近年来,学界探索建立了多种瘙痒动物模型,并在此基础上探讨瘙痒机制。本文总结了慢性瘙痒的小鼠模型制作和行为学评价方法,为今后开展瘙痒研究提供参考。

**【关键词】** 慢性瘙痒; 小鼠模型; 行为学评价

**【中图分类号】** R-332 **【文献标志码】** A **doi:** 10.3969/j.issn.1672-8467.2023.06.017

## Research progress on mouse models of chronic pruritus and behavioral evaluation

YI Ting<sup>1</sup>, MI Wen-li<sup>2,3</sup>, WANG Yan-qing<sup>1,2,3△</sup>

(<sup>1</sup>Chinese Medicine Research Institute, Guangdong Pharmaceutical University, Guangzhou 510006, Guangdong Province, China; <sup>2</sup>Department of Integrative Medicine and Neurobiology, School of Basic Medical Sciences, Fudan University, Shanghai 200032, China; <sup>3</sup>Shanghai Key Laboratory for Acupuncture Mechanism and Acupoint Function, Shanghai 200433, China)

**【Abstract】** Itch is an unpleasant physical sensation that can cause scratching behavior. Chronic itch is a burdensome clinical problem of many skin diseases and some systemic diseases. Stubborn and severe itch seriously affects the physical and mental health as well as the quality of life of patients. It is important to use assortments of preclinical itch models to identify itch mechanisms, and to foster the development of better anti-pruritus drugs. In recent years, a variety of animal models of itch have been established, and advances have been made in basic itch research. The present study summarizes the commonly used mouse models in the research of itch and the frequently utilized behavioral evaluation for assessing the scratching, that provides a reference for the future itching and antipruritic research.

**【Key words】** chronic itch; mouse model; behavioral evaluation

\* This work was supported by the STI2030-Major Projects (2022ZD0204700), the National Natural Science Foundation of China (82271248, 82271258) and the Program of Zhongshan-Fudan Joint Innovation Center (202106).

三百多年前,德国医生塞缪尔·哈芬雷弗(Samuel Hafenreffer)将瘙痒(itch or pruritus)定义为“一种不愉快的感觉,会引起抓挠的欲望或反射”<sup>[1]</sup>。

瘙痒一方面是动物面临威胁的保护性机制,另一方面也是皮肤病等疾病的典型症状之一。瘙痒严重影响人们的生活质量,包括情绪、注意力、饮食习

科技创新 2030(2022ZD0204700);国家自然科学基金(82271248,82271258);中山复旦联合创新中心项目(202106)

△Corresponding author E-mail: wangyanqing@shmu.edu.cn

网络首发时间:2023-08-22 16:04:58 网络首发地址: <https://link.cnki.net/urlid/31.1885.R.20230822.1019.002>

惯、性功能和睡眠<sup>[2]</sup>。流行病学结果显示<sup>[3]</sup>,皮肤病中瘙痒的发病率为54.5%,慢性瘙痒(持续时间超过6周)的治疗是悬而未决的医学挑战,影响全世界数百万人。慢性瘙痒具有多种表现形式,依据瘙痒的起源、发病机制和皮损表现,可对瘙痒进行多种方式的分类,因此国际瘙痒研究论坛创建了一个国际公认的标准化分类系统<sup>[2]</sup>(表1),不同类型的慢性瘙痒的病因、机制、诊断、治疗及预后各不相同。为了了解瘙痒的机制,寻找更有效的止痒方法,需要有针对性地相应研究。疾病的动物模型是指在

生物医学科学研究中建立的具有人类疾病模拟性能表现的实验动物<sup>[4]</sup>,建立具有明显、稳定和持续性瘙痒行为的动物模型是研究慢性瘙痒潜在机制的基础。基于不同动物模型已有研究发现多种分子、受体和细胞在慢性瘙痒的发生发展中发挥重要作用。本文按照国际瘙痒研究论坛分类进行模型整理分析,简述目前慢性瘙痒研究中常用的小鼠模型及行为评价(表2),为慢性瘙痒机制研究中实验动物模型的选择提供参考。

表1 国际瘙痒研究论坛慢性瘙痒分类  
Tab 1 Classification of chronic pruritus by International Forum for the Study of Itch

Category	Diseases
I Dermatological	Dermatoses such as psoriasis, xerosis, atopic dermatitis, scabies, and urticaria
II Systemic	Systemic diseases involving the liver (e.g. primary biliary cirrhosis), kidneys (e.g. chronic renal failure), blood (e.g. Hodgkin's lymphoma), and certain drugs
III Neurological	Diseases or disorders of the central or peripheral nervous system, e.g. nerve damage, compression, or irritation
IV Psychological/psychosomatic	Includes somatoform pruritus with comorbidities associated with psychiatric and psychosomatic diseases
V Mixed	The overlapping and coexistence of multiple diseases causing pruritus
VI Other	Of undetermined origin

常用慢性瘙痒小鼠模型

皮肤病瘙痒小鼠模型 过敏性接触性皮炎(allergic contact dermatitis, ACD)是由化学物质或金属离子(如镍[Ni]<sup>2+</sup>和铬[Cr]<sup>3+</sup>)与皮肤表面直接接触引起的一种炎症性湿疹性皮肤病<sup>[5]</sup>。ACD是T细胞介导的IV型超敏反应,涉及先天性和获得性免疫反应。机体皮肤最初暴露于有过敏源的环境下(没有临床症状或体征),此阶段为致敏阶段;再次暴露后,随着抗原特异性效应细胞和记忆T细胞的激活发展成ACD,此阶段为激发阶段<sup>[6-7]</sup>。ACD小鼠模型,即过敏性接触性皮炎小鼠模型通常是将半抗原应用于小鼠的颈背部、腹部敏化,于耳朵、颈背部、腿部等来激发皮肤炎症;常用的半抗原有二苯基环丙烯酮(diphenylcyclopropenone, DCP)、对2,4-二硝基氟苯(2,4-dinitrofluorobenzene, DNFB)、二硝基氯苯(2,4-dinitrochlorobenzene, DNCB)、方正酸二丁酯(squaric acid dibutylester, SADBE)、三硝基氯苯(2,4,6-trinitrochlorobenzene, TNCB)、恶唑酮(oxazolone, OXA)和漆酚(urushiol)等。DCP是用于治疗斑秃的局部免疫治疗剂,通常会导致严重的不良反应,比如过敏性皮炎及强烈瘙痒;DNFB是一种解耦剂,最早用于诱导豚鼠的接触性皮肤致

敏<sup>[8]</sup>。SADBE是一种小分子半抗原,用于治疗斑秃和疣<sup>[9]</sup>,极其不稳定,需要注意避光保存、现配现用。漆酚广泛存在于毒藤物种中,其诱导的ACD是最常见的环境过敏性疾病,伴有强烈而持续的瘙痒和疼痛感。早期漆酚诱导的ACD模型实验是在豚鼠身上进行的<sup>[10]</sup>,而当前小鼠漆酚模型可作为人类毒藤ACD的转化模型,能模拟人类接触毒藤的表现<sup>[11]</sup>。恶唑酮可共价修饰皮肤中的蛋白质,从而引发过敏反应,恶唑酮和漆酚模型小鼠均能导致24 h的持久抓挠行为<sup>[12]</sup>。

特应性皮炎(atopic dermatitis, AD)是一种慢性复发性炎症性疾病,其关键特征包括遗传易感性、表皮屏障破坏和免疫系统失调等<sup>[13-14]</sup>,但迄今为止,AD的致病机制仍然不完全清楚。有研究采用类似ACD造模的半抗原诱导进行AD小鼠模型造模模型,该模型在小鼠皮肤上施用半抗原,如恶唑酮、DNCB、DNFB和TNCB等,先进行初始致敏,后续进行多次激发以完全唤起AD样病变<sup>[15-16]</sup>。需要注意的是当半抗原的第二次激发在较短的时间内(不到一周)被激发几次时,通常被认为是ACD小鼠模型,而不是AD小鼠模型,AD小鼠模型制作的激发过程一般需要持续3周。卡泊三醇(calcipotriol,

MC903)是一种合成维生素D3类似物,用于治疗成人牛皮癣。但是MC903在局部施用于小鼠时会引起AD样病变<sup>[17]</sup>,由于其可重复性和易用性,被广泛用于AD模型候选药物。然而,有研究指出MC903不会在人类中诱导AD样病变,因而该模型可能并不适合研究人类AD发病机制<sup>[18]</sup>。卵清白蛋白(ovalbumin,OVA)是鸡蛋中主要过敏原,能引起各种过敏症状,OVA可以在不同年龄不同性别的小鼠诱发稳定的AD模型,因此该模型应用较为广泛<sup>[18]</sup>。Nc/Nga小鼠是一种近交小鼠品系,在SPF级实验小鼠房饲养的NC/Nga小鼠自发类似于人类的AD样皮肤病变,具有AD样病理和行为特征<sup>[19]</sup>,因此常用作自发AD样模型。此外,基因工程或修饰的小鼠,比如IL-13转基因小鼠模型或者博来霉素水解酶(bleomycin hydrolase,BLMH)敲除小鼠,也是研究特定基因参与AD发病机制的宝贵资源。目前各种各样的AD小鼠模型特征有多篇综述进行整理和描述<sup>[18,20-22]</sup>。

银屑病(psoriasis,PSO),又称牛皮癣,是一种迁延不愈的慢性非传染性自身免疫性皮肤病,影响着全世界6 000多万成人和儿童,并且易导致心理疾病<sup>[23-25]</sup>。银屑病的动物模型主要有自发性、人工诱导性、异位移植性及基因工程动物模型<sup>[26]</sup>。自发性瘙痒模型因与临床症状吻合度低,已很少使用。异位移植性模型是将患者皮肤移植于小鼠,接近临床银屑病瘙痒的模型,但因操作困难,成本昂贵而受到限制。基因工程小鼠模型是指使用某种或某几种基因缺陷或突变的小鼠(如CD18低表达PL/J小鼠)模型,但由于银屑病瘙痒是一种机制复杂、多基因参与的慢性疾病,所以该模型多作为辅助研究手段<sup>[26-27]</sup>。人工诱导性动物模型与临床银屑病瘙痒症状吻合度较高,尤其是咪喹莫特(imiquimod,IMQ)诱导的小鼠银屑病慢性瘙痒模型,其制作周期较短,成本较低,是目前实验室研究银屑病瘙痒的首选动物模型。

病理性干燥性皮肤病多发生在持续超过6周的慢性瘙痒疾病中,比如干燥症、特应性皮炎、银屑病等;也是慢性肾病、慢性肝病和糖尿病等瘙痒性全身性疾病中常见的皮肤表现,具体表现为出现鳞片状、粗糙和开裂等皮肤特征。研究表明,皮肤干燥症瘙痒与皮肤干燥和皮肤屏障破坏相关,皮肤干燥导致角质层水合作用降低,皮肤屏障破坏使表皮

皮肤水分流失增加<sup>[28]</sup>。目前最常用的皮肤干燥症瘙痒小鼠模型是丙酮/乙醚和水(acetone-ether-water,AEW)重复序贯涂抹,该模型破坏皮肤屏障,经皮水分损失增加,引起明显的皮肤干燥、瘙痒<sup>[29]</sup>。

紫外线皮炎是紫外线辐射(ultraviolet radiation,UVR)引起的皮肤光毒性反应,也称晒伤,常伴瘙痒。UVR主要来自太阳辐射,由于短波紫外线(ultraviolet radiation C,UVC)被臭氧吸收,所以阳光中主要是长波紫外线(ultraviolet radiation A,UVA)和中波紫外线(ultraviolet radiation B,UVB)<sup>[30]</sup>。2021年Cao等<sup>[31]</sup>首先建立了晒伤相关瘙痒的小鼠模型,发现单次暴露于功率 $\geq 400 \text{ mJ/cm}^2$ 的宽谱UVB(broad-band UVB,BB-UVB)照射的颈背区域能够诱发小鼠强烈的抓挠行为,而暴露在 $6\ 000 \text{ mJ/cm}^2$ 以上UVA照射的小鼠则没有明显的抓挠行为。

全身疾病导致慢性瘙痒小鼠模型 胆汁淤积性慢性瘙痒是患有胆汁淤积性肝病患者的伴随症状,美国肝病研究协会和欧洲肝脏研究协会更新了原发性胆汁性胆管炎(primary biliary cirrhosis,PBC)指南中关于瘙痒管理的治疗建议<sup>[32]</sup>。当前已经建立了几种胆汁淤积症的手术和转基因啮齿类动物模型,其中手术诱导胆汁淤积的小鼠模型更接近于人类疾病。最近,研究者<sup>[33]</sup>改善了胆总管结扎(bile duct ligation,BDL)诱导胆汁淤积性瘙痒的小鼠模型,结扎胆管以阻断前叶、右叶和左叶的胆汁分泌,但尾状叶除外。胆管结扎后血清总胆汁酸水平升高,小鼠出现了显著的搔抓行为,最重要的是该模型克服了先前的BDL模型存活时间较短的缺点。

糖尿病神经病变(diabetic peripheral neuropathy,DPN)诱发的慢性瘙痒可能反映了糖尿病患者皮肤或周围神经系统的功能障碍<sup>[34]</sup>。流行病学研究表明,27.5%的糖尿病患者伴有全身性瘙痒,瘙痒可能是糖尿病外周神经病变的症状和标志之一<sup>[35]</sup>。甲基乙二醛(methylglyoxal,MGO)是一种反应性 $\alpha$ -二羰基代谢物,刘通课题组<sup>[35]</sup>研究发现,皮内注射MGO可以剂量依赖性地诱发小鼠瘙痒行为;在链脲佐菌素(streptozotocin,STZ)100 mg/kg诱导的糖尿病小鼠模型上,小鼠在第1、3、5周均表现出显著的触诱发痒行为。

皮肤T细胞淋巴瘤(cutaneous T-cell

lymphomas,CTCLs)是一组异质性淋巴组织增生性肿瘤<sup>[36]</sup>,CTCLs患者经常伴有剧烈且较难缓解的瘙痒。Han等<sup>[37]</sup>开发了一种慢性瘙痒的异种移植小鼠模型,在免疫缺陷小鼠的颈背部皮内接种来自CTCLs患者的Myla细胞系(CD4+记忆T细胞)诱导了严重的淋巴瘤,淋巴瘤缓慢而持续地生长,第15天肿瘤直径明显增大。有意思的是,瘙痒出现在肿瘤增大之前,这种早发性瘙痒可能是由于接种人体细胞分泌的致痒原所引起的。

表2 常用慢性瘙痒小鼠模型制作与评价

Tab 2 Development and evaluation of chronic pruritus mouse models

Pruritus mouse models	Mice	Model	Test	
ACD	DNFB/TNCB <sup>[29]</sup>	C57BL/6	Shaving the abdomen and nape skin (2 cm <sup>2</sup> ), painting the abdomen with 50 μL 0.5% DNFB (or 100 μL 3% TNCB) (dissolved in a mixture of acetone: olive oil (4:1)). 5 days later, the mice were challenged by painting the nape skin with 30 μL 0.25% DNFB (or 20 μL 1% TNCB) (dissolved in a mixture of acetone: olive oil (4:1)) daily for 7 days.	Recording for 1 h on day 8 by video. The mice showed robust pruritus.
	DCP <sup>[29, 46]</sup>	C57BL/6	Shaving the nape skin (2 cm <sup>2</sup> ) and painting the nape skin with 200 μL of DCP (1% dissolved in acetone). 5 days later, the mice were challenged by painting the nape skin with 200 μL DCP (0.5% dissolved in acetone) daily for 7 days.	Recording for 1 h after the final challenge or immediately after each challenge by video. The mice exhibited robust and persistent itch for more than 2 weeks.
	SADBE <sup>[9]</sup>	C57BL/6	Shaving the nape skin (2 cm <sup>2</sup> ) and painting the nape skin with 20 μL of SADBE (0.5% dissolved in acetone) once a day for the 3 consecutive days. 5 days later, the mice were challenged by painting the one ear with 20 μL SADBE (0.5% dissolved in acetone) once a day for 3 consecutive days.	Recording for 1 h on 3 days later after the final challenge by video. The mice exhibited persistent pruritus.
	Urushiol/OXA <sup>[11-12]</sup>	C57BL/6	Shaving the abdomen and nape skin (2 cm <sup>2</sup> ), painting the abdomen with urushiol or OXA (2% dissolved in a mixture of acetone: olive oil (4:1)). 5 days later, the mice were challenged by painting the nape skin with 30 μL urushiol or OXA (0.5% dissolved in a mixture of acetone: olive oil (4:1)) every other day.	Recording at time points of 0 h and 4 h after each allergen challenge for 1 h by video. Scratches increased after each challenge, and the most noticeable in the first few hours, then gradually decreasing and stabilizing.
	UVR <sup>[31]</sup>	C57BL/6J	The side area was shaved from the nape to the lateral abdomen. The UV phototherapy device (a single exposure to BB-UVB irradiation with power ≥400 mJ/cm <sup>2</sup> ) was placed on the top of the round gasket, allowing circular light stimulation only to the shaved skin area by a single.	After UV irradiation, the mice were immediately videotaped, and then recorded daily for 1 h for 1 week. The number of scratches was counted, reaching a plateau on day 3 and persisting for more than 1 week.
AD	DNCB <sup>[47]</sup>	BALB/c	Shaving the abdomen and nape skin (2 cm <sup>2</sup> ), painting the abdomen with 200 μL DNCB (1% dissolved in a mixture of acetone: olive oil), every other day in the first week. Then the mice were challenged by painting the nape skin with 200 μL DNCB (0.5% dissolved in a mixture of acetone: olive oil (4:1)) twice a week for 3 weeks.	Recording before or half an hour after each challenge for 1 h by video.
	MC903 <sup>[17,48]</sup>	C57BL/6J	MC903 was dissolved in 100% ethanol and topically applied on mouse ears (1 nmol in 20 μL, 10 μL per side of ear) for 12 days or treated once daily with 2 nmol of MC903 for 7 days.	Scratching bouts recorded for 1 h before daily application. Scratches increased after each challenge.
	OVA <sup>[49]</sup>	BALB/c	Mice were given an intraperitoneal injection of OVA (100 μg). 5 days later, they received a subcutaneous injection of OVA (50 μg). On day 14 to day 39, gauze (1 cm <sup>2</sup> ) soaked with 0.1% OVA (100 μL) was applied to the shaved skin area. The treated skin area was covered with a patch.	Starting at day 14, mice were videotaped for 1 h twice a week to count scratching behavior. By day 21, counts of spontaneous scratch bouts had increased significantly to a plateau.
PSO	IMQ <sup>[27]</sup>	BALB/c	Mice received the drug (5% Aldara) at a dose of 62.5 mg daily for 5–7 days to the shaved nape skin.	Recording 20 h to 22 h after each application for 1 h. The number of scratches increases gradually over time.



(续表 2)

Pruritus mouse models	Mice	Model	Test	
DRY	AEW <sup>[28, 50]</sup>	C57BL/6J	Mice were applied acetone and diethylether (1:1) for 30 s followed by clean water for 30 s twice a day (9:00 am and 16:00 pm) for 5 days to the shaved nape skin.	Recording for 1 h before modeling every morning by video. Scratches gradually increased from day 3.
PBC	BDL <sup>[33]</sup>	ICR	After midline laparotomy (2 cm) , the common bile duct was ligated with 4–0 silk sutures between the right and caudate lobes.	Pruritus behavior records were performed for 1 h every week after BDL procedure. The number of spontaneous scratching events was significantly increased in BDL mice from week 5 after BDL procedure and was maintained at the same level at least up to week 9.
DPN	MGO <sup>[35]</sup>	C57BL/6J	By intradermal injection MGO (1–40 μmol) into the shaved nape skin.	Recording for 30 min immediately after the injection , the dose-response curve shows a typical “invert-U” shape.
	STZ <sup>[35]</sup>	C57BL/6J	STZ was freshly dissolved in citrate buffer (0.1 mol/L , citrate : NA citrate=1:1 , pH 4.2–4.4). The model was induced by a single intraperitoneal injection of STZ (100 mg/kg).	Model displayed significant mechanical itch rather than spontaneous itch at the 5th week after STZ injection.
CTCL	Myla cells <sup>[37]</sup>	NOD. CB17-Prkdc <sup>scid</sup> /J	By intradermal injection of CD4 Myla cells (1×10 <sup>5</sup> cells/μL , 100 μL) into the shaved nape skin.	By recording for 1 h every 5 days after injection. Pruritus began on day 5 and reached to a peak on day 15 , declined on day 25 and day 30 , but returned to the peak level on day 40.

Mice were habituated to the environment for at least 2 days before testing.

神经源性瘙痒小鼠模型 神经源性瘙痒 (neuropathic itch, NI)没有原发性皮肤病,可由任何外周或中枢神经系统的结构或功能损伤引起<sup>[38]</sup>,且可因瘙痒抓挠导致表皮脱落、苔藓样变<sup>[39-40]</sup>。由于缺乏合适的体内模型,NI的研究受到限制。一些研究小组发现<sup>[41-42]</sup> *Bhlhb5* 突变小鼠的脊髓抑制性中间神经元丧失伴随异常瘙痒,很可能模拟神经性瘙痒,但该转基因小鼠总体健康状况不佳,很难长期存活。伪狂犬病病毒 (pseudorabies virus, PRV)是一种高度传染性的病原体,非自然宿主感染 PRV 后会引发急性神经病变而出现剧烈瘙痒,通常在 2 天内死亡;由于 PRV 感染与水痘-带状疱疹病毒 (varicella-zoster virus, VZV)感染在基因组序列、临床体征、发病机制和免疫力方面具有多种相似性,PRV 诱导小鼠 NI 可能可以用于探讨由水痘-带状疱疹病毒感染引瘙痒的发病机制<sup>[43-44]</sup>。另外,Chen 等<sup>[45]</sup> 在小鼠淋巴瘤中发现了明显的神经支配,预示了 CTCLs 淋巴瘤小鼠模型也可用于神经性瘙痒机制和治疗方法的研究。

慢性瘙痒小鼠模型行为学

瘙痒行为评估 慢性瘙痒常表现为自发性瘙

痒和触诱发痒,常形成瘙痒-搔抓-瘙痒恶性循环,可导致搔抓紊乱、皮肤损伤、睡眠障碍以及抑郁、焦虑等精神心理问题,具有多因素特性及多维度表现,临床上常通过瘙痒及相关症状的评估问卷及量表进行综合评估。研究人员根据研究目的采用不同的慢性瘙痒小鼠模型,各种模型症状有很大不同,但抓挠行为是评估瘙痒的一个关键指标,因此需要在实验小鼠上进行自发性瘙痒或触诱发痒等痒觉异常评价。不同模型的搔抓程度和搔抓持续时间不同,目前测量抓挠的方法有人工计数和自动化系统 (如电磁场检测和声学检测<sup>[51-52]</sup>等),这些方法准确并广泛用于研究。人工计时费时费力,电磁场检测和声学检测方法需要专门的设备和复杂的分析软件,随着人工智能等技术的发展,全自动的瘙痒行为记录系统将为小动物瘙痒行为学评价带来新的助力。

自发性行为评估 (人工计数):一般是小鼠从抬起后爪快速连续搔抓造模部位 (3 次或以上),并以舔舐脚趾或后爪放回地面记为一次搔抓。

自发性行为评估 (自动记录系统):目前常使用的抓挠自动记录系统 (MicroAct)<sup>[52]</sup>是一种基于磁场的定量抓挠分析系统,利用切割磁力线的原理进行

瘙痒行为记录,具体是将埋置磁铁的小鼠单独放置于自动记录系统的塑料盒并记录抓挠行为30 min或1 h。但该方法也具有一定的局限性,在小鼠后脚皮肤下嵌入一个磁铁异物,可能出现致炎使小鼠啃咬脱落的现象。另外,Ishii等<sup>[53]</sup>开发了一种使用图像分析的抓挠分析系统SCLABA-Real,能成功量化患上类似特应性皮炎的小鼠的抓挠行为;Marino等<sup>[54]</sup>建立了爪子运动检测(paw motion detector, PMD)系统,该系统在后爪上放置小型可拆卸金属带,该后爪通过电磁场的扰动提供爪子运动的信号,虽然这种方法量化了鼠抓挠的次数,但不能测量抓挠的持续时间;Kobayashi等<sup>[55]</sup>建立了卷积递归神经网络(convolutional recurrent neural network, CRNN),能够准确识别录制视频文件中的抓挠行为,进而用于小鼠瘙痒行为评估。

**触诱发痒行为评估:**与触诱发痛类似,一些瘙痒小鼠模型比如组胺诱发的急性瘙痒模型和AEW诱发的皮肤干燥症瘙痒模型,出现对无害机械刺激诱发的瘙痒敏感性增强现象。具体操作是在注射部位附近(约7 mm处)使用von Frey细丝(弯曲力为0.7 mN的力度不会引发正常小鼠的抓挠行为,却是在组胺注射或皮肤干燥部位周围的皮肤处引起抓挠发作的最小强度)随机选择3个部位来接受无害的机械刺激,每根von Frey细丝刺激5次,每次间隔10 s,对于每个刺激,都注意是否存在阳性反应,即后肢抓挠机械刺激部位,记录5次刺激中小鼠出现抓挠的次数。触诱发痒评分是由3种刺激(即0、1、2或3)引发的阳性反应总数。以5 min的间隔重复,直到应用致痒物60 min后。并在第90 min和120 min的时间点再次重复机械刺激。在许多实验中,每30 min的总触诱发痒评分为从注射后30 min内每5 min间歇期的单个触诱发痒评分的总和<sup>[56]</sup>。

**瘙痒情绪行为评估** 与具有厌恶成分的疼痛感相似,瘙痒也具有强烈的情感成分。瘙痒感诱发抓挠行为导致慢性瘙痒患者出现严重的组织损伤和精神障碍<sup>[57]</sup>。Mu等<sup>[58]</sup>研究发现颈后皮内注射瘙痒剂(氯喹和组胺)会引起至少持续两周的条件性位置厌恶(conditioned place aversion, CPA),并证实了瘙痒诱导的CPA依赖脊髓瘙痒回路,新建立的瘙痒CPA范式可用于研究与瘙痒相关的负面情绪的潜在机制。Hashimoto等<sup>[59]</sup>使用恶唑酮诱导青春期C57BL/6J雄性小鼠产生的AD模型,发现青春期

AD模型小鼠极易受到全身性炎症的影响,导致抑郁行为,并伴有犬尿氨酸代谢异常。Yeom等<sup>[60]</sup>将MC903反复皮内施用于小鼠的脸颊来诱导AD样病变,发现AD样皮肤病变引起焦虑和抑郁样表型,这些表型与奖励回路中与神经可塑性相关的变化有关。Zhao等<sup>[61]</sup>通过黑白箱和强迫游泳测试等行为范式评估3~4周的AEW小鼠模型的焦虑和抑郁行为表型,为研究慢性瘙痒情绪及潜在机制提供了临床前模型,揭示了下丘脑-垂体-肾上腺轴功能的损害可能是慢性瘙痒背景下出现情绪障碍的主要病因或相关病理生理学因素,为探索慢性瘙痒的情感成分提供了一个机制框架。此外,Wang等<sup>[62]</sup>建立DNFB诱导的慢性瘙痒模型,通过强迫游泳实验、悬尾实验和飞溅实验测量抑郁指数,建立了慢性不可预知刺激诱导的抑郁模型,证明瘙痒和抑郁交叉加重。

局部施用组胺或其他瘙痒剂后,许多大脑区域被激活,而这些大脑区域与奖励或厌恶相关的行为有关,如岛叶皮层、扣带皮层和丘脑;但是,瘙痒情感成分的神经机制仍然难以捉摸,因此需要利用目前已有或新建行为范式研究瘙痒的情绪成分。

**结语** 总而言之,使用各种类型的瘙痒模型可以深入研究瘙痒发病机制,为诊断和治疗提供宝贵的工具。虽然小鼠以外的物种,例如狗和豚鼠,均可以发展出类似慢性瘙痒病变,但小鼠模型易于操作,成本低,最重要的是易于进行基因工程改造,因而最为常用。此外,还要注意小鼠的品系差异、性别差异,不同品系小鼠模型的易感性、稳定性等均存在不同。当然,在实际操作过程中,可根据实验具体情况调整相关指标,比如造模持续时间、观察时间点、造模部位、药物浓度和剂量等。随着研究的发展,一些慢性瘙痒小鼠模型逐渐被淘汰,因此选择模型时要根据研究目的和实验需求,查阅国内外最新研究,全方位考虑模型的类型、病理机制、优缺点以及动物饲养、经费、伦理等诸多因素。

需要注意的是,和其他动物模型的局限性一样,目前尚没有能够完全模拟临床表现的理想小鼠模型,还是需要根据临床实际不断探索新的模型。此外,目前瘙痒研究主要集中在皮肤源性瘙痒上,还有一些临床常见的瘙痒如尿毒症性瘙痒、神经病源性瘙痒、精神源性皮肤病瘙痒等模型尚有待进一步开发。

**作者贡献声明** 易婷 文献查阅,论文构思、撰写和修订。米文丽 文献查阅,论文构思、指导和修订。王彦青 论文指导、修订和审校。

**利益冲突声明** 王彦青是本刊编委,未参与此文的同行评议和终审决策。没有其他利益冲突需要声明。

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- (收稿日期:2022-12-16; 编辑:张秀峰)

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- (收稿日期:2022-09-29; 编辑:张秀峰)