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·专论与综述·

特发性脊柱侧弯鼠类模型的研究现状 *

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摘要：特发性脊柱侧弯是一种严重影响青少年身心健康的脊柱畸形，其病因和发病机制至今不明，部分原因是缺乏合适的建模系统，其中鼠类因其易感性且与人类基因高度相似，而被大量用于建立脊柱侧弯模型。本文讨论了多种建模方法，包括杂交形成脊柱侧弯大鼠、双足大鼠模型、增强瘦素活性诱导模型、雌激素诱导模型、降低体内褪黑素含量以诱导模型、基因修改和无创实验模型诱导脊柱侧凸。这些模型揭示了遗传因素、激素水平和生物力学因素在脊柱侧弯发展中的作用。尽管动物模型无法完全复制人体脊柱，存在局限性，但它们有助于研究脊柱侧弯的发病机制、进展并为未来治疗提供了重要工具，对早期诊断和干预策略的发展具有重要意义。在此，我们总结了鼠类脊柱侧弯模型的发展现状，讨论了其优缺点，并展望了其应用前景。

关键词：脊柱侧弯；特发性脊柱侧弯；脊柱侧凸模型；大鼠模型；小鼠模型
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The State of the Art of the Rats Model for Idiopathic Scoliosis*

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ABSTRACT: Idiopathic scoliosis is a spinal deformity that severely affects the physical and mental health of adolescents. The etiology and pathogenesis of idiopathic scoliosis continues to be unknown, partly due to the shortage of appropriate modeling systems, of which rodents have been widely used to model scoliosis due to their susceptibility and high genetic similarity to humans. Various of modeling methods are discussed, including inbreeding to produce scoliosis rats, bipedal rat models, enhanced leptin activity induction models, estrogen induction models, lowering melatonin levels in vivo to induce models, genetic modification and non-invasive experimental models to induce scoliosis. These models reveal the role of genetic factors, hormone levels and bio-mechanical factors in the development of scoliosis. Despite the limitations of animal models, which do not exactly mimic the human spine, they help to study the pathogenesis and progression of scoliosis and provide an important tool for the future treatment of scoliosis and are important for the development of early diagnosis and intervention strategies. We summarize the current state of development of rat scoliosis models, discuss their advantages and disadvantages, and look

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forward to their application prospects.

Key words: Scoliosis; Idiopathic scoliosis; Scoliosis model; Rat model; Mouse model
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前言

脊柱侧凸是一种三维脊柱畸形，其中一个或多个节段在冠状面上偏离身体中线并向侧方弯曲。通过测量侧曲率（Cobb 角≥10°）可确诊脊柱侧弯[1]。脊柱侧弯的发生和发展通常伴随着脊柱旋转和矢状后凸或前凸，这可能会导致椎体周围的生物力学和结构发生变化[2,3]。据统计，全球青少年脊柱侧弯症的发病率为 1%至 3%。一般来说，脊柱侧弯分为四种类型，即综合征型、先天性、特发性和神经肌肉型[4,5]。特发性脊柱侧弯的病因尚不确定[6]。脊柱侧弯症是一种多因素疾病，具有很强的遗传易感性。神经系统、激素、生化、肌肉骨骼和环境因素都被认为是脊柱侧弯的致病因素[7-13]。我们建立脊柱侧弯模型旨在了解这种畸形的发病原因、进展和治疗方法。

青少年特发性脊柱侧凸（Adolescent idiopathic scoliosis，AIS）是最常见的脊柱畸形之一[14,15]。然而，AIS 的发病机制尚不清楚。已经提出了许多导致特发性脊柱侧凸因素，如遗传因素[16]，生化因素[17]，骨骼因素[18]，激素因素以及神经肌肉异常[19-21]。

研究人员已经成功地在鸡[22,23]，鱼[24,25]，兔子[26-28]，青蛙[29]，猪[30]，山羊[31]，绵羊[32,33]和灵长类动物[34,35]身上建立了脊柱侧凸模型。每种模型都有其各自的优点和缺点。相比之下，使用大鼠或小鼠模型的优点包括易于检测抗体和微阵列，了解其基因组成，能够产生基因工程敲除和转基因物种，以及繁殖迅速，操作简单，更低的维持费用，可以在短期内大量获得。作为脊椎哺乳动物，它们与人类有更多的遗传相似性，这使它们成为脊柱侧弯研究的有希望的模型[36]。

1 杂交形成脊柱侧弯大鼠

IS 大鼠由 Ishibashi 于 1968 年培育，是一种来自雄性野生型（WT）大鼠和雌性 Wistar 大鼠杂交的近交系[37-39]。Wistar 大鼠，中等大小的白化啮齿动物，其血统可追溯到美国宾夕法尼亚州费城著名的 Wistar 研究所。IS 大鼠脊柱异常的表现完全是自发的，没有任何人为的基因改变。几乎所有由雄性和雌性 IS 大鼠交配产生的后代，当纯合子时，它们的椎骨都表现出明显的异常[40]。除了特征性的后凸，在成年 IS 大鼠中，仅在腰骶过渡区观察到独特的同源性转化。IS 大鼠被广泛认为是理解人类脊柱畸形的有价值的动物模型[41]，提供了对主要局限于脊椎骨的骨畸形的见解。

2 双足大鼠构建模型

SALZMAN [42] 等人选取 51 只 18-21 日龄的雄性 Sprague-Dawley 大鼠，其中 29 只诱发侧凸，通过将左肩胛骨与同侧骨盆缝合，来产生右侧侧弯。系带缝合收紧后，脊柱立即出现后凸，系带缝合 8 周后，脊柱后凸变得永久稳定。随后，松开系带，对动物的前、后和侧位进行 X 射线摄影，平均 Cobb 为 31.7± 4.2°。彭[43]等人在以上操作的基础上，切除肱骨高位的前肢和根部的尾巴来创造双足大鼠。在去除前肢和尾巴后[44]，将两足大鼠饲养在特殊的高笼子里，并提高食物和水，以确保它们的维持站立姿势。双足大鼠们已被用作动物模型来研究与直立姿势和重力伴随效应相关的各种人类状况和疾病[45,46]。

3 增强瘦素活性诱导模型

瘦素是一种脂肪细胞衍生的激素，它穿过血脑屏障，作用于下丘脑的神经元，参与食物摄入和能量平衡[47]。Araujo[48]等人发现 AIS 女孩脊柱侧凸曲线大小与瘦素水平有显著相关性。吴涛 [49] 等人选取 3 周龄雄性 C3He/ej 小鼠 50 只，在氯胺酮和地西泮麻醉下行双侧前肢切除和尾部切除。截肢后将小鼠随机分为两组：A 组（25 只）下丘脑注射过表达瘦素的慢病毒载体，B 组（其余 25 只）脑内注射表达绿色荧光蛋白的对照慢病毒载体。两天后，双足截肢的老鼠开始筑巢，它们必须保持站立的姿势才能获取食物和水。随后，每 4 周监测一次体重，并在第 20 周在麻醉状态下拍摄 X 光片，以评估脊柱畸形的发展情况。结果显示，a 组的发生率

(92%)和曲率(30.2°)明显高于B组(52%,18.4°)。此外,与B组(105.0± 59.5 pg/mL)相比,A组的循环瘦素水平显著升高(222.1± 83.8 pg/mL)。该方法成功构建了双足小鼠IS模型,该研究表明,中枢瘦素活性的增强可能在脊柱侧凸的发病机制中起着至关重要的作用,增加了两足小鼠脊柱侧凸的风险和病情进展。不过,该研究承认,瘦素过表达小鼠模型与人类AIS之间存在关键差异。这些差异包括瘦素的细胞来源、血清瘦素水平以及可溶性瘦素受体的作用。这项研究需要进一步研究来解决这些局限性。

4 利用雌激素诱导双足大鼠模型

Kareen[50]和Leboeuf[51]等人证明雌激素在脊柱侧凸的发生和发展中起了作用。Leboeuf认为雌激素可能通过与调节骨骼生长、生物力学和结构的因素相互作用而影响脊柱侧凸。郑[52]等人将120只Sprague-Dawley大鼠分为6组,每组20只:双足雌性大鼠组(雌鼠组)、卵巢切除双足雌性大鼠组(OVX组)、卵巢切除+E2双足雌性大鼠组(OVX+E2组)、双足雌性大鼠+曲谱瑞林组(Triptorelin组)、假手术组(假手术组)、双足雄性大鼠组(雄性组)。在第15周采集血液并测量脊柱侧凸,评估循环血清雌激素水平和脊柱侧凸Cobb角。根据结果,与其他四组相比,雌性组和OVX+E2组有更高的脊柱侧弯率和更严重的弯曲程度的发生率。雌激素不仅会增加脊柱侧弯症的发病率,还会增加大鼠双足畸形的发展。雷普妥林在预防脊柱侧凸曲线发展方面与卵巢切除术一样有效。这一结果与Monica[53]以前的报道相符。

5 降低体内褪黑素含量以诱导模型

褪黑素主要由松果体产生[54,55]。褪黑素会影响人类的昼夜节律、睡眠障碍、情感障碍、性成熟等。Machida[56]等人发现,切除鸡的松果体会导致持续性脊柱侧弯,其解剖学特征与人类特发性脊柱侧弯相似。切除松果体会导致血清褪黑激素水平显著下降[57-59]。切除松果体的鸡服用褪黑激素可防止脊柱侧弯的发生[60]。切除松果体的鸡和大鼠在接受褪黑激素治疗后,脊柱侧凸的发生率和恶化程度均有所降低[61,62]。由于生理原因,鸡的模型不能简单地推断给人类身上[63]。与鸡相比,鼠在系统发育和生理上更接近人类,因此更适合作为脊柱侧弯症的研究模型[64,65]。NAT基因在C57BL/6J鼠体内被自然敲除,褪黑素合成受到自然抑制。C57BL/6J鼠松果体内缺乏褪黑素合成的限速酶[66,67]。Junko[68]等人研究发现,C57BL/6J小鼠体内的褪黑激素循环水平和松果体含量都很低,而且在光照和黑暗阶段没有区别。C57BL/6J鼠先天性缺乏褪黑激素。Masafumi[60]等人将100只3周龄C57BL/6J小鼠分为4组:四足小鼠20只作为对照组,双足小鼠30只未接受褪黑素治疗,四足小鼠20只接受褪黑素治疗,双足小鼠30只接受褪黑素治疗。每天腹腔注射褪黑素。对每只小鼠在5月龄时进行的处死,结果表明,在每个实验组中,未接受褪黑素的小鼠和恢复正常的小鼠之间,血清褪黑素水平有显著差异。在97%的双足小鼠和25%的四足小鼠(作为对照)中观察到脊柱侧凸、肋骨强化和椎体旋转,这两种小鼠均未接受褪黑素治疗。与四足小鼠相比,双足小鼠的脊柱侧弯更为严重。接受褪黑素治疗的小鼠均未发生脊柱侧凸。上述结果提示,C57BL/6J小鼠褪黑素水平的恢复可抑制脊柱侧凸的发展,双足小鼠褪黑素水平的降低在脊柱侧凸的发展中起关键作用。这在刘[69]和杨[70,71]等人的实验中等到了验证,并进一步证明了,褪黑激素能刺激骨骼生长,抑制破骨细胞活性,并能促进成骨细胞分化[72-74]。

我们需要进一步探索褪黑素在人体中的作用,褪黑素在不同病理条件下的临床疗效和安全性,以及破骨细胞的变化与脊柱侧弯的发生有直接关系,这些问题都有待研究。

6 基因修改诱导脊柱侧弯

Sharma[75,76]等人的一项全基因组关联研究(genome-wide association study,GWAS)报道了一个女性特异性基因PAX1与AIS相关。基于大量患者和对照,研究者们证实了LBX1[77-79],COL11A1[80],GPR126[81-84]and BNC2[85,86]等14个基因与AIS相关。李[87-95]等人证明了特发性脊柱侧凸患者的miRNA表达或miRNA编码基因的改变。这些miRNA通过靶向作用于骨形态发生蛋白,参与成骨分化、成骨细胞矿化和骨密度的调节,在脊柱侧凸的发病机制中建立了可能的通路[96-102]。LAT1是一种介导细胞摄取大中性氨基酸的氨基酸转运体,由Slc7a5基因编码[103]。Makoto[104]等人有条件地敲除小鼠Slc7a5基因以

评估软骨细胞特异性失活 LAT1 对脊柱畸形的影响。结果表明,小鼠在成长过程中出现了后天性胸椎畸形,并迅速发展为不同的弯曲模式和发育不良的椎骨。

病理检查显示生长板增厚,成骨细胞减少,提示软骨内骨化缺陷可能影响生长,导致脊柱侧凸和骨密度降低。这与 Sayuki[105]等人的发现一致符合。Yusuke[106]等人在人肌动蛋白启动子的控制下,有条件地去除 Lbx1 等位基因,得到了前肢发育不全的突变小鼠,并随着年龄的增长发展为脊柱中度后凸。由此得出结论,骨骼肌中 Lbx1 的缺失导致小鼠的肢体发育不全和进行性脊柱后凸。吴[107]等人从转基因新生小鼠的软骨中剔除 Mapk7 基因,8 周龄小鼠出现明显的后凸、椎体高度降低、椎体宽度增加和足弓畸形。这需要更多的实验来更深入地了解调控机制。基因改变的研究可以为 IS 的发病机制提供新的见解,并可能有助于识别脊柱侧凸的特定生物标志物,并随后将这些研究结果的发现扩展到整个人群中,以帮助阐明哪些因素直接参与脊柱侧凸的发生和进展。

7 无创实验模型诱导脊柱侧凸

Silva [108] 认为侵入性方法构建 IS 模型存在耗时和实验动物死亡率高的风险。他们为了不干扰脊柱周围的组织,不进行手术,设计了一种非侵入性方法来诱导大鼠脊柱侧凸。Silva 和 Banala [109]等人将 24 只雄性 Wistar 大鼠随机分为两组,每组 12 只大鼠。实验组从 4 周龄开始穿一件 PVC 背心(边缘覆盖合成树脂以避免皮肤破裂和限制呼吸和活动,有 9 种不同的尺寸以适应生长),持续 12 周。在为期 16 周的时间内,每 30 天进行一次影像学报告,经过 3 个月的固定和 1 个月的移除背心,PVC 背心可以有效地保持脊柱侧曲的速率稳定,从而促进脊柱侧曲的发展。固定后 30 天,脊柱侧凸稳定角度为 28± 5° 。结果显示,大鼠 X 线检查证实为永久性结构畸形,多种基因在脊柱侧凸大鼠不同器官中的表达显著上调于对照组。这种非侵入性脊柱侧凸模型的最大优点是,它可以在没有任何类型的手术或药物的情况下发展脊柱侧凸,这些干预不仅会影响脊柱,还会影响邻近组织。另一个重要的方面是在固定或治疗干预后保存所有可以分析的组织或结构。此外,该模型易于制备,可在短时间内以较低的成本应用于大量动物。这个机械模型未能为特发性脊柱侧弯的病因提供重要的信息,但它们可以帮助设计新的治疗模型。

8 结论

综上所述,尽管动物模型可能无法复制人体脊柱,也不能简单地推断出人体模型,但动物模型仍然是研究脊柱侧弯的最佳方法,尤其是在需要多个时间点的组织样本时,这在人体中可能无法实现。尽管进行了大量的动物实验研究,但脊柱侧弯症的病因和发病机制仍未完全明了。基因研究应是未来研究的重点。这种疾病影响着许多儿童和青少年。早期发现和早期治疗可能最终会根除这种疾病。

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