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基于中西医临床病证特点的宫颈癌动物模型分析

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【摘要】 宫颈癌发病呈年轻化趋势, 严重危害女性生命健康, 目前针对该病仍缺乏显著有效的治疗方案。为推进宫颈癌临床诊治的发展, 筛选出符合宫颈癌病证特点的动物模型十分重要。总结现有宫颈癌动物模型, 主要包括自发性宫颈癌、诱发性宫颈癌、移植性宫颈癌以及基因工程性宫颈癌等动物模型。基于宫颈癌中西医临床病证特点对各模型赋值进行分析, 发现移植性宫颈癌动物模型的中西医吻合度相对较高, 其中皮下移植法西医临床吻合度达70%且最为常用, 宫颈原位移植法中医临床吻合度达68.5%; 自发、诱发性宫颈癌模型造模成功率不高, 模型间差异大, 且吻合度不高, 较少使用。总体来看, 模型中医临床吻合度均较低, 不利于宫颈癌的中西医结合诊治发展, 故又提出施加中医致病因素、中医模型评判标准等建议, 以期完善宫颈癌模型发展, 推动临床疾病研究。

【关键词】 宫颈癌; 动物模型; 病因病机; 中西医结合

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Analysis of cervical cancer animal models based on clinical characteristics of traditional Chinese and Western medicine

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【Abstract】 Cervical cancer (CC) exhibits a relatively young age of onset and represents a severe danger to women's life and health; however, there is currently a lack of effective therapeutic regimens for this disease. The development of clinical diagnostic and therapeutic approaches for CC require the screening of animal models that conform to the clinical syndrome characteristics of CC. Existing animal models of CC mainly include spontaneous, induced, transplanted, and genetically engineered CC. The analysis of each of these models based on the clinical syndrome characteristics of CC in traditional Chinese and Western medicine (TCM-WM) showed that transplanted

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animal models of CC had a relatively high degree of TCM-WM consistency. Among them, the subcutaneous transplantation method had a Western medicine clinical consistency of 70% and was the most commonly used, while the orthotopic cervical transplantation method had a TCM clinical consistency of 68.5%. Spontaneous and induced models were less frequently used because of low modeling-success rates, significant inter-model differences, and poor consistency. Overall, the TCM consistency of all models was relatively low, which is not conducive to the development of integrated TCM-WM diagnosis and treatment approaches for CC. Therefore, applying TCM pathogenic factors and establishing TCM model-evaluation criteria are required to improve the development of CC models and promote clinical disease research.

【Keywords】 cervical cancer; animal models; etiology and pathogenesis; integration of traditional Chinese and Western medicine

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

宫颈癌(cervical cancer, CC)又称子宫颈癌,发生于子宫颈部位,是继乳腺癌、肺癌和结直肠癌之后影响全球女性健康的第四大常见恶性肿瘤,发病率约占全球女性癌症的 6.8%,死亡率高达 8.1%,严重影响女性的身体健康及生活质量^[1]。CC 主要包含两种组织学亚型,一种是鳞状细胞癌,好发于宫颈外口,约占 75%;另一种为腺癌,该亚型发生于宫颈内口^[2]。绝大多数 CC 是由人乳头瘤病毒(human papilloma virus, HPV)感染引起的,其中 HPV16 和 HPV18 是 CC 的主要致病因素^[3,4]。手术和放疗仍然是目前治疗 CC 的主要方法,但易出现肿瘤转移和复发,对患者的生理和心理极不友好^[5]。CC 作为一种女性常见疾病,严重危害女性健康,体现临床病症特点的动物模型是 CC 研究的重要工具,但目前 CC 动物模型繁杂,缺乏公认的模型评价方法。基于课题组前期提出的基于临床病症特点的动物模型评价体系^[6],本文旨在对现有 CC 动物模型与临床的吻合度进行评价,并归纳总结模型构建方法、特点、应用及局限性等,为 CC 的模型选择和实验设计提供参考,以促进 CC 基础研究与临床治疗的进一步发展。

1 CC 病因病机

1.1 CC 西医病因病机

CC 的发病机制比较复杂,其发生发展是一个连续的病理过程。其中,HPV 的持续感染被公认为是导致 CC 的最主要原因,HPV 有严格的嗜上皮特性,可导致人类皮肤或黏膜发生病变^[7]。CC 的发生也与机体的免疫机制密切相关,免疫能力下降时,感染细菌、病毒的概率就会升高^[8]。研

究发现,宫颈阴道菌群与 CC 病变进展密切相关,宫颈正常者以乳杆菌为优势菌,菌群多样性低;而病变进展者乳杆菌减少、多样性增加^[9,10]。除此之外,多孕多产与性生活紊乱^[11]、生殖道炎症^[12]、不健康的生活方式与营养失衡、恶性肿瘤家族史、肥胖体质、糖尿病或长期暴露于二手烟环境^[13]等都会增加患 CC 的风险。

1.2 CC 中医病因病机

CC 在中医古籍中并无直接对应的病名,但相关症状可见于古籍记载。《内经》有云:“任脉为病,男子内结七疝,女子带下瘕聚”^[14];《诸病源候论》曰:“崩中之病,是伤损冲任之脉……冲任气虚,不能约制经血,故忽然崩下,谓之崩中”^[15];《千金翼方》云:“妇人崩中漏下,赤白青黑,腐臭不可近”^[16],上述与 CC 临床的表现特征(阴道不规则出血、白带分泌异常、腹部疼痛等)相应,因此可将 CC 归属于中医“五色带”“崩漏”“带下”“瘕瘕”“阴疮”等病症范畴。情志不畅(如长期抑郁、焦虑)、饮食不节或房事不洁等可致肝、脾、肾功能失调,冲任气血损伤,机体正气亏损,从而导致湿热、痰湿、淤毒袭于胞宫,相互兼并,遂发病。由此可见 CC 的形成是由于正虚邪实,机体内虚时湿邪外侵,客于胞门,渐生渐长,表现出实证,而后机体又因癌肿侵袭导致机体功能失常,遂表现出虚证^[17]。

2 CC 的中西医诊断标准

2.1 CC 西医诊断标准

标准的制定参照 2025 年第 1 版《NCCN 子宫颈癌临床实践指南》^[18],依据田硕等^[6]提出的动物模型评价新方法对西医诊断指标进行赋值,总赋值为 100%。细胞与组织病理检查常作为 CC

的诊断依据,故将①、②、③作为 I 类指标(直接相关指标),其中宫颈活组织检查是 CC 临床诊断的金标准,故将②赋值 30%,①、③各赋值 15%。在临床诊断中,体征检查常作为 CC 筛查的第一步,除常规的全身检查,还包括盆腔阴道检查,拟定其为 II 类指标,符合其中 1 项赋值 10%。影像学检查常与液基细胞学联用于 CC 诊断中,拟定为 III 类指标(间接相关指标),符合 1 项赋值 3.3%,CC 西医诊断标准见表 1。

2.2 CC 中医辨证分型

CC 的中医辨证参照中国中医药出版社出版的《中西医结合妇产科学》^[22]分为肝郁化火型、湿热瘀毒型、脾肾阳虚型和肝肾阴虚型 4 个证型(表 2)。对各证型的病证特点归纳总结,主证:①白带量异常增多;②阴道不规则出血;③分泌物有异味,符合其中 1 项赋值 20%。次证:④烦躁易怒;⑤口干咽燥;⑥倦怠乏力;⑦纳少便溏;⑧畏冷;⑨便秘;⑩下腹疼痛,共赋值 40%,符合其中 1 项赋值 5.7%。

3 CC 动物模型评价

3.1 CC 模型动物选择

CC 造模常选用啮齿类动物,啮齿类与人的生

殖器官发育情况相近,基因组和人具有高度同源性,且有体型小,易控制,繁殖周期短,后代多等优点^[23,24]。自发性 CC 动物模型常用近交系小鼠,如 C57BL/6 小鼠和 BN/Bi 大鼠。诱发性 CC 动物模型常使用 KM 小鼠,该品系小鼠对化学诱导、病毒诱导等外界刺激具有稳定的反应,在诱导剂的作用下能够较为规律地出现 CC 前病变乃至癌变的病理过程,且病变发生率高、成模时间可控^[25]。移植性 CC 动物模型通常使用免疫缺陷型鼠,如 BALB/c 裸鼠、NOD/SCID 小鼠等,其中 BALB/c 裸鼠的使用率最高,该小鼠具有免疫缺陷、背景明确、性状稳定、对外源移植的人 CC 组织或细胞几乎不产生免疫排斥反应等特点,能够支持肿瘤组织存活、增殖与转移,能较好地模拟人 CC 的体内生长环境,且可在活体动物免疫荧光实验中动态监测模型是否成功^[25]。基因工程性 CC 模型常使用 K14-HPV、K14-E6、K14-HPV-E6/E7 以及 HPV16 转基因小鼠。

3.2 CC 模型评价指标

模型评价指标是判断 CC 动物模型是否成模的重要依据,但由于该疾病存在复杂性,不同动物之间存在差异,目前尚未对 CC 动物模型成模评价标准进行统一制定^[26]。CC 动物模型评价指

表 1 CC 西医诊断标准
Table 1 Western medicine diagnostic criteria for CC

检测指标 Detection indicators	检测手段与诊断标准 Detection methods and diagnostic criteria
I. 细胞与组织病理检查 I. Cellular and histopathological examinations	①宫颈刮片细胞学检查:薄层液基细胞学阳性、HPV 检测阳性 ① Cervical cytology: Positive liquid-based thin-layer cytology and positive HPV test ②宫颈活组织检查:可见鳞状细胞癌、腺癌等相关癌细胞 ② Cervical biopsy: Squamous cell carcinoma, adenocarcinoma, and other related cancer cells are observed ③肿瘤标志物:血清肿瘤标志物 miR-424、SCCA、CA242、CA19-9 或 CA15-3 等高表达 ^[19-21] ③ Tumor markers: High expression of serum tumor markers including miR-424, SCCA, CA242, CA19-9 or CA15-3
II. 体征检查 II. Physical examinations	④消瘦,贫血 ④ Emaciation and anemia ⑤腹股沟淋巴结或锁骨上淋巴结肿大 ⑤ Enlargement of inguinal lymph nodes or supraclavicular lymph nodes ⑥盆腔检查显示阴道分泌物增多,有不规则出血,宫颈粗、大、硬,呈火山口状 ⑥ Pelvic examination findings: Increased vaginal discharge, irregular vaginal bleeding, and a thickened, enlarged, indurated cervix with a crater-like appearance
III. 影像学检查 III. Imaging examinations	⑦超声:宫颈增大,回声不规则,组织结构不清,网状血流信号丰富 ⑦ Ultrasound: Cervical enlargement, irregular echotexture, unclear tissue structure, and abundant reticular blood flow signals ⑧CT:增强扫描可见不规则形态和边缘的肿块,呈不均匀密度影,宫旁肿块显示软组织低密度影 ⑧ CT: Enhanced scan shows irregularly shaped masses with ill-defined margins, heterogeneous density shadows, and parametrial masses presenting as soft tissue hypodense shadows ⑨MRI:圆形肿块,边界不清 ⑨ MRI: Round masses with ill-defined boundaries

表 2 CC 中医辨证分型
Table 2 Traditional Chinese medicine syndrome differentiation types of CC

辨证分型 Syndrome differentiation type	主证 Main symptoms	次证 Secondary symptoms	舌脉 Tongue and pulse manifestations
I. 肝郁化火 I. Liver stagnation transforming into fire	白带增多,偶夹血性;月经不调,经血暗红,伴血块 Increased leukorrhea, occasionally mixed with blood; irregular menstruation, dark red menstrual blood with clots	心烦易怒,口干欲饮;乳房胀痛,善太息;情志抑郁,少腹胀痛 Irritability, restlessness, dry mouth with desire to drink; distending pain in breasts, frequent sighing; emotional depression, distending pain in lower abdomen	舌红,苔薄黄或黄腻,脉弦数 Red tongue with thin yellow or yellow greasy coating, wiry and rapid pulse
II. 湿热瘀毒 II. Damp-heat and stasis-toxin	带下量多,色黄如脓或呈血性,秽臭难闻;阴道不规则出血,色暗红或夹血块 Profuse leukorrhea, yellowish purulent or bloody, with foul odor; irregular vaginal bleeding, dark red blood or mixed with clots	口干咽燥,下腹疼痛,不欲饮食;小便短赤,大便黏滞或干结 Dry mouth and throat, lower abdominal pain, lack of desire to eat; scanty dark urine, sticky or dry stool	舌淡红有瘀点,苔黄腻,脉滑数 Light red tongue with ecchymoses, yellow greasy coating, slippery and rapid pulse
III. 脾肾阳虚 III. Spleen-kidney Yang deficiency	带下清稀量多,无臭,不断;阴道出血色淡质稀,淋漓不尽 Profuse clear and thin leukorrhea, odorless, continuous; light-colored, thin vaginal bleeding, dripping endlessly	潮热盗汗,口干咽燥,失眠多梦;月经提前,量少,或经闭 Low-grade fever, night sweats, dry mouth and throat, insomnia with many dreams; advanced menstruation with scanty amount, or amenorrhea	舌淡胖,边有齿痕,苔薄,脉沉细 Pale and swollen tongue with tooth marks on the edges, thin coating, deep and thready pulse
IV. 肝肾阴虚 IV. Liver-kidney Yin deficiency	阴道出血,量少或淋漓不尽,色鲜红;带下量少,色黄或夹血丝 Vaginal bleeding, scanty or dripping endlessly, bright red color; scanty leukorrhea, yellowish or mixed with blood streaks	腰骶疼痛,手足心热,口干便秘 Lumbosacral pain, heat in palms and soles, dry mouth and constipation	舌红嫩,苔薄少或光剥,脉细数 Pale red and tender tongue, thin scanty or denuded coating, thready and rapid pulse

标包括对实验动物的肿瘤形态观测、行为学情况观察、病理组织切片检查及免疫组织化学等^[27],详见表 3。肿瘤生物学指标(肿瘤体积与质量、肿瘤生长曲线)用于直接判断肿瘤是否成功构建及生长状态,是 CC 模型验证的首要评估项目。通过病理形态学指标微观层面观察肿瘤的组织特征,验证 CC 模型是否符合人 CC 的病理表现。其中 Ki-67 阳性细胞比例,是评价 CC 肿瘤细胞增殖活性的最常用指标。此外,血管内皮生长因子(vascular endothelial cell growth factor, VEGF)受体的表达在研究 CC 动物模型的肿瘤血管生长中起重要作用,fms 相关酪氨酸激酶 1(fms-related tyrosine kinase 1, FLT-1)在 CC 中不仅定位于肿瘤血管内皮细胞,而且在肿瘤细胞中也有较高水平表达^[28]。

3.3 现有 CC 模型与临床吻合度

通过检索中国中网(CNKI)、万方、PubMed 等国内外数据库相关文献,总结分析显示,目前 CC 研究常用的动物模型主要有 4 种,分别为自发性、

诱发性、移植性以及基因工程性。自发性 CC 动物模型不经人工干预自然发生疾病。诱发性 CC 动物模型通过化学致癌剂如二甲基苯并蒽(7,12-dimethylbenz [a] anthracene, DMBA)、甲基胆蒽(3-methylcholanthrene, MCA)或病毒(如人巨细胞病毒(human cytomegalovirus, HCMV))作用于动物宫颈组织,诱导肿瘤发生^[29]。移植性 CC 动物模型按照对实验动物造模位置的不同又分为皮下移植瘤模型、原位移植瘤模型和肾包膜下移植瘤模型^[25]。移植性 CC 模型通过将患者肿瘤组织人 CC 细胞系(如宫颈腺癌 HeLa 细胞、宫颈鳞状细胞癌 SiHa 细胞、CaSki 细胞^[30]等)或患者来源的肿瘤组织移植到免疫缺陷动物(如 BALB/c 裸鼠、NOD/SCID 小鼠)体内,快速建立肿瘤模型,广泛应用于药物筛选和肿瘤生长特性研究^[31]。基因工程性 CC 动物模型利用基因改造或修饰,如通过过表达 HPV E6/E7 基因^[32,33]构建的 CC 模型,为深入研究 CC 相关基因功能及信号通路提供有力工具。见表 4,基于 2.1、2.2 诊断标准以

表 3 CC 动物模型常用检测评价指标
Table 3 Common detection and evaluation indicators for CC animal models

检测类型 Detection types	检测指标 Detection indicators
一般状态 General status	体质量、进食量、活动度、毛发状态及生存时间等 Body weight, food intake, activity level, hair condition, survival time, etc.
肿瘤生物学 Tumor biology	肿瘤位于浅表:成瘤率、肿瘤直径、形态及质地(肿瘤的形状、边界、颜色、有无坏死或出血区域) Superficial tumors: Tumor formation rate, tumor diameter, morphology, and texture (tumor shape, boundary, color, presence of necrosis or hemorrhage areas) 肿瘤位置较深:超声检查或 MRI 评价生长状况、回声类型及血供变化 Deep-seated tumors: Growth status, echo pattern, and blood supply changes evaluated by ultrasound or MRI
行为学 Behavioral indicators	观察进食情况、体质量、活动情况、疼痛表现 Observation of food intake, body weight, activity, and pain manifestations
病理组织切片 Pathological tissue sections	肿瘤细胞的大小、形状、核质比、核分裂现象、细胞排列方式、肿瘤的类型(如鳞状细胞癌、腺癌等)、分化程度、浸润深度、有无转移等,肿瘤组织与周围组织的关系,是否存在炎症反应 Tumor cell size, shape, nuclear-cytoplasmic ratio, mitotic activity, and arrangement; tumor type (squamous cell carcinoma, adenocarcinoma), differentiation degree, invasion depth, and presence of metastasis; relationship between tumor tissue and surrounding tissues; presence of inflammatory response
免疫组化(IHC) Immunohistochemistry (IHC)	Ki-67(核蛋白质)、Survivin(凋亡抑制基因)、P16(抑癌基因)、P53(抑癌基因)、HPV E6/E7(癌蛋白)、CD34/CD31(血小板内皮细胞黏附分子)、FLT-1 等 Ki-67 (nuclear protein), Survivin (apoptosis inhibitor gene), p16 (tumor suppressor gene), p53 (tumor suppressor gene), HPVE6/E7 (oncoprotein), CD34/CD31 (platelet endothelial cell adhesion molecule), etc.
生化指标 Biochemical indicators	血清:SCC-Ag、CA-125、IL-6、IL-12、TNF-α、IFN-γ、Gal-3、VEGF、肌酐、尿素氮、谷丙转氨酶、谷草转氨酶等 Serum: SCC-Ag, CA-125, IL-6, IL-12, TNF-α, IFN-γ, Gal-3, VEGF, creatinine, urea nitrogen, ALT, AST, etc. 肿瘤组织上清:MMP-2、MMP-9、VEGF、VEGFR-2、HIF-1α、BAX、BCL-2 等 Tumor tissue supernatant: MMP-2, MMP-9, VEGF, VEGFR-2, HIF-1α, BAX, BCL-2, etc.
肿瘤侵袭与转移指标 Tumor invasion and metastasis indicators	原位肿瘤对宫颈基层、周围结缔组织、血管、神经以及邻近器官(如膀胱、直肠)的侵袭深度和范围,淋巴结是否肿大、质地是否变硬,肝、肺等器官是否具有微小转移灶 Invasion depth and scope of primary tumors into cervical stroma, surrounding connective tissues, blood vessels, nerves, and adjacent organs (e. g., bladder, rectum); lymph node enlargement and hardening; presence of micro-metastases in organs such as liver and lung

表 4 常见 CC 动物模型建立方法及吻合度分析
Table 4 Establishment methods and consistency analysis of common CC animal models

模型分类 Model classification	造模方法 Modeling methods	模型特点 Modeling methods	中西医临床吻合度 Clinical consistency with TCM-WM
诱发性 CC Induced CC	化学诱发 Chemical induction 小鼠阴道内涂抹 0.1% DMBA,每周两次,持续 6 周 ^[34] 。KM 小鼠宫颈部位埋入含 DMBA 0.5 mg/cm 的棉线,持续 5 个月 ^[35] 。KM 小鼠宫颈管埋入含有 600 μg MCA 蜂蜡的无菌双棉线 ^[36, 37] 。将己烯雌酚溶于芝麻油中, BALB/c 小鼠每日皮下注射,剂量为 67 μg/kg ^[38] 。 Apply 0.1% DMBA intravaginally to mice twice a week for 6 weeks. Implant cotton thread containing 0.5 mg/cm DMBA into the cervical region of KM mice for 5 months. Implant sterile double cotton thread soaked with 600 μg MCA beeswax into the cervical canal of KM mice. subcutaneously inject BALB/c mice daily at a dose of 67 μg/kg	优点:诱导过程可控(剂量、频率、部位) 缺点:周期长,易诱导其他癌症 Advantages: Controllable induction process (dose, frequency, site) Disadvantages: Long cycle and high risk of inducing other cancers	符合西医诊断标准中②③④⑥项,吻合度为 65%; 符合中医病证③④⑥⑦⑩项,吻合度为 42.8% Consistent with WM diagnostic criteria ② ③ ④ ⑥, consistency rate: 65%; Consistent with TCM syndrome types ③ ④ ⑥ ⑦ ⑩, consistency rate: 42.8%

续表4

模型分类 Model classification	造模方法 Modeling methods	模型特点 Modeling methods	中西医临床吻合度 Clinical consistency with TCM-WM
诱发性 CC Induced CC	病毒诱发 Viral induction 浸透 HCMV 母液的明胶海绵块塞入 KM 小鼠阴道,直抵宫颈,持续 31 周 ^[39] Insert gelatin sponges soaked with HCMV stock solution into the vagina of KM mice, reaching the cervix, for 31 weeks	优点:诱导过程可控(剂量、频率、部位) 缺点:建模耗时长;诱发肿瘤程度良莠不齐 Advantages: Controllable induction process (dose, frequency, site) Disadvantages: Long modeling time; inconsistent degree of induced tumors	符合西医诊断标准中①②④⑥项,吻合度为 65%; 符合中医病证③④⑦⑩项,吻合度为 37.1% Consistent with WM diagnostic criteria ① ② ④ ⑥, consistency rate: 65%; Consistent with TCM syndrome types ③ ④ ⑦ ⑩, consistency rate: 37.1%
自发性 CC Spontaneous CC	— 自发肿瘤形成 ^[40] Spontaneous tumor formation	优点:与人 CC 发生发展过程相似 缺点:时间长,不稳定,数量有限 Advantages: Be similar to the occurrence and development process of human CC Disadvantages: Long duration, instability, and limited quantity	符合西医诊断标准中②③⑤⑥项,吻合度为 65%; 符合中医病证②④⑧⑨⑩项,吻合度为 42.8% Consistent with WM diagnostic criteria ② ③ ⑤ ⑥, consistency rate: 65%; Consistent with TCM syndrome types ② ④ ⑧ ⑨ ⑩, consistency rate: 42.8%
移植性 CC Transplantable CC	皮下移植 Subcutaneous transplantation NOD-SCID 小鼠右臀部移植患者的 CC 组织 ^[41] 。裸鼠、SCID 小鼠、NOD-NCG 小鼠、NOD-SCID 小鼠、NOG 小鼠皮下移植人 CC 新鲜肿瘤标本 ^[26, 42-44] 。NOD. CB17-PrkdcSCID/J 小鼠背部皮下用 22 号针头注射 3 mm ³ 肿瘤组织 ^[45] 。裸鼠左侧腋窝外侧皮下接种 CC Caski 细胞 ^[46, 47] 、SiHa 细胞 ^[48] 悬液 0.2 mL。KM 小鼠 ^[49] 、C57BL/6 小鼠 ^[50] 右前肢腋窝部位接种 U14 细胞 0.1 mL。BALB/c 裸鼠、Wister 大鼠皮下注射 HeLa 细胞 ^[51-54] 。SCID 小鼠侧腹皮下植入 CaLo 或 Caski 细胞 ^[55] 。裸鼠侧腹皮下注射 C-4I 细胞(4×10 ⁶ 个)0.1 mL ^[56] 。 Transplant human cervical cancer tissue into the right hip of NOD-SCID mice. Nude mice, SCID mice, NOD-NCG mice, NOD-SCID mice, and NOG mice subcutaneously implanted with fresh human CC tumor specimens. Inject 3 mm ³ tumor tissue subcutaneously in the back of NOD. CB17-PrkdcSCID/J mice using a 22-gauge needle. Inject 0.2 mL suspension of cervical cancer Caski cells or SiHa cells subcutaneously outside the left axilla of nude mice. Inject 0.1 mL U14 cells into the axillary region of the right forelimb of KM mice and C57BL/6 mice. Subcutaneously inject HeLa cells into BALB/c nude mice and Wister rats. Implant CaLo or Caski cells subcutaneously in the flank of SCID mice. Inject 0.1 mL C-4I cells (4×10 ⁶ cells) subcutaneously in the flank of nude mice.	优点:CC 成瘤率高,操作相对简便;肿瘤表浅,易于观察及测量大小、肿瘤生长速度快 缺点:肿瘤微环境与宫颈原位差异大,转移率低 Advantages: High CC tumor formation rate, relatively simple operation; superficial tumors, easy to observe and measure size, fast tumor growth rate Disadvantages: Significant difference in tumor microenvironment from orthotopic cervix, low metastasis rate	符合西医诊断标准中①②③④项,吻合度为 70%; 符合中医病证③④⑤⑥⑦项,吻合度为 42.8% Consistent with WM diagnostic criteria ① ② ③ ④, consistency rate: 70%; Consistent with TCM syndrome types ③ ④ ⑤ ⑥ ⑦, consistency rate: 42.8%

续表4

模型分类 Model classification	造模方法 Modeling methods	模型特点 Modeling methods	中西医临床吻合度 Clinical consistency with TCM-WM
移植性 CC Transplantable CC	宫颈原位 移植 Orthotopic cervical transplantation	NCR 裸鼠子宫接种 3 mm ³ CC 患者肿瘤组织 ^[57] 。SCID 和 NOD/SCID 小鼠子宫原位植入 1~2 mm 新鲜子宫颈活检 ^[58] 。SiHa 和 ME180 细胞构建 NOD-SCID 小鼠皮下肿瘤, 并将 1~2 mm 的皮下肿瘤植入子宫颈 ^[59] 。 Implant 3 mm ³ patient tumor tissue into the uterus of NCR nude mice. Orthotopically implant 1 ~ 2 mm fresh cervical biopsy specimens into the cervix of SCID and NOD-SCID mice. Construct subcutaneous tumors in NOD-SCID mice using SiHa and ME180 cells, and implant 1~2 mm subcutaneous tumors into the cervix.	优点:能形成原位瘤和远处转移瘤 缺点:肿瘤形成过程不易观察;造模成本高,手术难度大 Advantages: Capable of forming orthotopic tumors and distant metastases Disadvantages: Tumor formation process is not easy to observe; high modeling cost and surgical difficulty 符合西医诊断标准中①②③⑤⑥项,吻合度为 80% 符合中医病证②③④⑥⑦⑧⑩项,吻合度为 68.5% Consistent with WM diagnostic criteria ①②③⑤⑥, consistency rate: 80%; Consistent with TCM syndrome types ②③④⑥⑦⑧⑩, consistency rate: 68.5%
	肾包膜下 移植 Subrenal capsule transplantation	NSG 小鼠肾囊移植 1 mm ³ 活检组织芯片 ^[60] Transplant 1 mm ³ biopsy tissue microarrays into the renal capsule of NSG mice	优点:瘤体保持了癌组织生物学特性、较高移植成功率 缺点:肿瘤生长位置较深,不便观察、操作要求高 Advantages: Maintains tumor biological features, high graft success rate Disadvantages: Deep tumor growth site, hard to observe, technically demanding 符合西医诊断标准①②⑦⑧⑨项,吻合度为 55%; 符合中医病证②④⑤⑦⑧⑩项,吻合度为 48.5% Consistent with WM diagnostic criteria ①②⑦⑧⑨, consistency rate: 55%; Consistent with TCM syndrome types ②④⑤⑦⑧⑩, consistency rate: 48.5%
基因工程 性 CC Genetic engineering CC	-	将表达载体 HPV16-E6-E7-Rosa26 采用同源重组显微注射到 C57BL/6 N 小鼠受精卵中,构建 HPV16-E6-E7 转基因小鼠 ^[32] ;将 dpc DNA3.1(-)-PINV-E6 载体注入 KM 小鼠受精卵,构建皮肤组织中特异表达 HPV16-E6 基因的小鼠 ^[61] Microinject the expression vector HPV16-E6-E7-Rosa26 into fertilized eggs of C57BL/6 N mice via homologous recombination to construct HPV16-E6-E7 transgenic mice; inject dpc DNA3.1(-)-PINV-E6 vector into fertilized eggs of KM mice to construct mice with specific expression of HPV16-E6 gene in skin tissue	优点:可在自然免疫背景下观察 CC 肿瘤发生过程 缺点:发病率和潜伏期受雌激素剂量影响,模型建立周期较长,转基因鼠成本高 Advantages: Allows observation of CC tumorigenesis process in a natural immune background Disadvantages: Incidence rate and incubation period are affected by estrogen dose, long model establishment cycle, high cost of transgenic mice 符合西医诊断标准中①②③项,吻合度为 60%; 符合中医病证④⑥⑧⑨项,吻合度为 37.1% Consistent with WM diagnostic criteria ①②③, consistency rate: 60%; Consistent with TCM syndrome types ④⑥⑧⑨, consistency rate: 37.1%
其他 Others	-	HPV E6/E7 癌基因整合到 C57BL/6N 小鼠宫颈阴道,局部诱导 HPV ⁺ 癌症 ^[62] 。C57BL/6 小鼠子宫颈阴道上皮破坏后阴道滴注 CC TC-1 细胞系 1×10 ⁵ 个 ^[63] 。KM 小鼠阴道黏膜下层注射 U14 细胞(2×10 ⁷ /ml) 25 μL,持续 7 d ^[64] 。 Integrate HPV E6/E7 oncogenes into the cervicovaginal epithelium of C57BL/6N mice to locally induce HPV ⁺ cancer. After damaging the cervicovaginal epithelium of C57BL/6 mice, instill 1×10 ⁵ CC TC-1 cells intravaginally. Inject 25 μL U14 cells (2×10 ⁷ /ml) into the submucosa of the vaginal mucosa of KM mice for 7 consecutive days.	优点:贴近临床解剖路径,适合研究局部药物递送、局部免疫微环境 缺点:手术难度高,术后并发症风险较大 Advantages: Closer to clinical anatomical pathway, suitable for studying local drug delivery and local immune microenvironment Disadvantages: High surgical difficulty and high risk of postoperative complications 符合西医诊断标准中①②④,吻合度为 55%; 符合中医病证④⑥⑧⑨项,吻合度为 37.1% Consistent with WM diagnostic criteria ①②④, consistency rate: 55%; Consistent with TCM syndrome types ④⑥⑧⑨, consistency rate: 37.1%

及 3.2 CC 模型评价指标对这 4 种动物模型的造模方法、特点及与中西医的临床吻合度进行分析。结果表明,宫颈原位移植性动物模型的中西医吻合度相对较高,西医诊断标准吻合度为 80%,中医临床吻合度为 68.5%。

4 讨论

宫颈活组织检查是 CC 诊断的金标准,因此权重最高,赋值 30%;宫颈刮片细胞学检查和肿瘤标志物检查是重要的筛查和辅助诊断手段,权重次之,分别赋值 15%,可反映临床诊断路径;全身及盆腔、淋巴结检查属于 CC 的常规检查和分期手段,对于评估疾病范围很重要,因此给予一定权重,分别赋值 10%。西医诊断标准赋值模拟的是临床诊断和评估 CC 的常规流程,权重分配大致依据各项检查在确诊和病情评估中的关键性。白带异常增多、阴道不规则出血、分泌物异味是 CC 最直接、最特异的局部症状,在中医辨证中属于“下焦湿热瘀毒”的直接体现,因此单项目权重高,分别赋值 20%。次证包括烦躁易怒、口干、乏力、纳差便溏、畏冷、便秘、下腹疼痛等,这些是反映患者全身机能状态(气血阴阳、脏腑功能)的症状,项目多、单权重低,体现了中医整体观念和辨证的复杂性。在本研究构建的“病-证结合”CC 动物模型中,对模型“全身功能性状态”与“局部病灶特征”同时给予关注,该评分体系为中医整体观的相关指标留出足够的评价空间,以验证二者相结合的可行性,但这可能无法完全反映各指标在现代临床诊疗中的实际决策权重。

对于实验动物的选择,CC 模型常选用免疫缺陷型鼠,如 NOD/SCID 小鼠、BALB/c 裸鼠、NOD-NCG、NSG、NOD-SCID、SCID 小鼠等,这些小鼠可以避免因异种移植排斥而造成的研究障碍,具有较高的移植成功率。然而使用免疫缺陷型鼠限制了 CC 免疫机制的相关研究,现也有用正常免疫鼠来构建 CC 模型的案例。高岢然等^[52]用皮下接种人宫颈癌 HeLa 细胞联合免疫抑制剂在正常免疫 Wistar 大鼠中成功构建出了 CC 模型,降低了科研成本,且大鼠与小鼠相比,体积更大,取材及观察较容易,更适合肿瘤的影像学研究;另有刘昆燕等^[65]采用 CC 细胞悬液复合 3D 微载体皮下接种于 C57BL/6 鼠构建 CC 模型等。这些基于

正常免疫鼠所构建的 CC 模型为 CC 的免疫治疗研究提供便利,也弥补了裸鼠饲养条件严苛且造价昂贵的缺点,但这些优化的模型不能弥补裸鼠在免疫荧光实验中的优势。因此不同品系动物适用的造模类型不同,应根据研究目的确定相应模型种类,并综合考量动物特点,从而选择出更合适的实验动物。

本文将 CC 动物模型根据构建的原理分为 4 类,并根据各模型的特点进行吻合度分析。通过对比赋值结果得出:(1)移植性 CC 模型中的原位移植和皮下移植与西医临床指标吻合度最高,吻合度分别为 80% 和 70%,该类模型保留了 CC 患者的癌组织特性,可用于患者的个性化治疗方案研究。其中宫颈原位移植 CC 模型可模拟晚期 CC 转移的生物学特性,但原位移植造模的部位位于宫颈,对于实验人员的操作要求较高,使得该模型的使用频率略低于皮下移植法。相比之下,皮下移植模型使用率最高,其操作简便,移植成功率高且肿瘤位置较浅,便于造模过程中瘤体的测量与观察。移植性 CC 模型中还有肾包膜下移植,该法的西医吻合度较低,肿瘤生长位置较深,且受操作所限使用率不高。(2)西医吻合度仅次于皮下移植性 CC 模型的是自发和诱发性 CC 模型,自发性 CC 模型最符合人类 CC 的发生发展过程,可用于研究 CC 前病变的临床进展,但模型数量有限、实验周期长且具有不稳定性。诱发性 CC 模型包括化学诱发性 and 病毒诱发性,该模型造模过程中诸多不可控因素,模型间差异较大,故较少使用。(3)基因工程性 CC 模型西医吻合度不高,其通过 DNA 水平改变动物性状,模拟疾病发生,可能会产生不可预测病变影响模型建立^[66]。(4)在与中医临床病证吻合度分析中,原位移植瘤动物模型的吻合度最高,达 68.5%,该类模型病变部位及特点较符合中医临床病证特点,其余各模型中医吻合度均不高,文献中对实验动物模型评价多以西医指标为主,缺少中医“四诊”信息,使得模型与中医病证特点不能很好对应^[67]。

CC 动物模型可通过客观表型、行为学及生化指标等研究模式体现中医“四诊”信息。“望诊”为观察动物模型的精神状态、毛色光泽、体型变化、活动度等,对应中医“神疲乏力、面色萎黄、形体羸瘦”等虚证或癌毒侵袭的表现;通过阴道镜

或解剖观察宫颈局部组织的外观,记录糜烂、出血等情况,对应中医“带下异常”“崩漏”等证候特征;观察排泄物,收集阴道分泌物,观察量、色、质等,对应中医“湿毒下注、瘀毒内阻”等证型。“闻诊”为记录动物的叫声频率、呼吸状态,对应中医“气虚喘促、瘀阻气机”等行为表现;检测阴道分泌物、排泄物的气味,对应中医“热毒炽盛、湿毒蕴结”的证候特点。“问诊”可通过行为学实验和生理监测替代,采用疼痛相关行为学实验(如悬尾实验、痛阈检测等)评估 CC 引发的盆腔疼痛,对应中医“瘀阻疼痛”;监测动物的摄食量、饮水量、体质量变化,结合自主活动计数,判断是否存在“纳差”“乏力”“消瘦”等脾虚或气血亏虚表现;记录动物的排便、排尿频率及性状,对应中医“脾虚泄泻”“湿热下注”等证候。“切诊”替代指标为心率、血压、血流动力学指标(如血流速度、血管阻力),对应中医“脉涩”“脉沉迟”等特征;解剖时观察瘤体大小、质地、腹腔内黏连情况,对应中医“癥瘕积聚”的瘀阻程度。将“四诊”与观察指标、生化检测结果结合,可实现检测 CC 动物模型微观指标与宏观证候的对应,血清炎症因子、肿瘤标志物对应中医“热毒”“癌毒”的病理表现;肝肾功能、电解质等评估脏腑损伤程度,对应“脾肾阳虚”证;氧化应激指标对应中医“正气亏虚、邪毒内盛”。

评估 CC 整体模型发现,模型中医吻合度普遍低于西医吻合度,且目前尚未有 CC 病证结合模型类型,不利于 CC 中医诊治的发展,且模型成功率与重复率参差不齐。据此问题提出建议以期完善模型制备方法:(1)可根据 CC 的中医致病机制施加相应致病因素。脾肾功能异常,感受湿热、湿毒之邪是宫颈 HPV 感染的主要病因,可在原有的模型基础上联合冰水冷冻形成“外湿”,或联合冰水灌胃形成“脾虚”,或联合房劳法形成“肾虚”,这也与房事不洁的病因相符。(2)判断该模型是否建立成功的标准多以西医为主,间接导致中医吻合度普遍低于西医,可建立并融合相应中医辨证指标体系,以契合中医临床的望闻问切,提高中医吻合度^[68]。(3)尝试建立标准体系来统一造模条件,以提高模型的复制成功率。刘晓雯等^[69]的实验探究中发现,若接种的细胞悬液浓度过高会导致瘤体生长速度过快,从而影响造

模成功率,建议统一细胞悬液浓度的高低、化学致癌试剂浓度及剂量、移植组织块的大小及形状等。(4)应注意环境因素和营养因素的影响^[70]。温度过高过低可致雌性动物性周期紊乱、强光可致动物持续发情、饲料中脂肪含量过多降低动物生殖力,考虑到 CC 与生殖系统密切关系,应格外注意上述因素对造模的影响。(5)CC 存在疾病分期,可控制造模周期及药物浓度剂量等制备出分期模型,对临床各分期患者的个性化治疗方案提供研究基础。

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