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文献综述 REVIEW

化疗致胃肠道黏膜炎动物模型构建方法的研究进展

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Progress towards the development of animal models of chemotherapy-induced gastrointestinal mucositis

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Abstract

The pathogenesis of chemotherapy-induced gastrointestinal mucositis is not fully elucidated, which makes it extremely difficult to develop effective interventions. Recently, the use of animal models of chemotherapy-induced gastrointestinal mucositis has led to advances in the understanding of cellular mechanisms and clinical pharmacology of various types of chemotherapy drugs. Tumor-bearing models, non-tumor-bearing models, transgenic models and gene knockout models have been developed to assess the effect of chemotherapy on chemotherapy-induced gastrointestinal mucositis. In this paper, we comprehensively analyze the advantages and disadvantages of various methods for developing chemotherapy-induced gastrointestinal mucositis to provide a reference for the choice of animal models for future research of chemotherapy-associated mucosal toxicity and the underlying mechanisms.

Key Words: Gastrointestinal mucositis; Intestinal mucosal barrier injury; Chemically induced; Animal model

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摘要

化疗后胃肠道黏膜炎的主要问题之一是其根本的发病机制尚未完全阐明, 研究者无法直接在人体上开展实验, 难以制定有效干预措施. 动物模型的应用在该领域的研究中起到极为关键的作用. 近年来, 研究者通过复制接近人体状态的动物模型, 在各类化疗药物的细胞机制和临床药理学研究方面取得了显著进展. 本文通过MeSH主题词结合自由词, 电子检索PubMed(1950-2011)、Science Direct(1823-2011)数据库, 对荷瘤大鼠化疗胃肠黏膜炎模型、胃肠黏膜炎非荷瘤模型、基因敲除和转基因动物模型进行综述, 全面分析各种化疗后胃肠道黏膜炎模型的造模方法及优缺点, 为今后研究化疗的胃肠黏膜毒性反应及其机制, 提供造模方面的选择和参考依据.

关键词: 胃肠黏膜炎; 肠黏膜损伤; 药物疗法; 动物模型

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0 引言

“黏膜屏障损伤”也称为“黏膜炎”, 是肿瘤患者化疗过程中主要的剂量限制性不良反应[1], ESMO(european society for medical oncology)将其定义为由肿瘤治疗引起的口腔和/或胃肠道的炎性病变和/或溃疡性病变[2]. 流行病学资料显示, 由肿瘤治疗所导致的口腔和胃肠道黏膜炎

■背景资料
化疗后胃肠道黏膜炎已成为近年来肿瘤支持治疗的研究热点, 由于其根本的发病机制尚未完全阐明, 研究者无法直接在人体上开展实验, 因此动物模型的应用在该领域的研究中起到极为关键的作用.

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■研发前沿
近年来, 基因敲除GIM模型和转基因GIM动物模型应用日益广泛, 值得关注. 但鉴于各类模型只侧重于表现化疗胃肠道黏膜炎的某些主要症状及病理生理变化, 目前在建立化疗GIM模型方面尚无统一标准, 对模型的探索仍是今后的科研焦点.

总发生率高达100%[3]. 根据化疗方案不同, 胃肠道黏膜炎(gastrointestinal mucositis, GIM)的发生率可达40%-76%, 成为近年来肿瘤支持治疗的研究热点[4,5]. GIM可引起恶心、呕吐、腹泻、食欲减退等一系列胃肠道症状; 严重时出现厌食、水电解质及酸碱平衡失调、贫血等反应, 甚至导致化疗相关性死亡[6-8]. 上述反应致使临床试验中的绝大多数患者不得不停止或减量化疗. 肿瘤学家意识到, 要加强药物预防性干预效果、改善预后, 则必须克服化疗相关毒性反应. 然而目前胃肠黏膜炎发病机制尚未完全阐明[9], 研究者无法直接在人体上开展实验, 难以制定有效干预措施. 因此, 开发和复制接近人体状态的动物模型显得尤为必要. 本文旨在对各种化疗致GIM的造模方法进行综述, 以期为化疗引起的各类胃肠道不良反应的预防、治疗、营养及预后提供安全、稳定和可靠的造模参考.

1 纳入文献研究方法

电子检索PubMed(1950/2011)、Science Direct(1823/2011)数据库收录的化疗后胃肠道黏膜炎模型的相关研究和论文报告. 采用MeSH主题词结合自由词检索, 英文主题词为“Mucositis/chemically induced; Models Animal”, 自由词为“Gastrointestinal Mucositis; Intestinal mucosal barrier injury; Chemotherapy-Induced Mucositis; Alimentary tract mucositis”, 不限定文章语言种类. 同时进行参考文献的追溯, 并注意“灰色”文献, 如未发表的学位论文、会议论文等.

纳入标准: (1)文献主体内容与GIM模型紧密联系的文章; (2)研究设计和研究方法可靠的实验研究类文章; (3)观点明确, 分析全面的理论研究类文章. 排除标准: (1)内容陈旧或重复文献; (2)体外实验文章; (3)非化疗药物(如放疗等)造成的胃肠道损伤; (4)研究设计为非随机对照研究.

经逐一仔细阅读全文, 严格按照纳入和排除标准筛选文献. 文献的筛选由2人独立完成, 将2人的筛查结果进行比对, 不一致处由2人讨论解决或第3方仲裁决定. 电子检索获取文献390篇, 其中PubMed 201篇、Science Direct 189篇, 阅读标题和摘要进行初筛, 共113篇文献符合标准, 进一步阅读全文, 二次筛选后, 共纳入70篇进行综述.

2 纳入文献综合分析

2.1 荷瘤大鼠化疗胃肠黏膜炎模型

Gibson等[10,11]在荷瘤模型基础上, 以♀DA(dark agouti)大鼠为受试对象, 构建化疗致GIM的荷瘤大鼠模型. 首先采用肿瘤细胞悬液接种法, 于化疗开始前9 d皮下植入乳腺腺癌细胞, 制备腺癌模型; 随后选用200 mg/kg伊立替康(Irinotecan, CPT-11)一次性腹腔注射, 制备GIM腺癌模型. 72 h内造模成功率为66%. 结果评价采用盲法, 可见模型大鼠出现腹泻, 喜卷缩、少动、消瘦等症状. 其中, 以腹泻症状最为严重, 72 h内达到腹泻高峰, 82%大鼠出现中重度腹泻, 96 h死亡率达50%. Kim等[12]将CT26结肠癌细胞株接种到小鼠体内后, 多次腹腔注射5-氟尿嘧啶[5-Fu 30 mg/(kg·d), 共4 d], 制备CT26小鼠GIM模型. 观察可见, CT26小鼠化疗后第3天出现腹泻和体质量下降(25.3%), 上皮细胞增殖减少. 另有早期研究[12,13]用1.5 mg/kg甲氨喋呤(Methotrexate, MTX)腹腔注射2 d造模, 结果显示化疗结束6 h后肠隐窝细胞凋亡增加28倍, 2-4 d可见绒毛萎缩增加. 同时可见化疗第1天后大鼠肿瘤扩散减少, 第2天肿瘤质量减低、肿瘤细胞凋亡增加.

上述荷瘤模型已被国外学者[14-16]反复多次应用于抗黏膜毒性药物(如微生物制剂、KGF等), 以及各种化疗药物(如MTX、CPT-11、5-FU等)胃肠黏膜损伤机制的研究. 被证实能够有效模拟人体黏膜炎的发展过程, 值得借鉴. 其优点在于受试动物在肿瘤生长和化疗黏膜毒性反应上具有高度的同质性, 可以保证受试动物个体间病理变化相对一致; 此外, 研究者可以同时观察肿瘤细胞和黏膜损害对大鼠的影响作用. 缺点是造模时间长、花费大, 致使研究受限.

2.2 基因敲除小鼠化疗胃肠黏膜炎模型

目前, 基因敲除小鼠化疗胃肠黏膜炎模型应用日趋广泛,其最常见造模药物为MTX和5-Fu[17,18]. 相对大鼠而言, 小鼠对MTX介导的胃肠黏膜损伤耐受性更强. Kato等[19]为研制mrp1基因敲除小鼠化疗GIM模型, 采用♂FVB野生型小鼠($mrp1^{+/+}$)和FVB基因敲除小鼠($mrp1^{-/-}$)连续4 d腹腔注射MTX 50 mg/(kg·d), 各组均未见造模后死亡. 实验第5天体质量减轻大于5%, $mrp1^{+/+}$组第7天体质量开始恢复, 而$mrp1^{-/-}$组体质量继续下降; 摄食和饮水与体质量下降水平相一致, 化疗后第4天摄入量$mrp1^{-/-}$组显著低于$mrp1^{+/+}$组; 化疗第7天, $mrp1^{-/-}$组全部出现嗜睡、拱背和皮毛枯槁, 并出现严重腹泻等GIM典型症状. 另有研究[20]通过皮下注射300 mg/kg MTX诱导TGF-α基因敲除小鼠GIM模型, 成活率为100%. 观察发现模

型小鼠近端小肠有丝分裂减少, 隐窝损失或失真, 绒毛萎缩、缩短以及炎症细胞浸润等病理改变, 提示模型复制成功. Tran等[21-23]以C57BL/6金属硫蛋白基因敲除小鼠MT$^{-/-}$和C57BL/6野生型小鼠MT$^{+/+}$为对象, 分别给予一次性皮下注射MTX 500 mg/kg, 制备MT基因敲除小鼠GIM模型和MTX诱导的野生型小鼠GIM模型. 通过比较发现, 前者肠道组织的损害和中性粒细胞的浸润更严重, 对MTX引起的肠黏膜损伤较后者更为敏感, 说明MT基因可能在MTX引起肠道损伤中发挥保护作用. 除此之外, Tucker等[24-27]采用5-FU一次性大剂量(450 mg/kg)或分次腹腔注射(40 mg/kg 5-Fu, 共5 d)造模, 分别对caspase-11、血小板活化因子(platelet-activating factor, PAF)、叶酸(folic acid)、肠三叶因子(intestinal trefoil factor, ITF)等基因敲除小鼠进行研究, 从而为化疗致GIM的预防和修复提供科学依据.

以上模型具有靶向性特点, 对于研究动物遗传与GIM相关基因的功能十分有用, 但仍有其局限性. 首先, 基因敲除小鼠的培育成功较为复杂和困难, 特别是基因重组时, 同源基因位点和重组率相当低, 是获得成功的主要障碍. 其次, 若所敲除的基因是具有致命功能的基因, 小鼠将在胚胎早期死亡(如早期出血致死); 若敲除的基因可被多功能的其他基因功能代偿, 这样就会使表型改变模糊, 致使结果难以分析.

2.3 转基因小鼠化疗胃肠黏膜炎模型 转基因小鼠又称为“智能检测试管”, 可用来研究人类疾病的生物学基础和各种治疗方案, 检测潜在的治疗药物, 也可根据意愿在特定类型细胞中打开或关闭转基因的表达. Huang等[28]利用肠道表皮细胞生在因子(epidermal growth factor, EGF)广泛表达的转基因小鼠模型, 评估EGF对化疗引起的肠道损伤的影响. 经RT-PCR确认EGF在转基因小鼠回肠中广泛表达后, 持续4 d给予5-FU 50 mg/(kg·d)腹腔注射造模. 转基因小鼠化疗GIM模型存活率为100%. 症状观察发现, 造模后第4天小鼠体质量开始下降, 第6天下降达到10%, 直至实验结束仅恢复至基线水平的50%. 病理显示绒毛高度显著缩短, 隐窝深度增加. 转基因小鼠模型的优点之一是能够最大限度地减少因给药所致的混杂因素, 如口服、皮下或腹腔给药所致差异; 其次是具有器官特异性, 基因在特异组织(如肠道)中表达, 避免肠内或肠外给予外源性生长因子对机体带来的系列影响. 但小鼠与人类具有很大差别, 因此医学上转基因模型提供的信息与人体并不总是相关; 实际应用中, 制作和维持转基因动物相对耗时、耗钱, 使转基因小鼠的应用受到一定限制.

2.4 化疗致胃肠黏膜炎非荷瘤模型 为了排除混杂因素, 单独研究化疗药物对胃肠黏膜的毒性作用, 国外学者根据自身研究目的和观测指标, 开发了各种胃肠黏膜炎非荷瘤模型. 根据所用化疗药物的种类、剂量、间隔时间和给药方式不同, 所造模型的侧重点也各不相同. 因模型动物黏膜损伤的严重程度和主要症状与给药方案关系密切, 现根据不同给药方案, 分为以下3类.

2.4.1 一次性注射给药: (1)5-Fu. 化疗药物对肠黏膜屏障损伤的众多试验中, 针对5-Fu的研究较多. 40多年来, 5-Fu作为一种抗嘧啶类抗代谢药, 已被广泛应用于治疗多种人类肿瘤. Pedro等[29]采用♂Wistar大鼠, 给予5-Fu 150 mg/kg一次性腹腔注射, 动物成活率为100%. 大鼠体质指数于化疗后3 d、5 d、15 d明显下降, 其中以化疗后第3天减低最为显著. 化疗后第3天, 病理可见胃黏膜固有层存在散在的嗜酸性粒细胞; 肠绒毛变短变粗, 互相融合, 并且存在绒毛断裂现象, 肠腔内出现大小不等的绒毛碎片; 上皮细胞大小不一, 排列紊乱; 回肠、结肠黏膜层及固有层厚度变薄, 并见大量炎症细胞, 小肠腺体成萎缩样变. 以上病变至第15天开始恢复, 可观察到绒毛和隐窝尚存, 十二指肠肌层仍有少许中性粒细胞浸润. 学者们[30-38]通过评价各代谢指标(体质量、摄食量、饮水量和尿量)和病理变化, 分别在BALB/L小鼠、DBA/2小鼠、SD大鼠、DA大鼠等不同实验动物中验证了该类造模方法的可行性. 但该方法未见或少见腹泻症状[39], 研究者若以腹泻为主要研究内容, 不适合选此模型. (2)CPT-11. 与5-Fu相比, CPT-11可使患者3-4度GIM的发生率增加15%[40]. Stringer等[41-44]采用200 mg/kg伊立替康对DA大鼠行一次性腹腔注射, 观察可见化疗2 h后23%动物出现腹泻, 24 h腹泻发生率高达44%, 72 h后33%大鼠轻度腹泻, 144 h后腹泻停止[45,46], 符合急性肠黏膜损伤过程. 组织形态学发现, CPT-11早期引起腺体严重萎缩和退化, 胃腺窝、空结肠隐窝细胞凋亡增加, 化疗后6 h达到凋亡高峰[47,48]. 黏膜中大量炎性细胞浸润, 黏液分泌增加[41,48]. 由于CPT-11剂量限制性不良反应以腹泻为主[49], 且模型大鼠腹泻症状与肠隐窝细胞增殖、凋亡等改变相一致[50]. 因此, 该方法较侧重于化疗黏膜毒性所致腹泻的研究. 其局限性在于造模存活率低, 有研究报道注射高剂量

■相关报道
Hirata等运用不同化疗药物成功建立起非荷瘤模型, 在一定程度上符合人类GIM形成的病理过程, 方法简便, 可操作性强, 但缺乏靶向性特点, 难以对GIM遗传学和发病机制方面进行深入和透彻研究.

■创新盘点
本文对各种化疗后胃肠道黏膜炎模型的造模方法进行全面分析, 为学者研究化疗的胃肠黏膜毒性反应及其机制提供造模选择和参考依据.

CPT-11 96 h后动物全部死亡[24], 但目前对此说法不一[41,45].

MTX: 能够诱发大鼠典型黏膜炎的病理改变, 致使黏膜炎发生率达40%. 若短时间内大剂量MTX进入体内, 发生率可增至76%. Gulgun等[51]给予大鼠单剂量MTX 20 mg/kg腹腔注射, 模型存活率为57%. 大鼠体质量显著下降, 并伴有腹泻; 病理显示化疗后24 h即出现明显的肠道损伤, 第3天损伤最重, 表现为小肠绒毛变短变粗, 上皮细胞脱落, 黏膜固有层炎性细胞浸润, 出现溃疡. Fijlstra等[52]通过剂量筛选, 给予Wistar大鼠MTX 60 mg/kg一次性尾静脉注射. 观察发现大鼠化疗后3-4 d摄食、饮水、体质量下降最为严重, 并于第3天出现水样便. 处死后发现大鼠呈现轻至重度GIM病理变化, 小肠黏膜绒毛萎缩, 降至正常55.6%. 肠隐窝长度增加至1.3倍, 杯状细胞分布不均, 黏膜层炎细胞浸润, 肠黏膜蛋白质、mRNA含量显著下降. MTX单剂量注射诱发模型具有迅速恢复、过程短暂的特征, 缩短了造模时间[53].

2.4.2 持续性注射给药: (1)腹腔注射给药. 5-Fu对肠黏膜的不良反应的剧烈程度与给药方案有一定关系, 在大剂量给药条件下, 剂量分次连续给予较一次性给予对肠屏障的损伤更大, 损伤恢复较慢. 各研究中对于5-Fu分次连续给药造模的剂量和持续时间各有不同, 其动物黏膜损伤的严重程度和主要症状也不尽相同[54-56]. Hirata等[57]采用Wistar大鼠, 连续4 d的给药剂量为5-Fu 30 mg/kg, 与空白组相比, 模型组小肠的干重和湿重均有明显降低, 小肠MPO活性显著降低, 肠通透性增加. 但该研究对模型的评价不够全面, 无法完全反应出模型的损伤程度. (2)皮下注射给药: 多项研究结果发现[58-60], MTX诱导的GIM大鼠体质量变化呈现剂量依赖性. Leblond等[28]通过不同剂量比较, 选用2.5 mg/kg MTX皮下注射, 持续3 d. 实验第2-3天, 大鼠体质量和摄食量开始下降, 第5-6天降到最低, 至实验第7天开始恢复, 但仍无法恢复到正常水平[58-61]. 第4天开始出现严重的胃肠黏膜损伤, 形态学方面, 表现为肠上皮细胞增生减慢导致绒毛萎缩、隐窝细胞增殖降低、杯状细胞排空增加[62,63]; 功能方面, 肠黏膜屏障受损, 通透性增加, 伴随有细菌移位[58,59]. 肠系膜淋巴结细菌培养阳性; 生化方面, 肠黏膜蛋白质、DNA及RNA含量显著下降[58,60]. 以上损伤于第7天开始恢复. (3)中心静脉给药. Tsuji等[55]以9周龄♂Wistar大鼠为对象, 通过中心静脉进行100 mg/(kg·d) 5-Fu滴注, 持续4 d(0-3 d). 实验共7 d(0-6 d). 72 h内无明显症状发生, 第4天73.9%模型组大鼠出现急性腹泻, 大便呈水样. 86.2%出现呕吐(异食癖反应), 符合GIM症状表现, 肉眼可见空肠长度较空白组短. 实验第6天, 模型组所有大鼠均出现毛发竖立和眼底渗血等败血症症状; 检查发现急性炎性细胞因子升高, 内毒素含量增加, 出现肠道细菌易位. 病理显示胃肠黏膜的萎缩和广泛糜烂, 空肠肠壁变薄, 出现点状溃疡; 黏膜下层基本消失, 仅残余少许腺体及黏膜下层水肿组织. 该模型后期累积毒性反应较重, 可用于5-FU对胃肠黏膜迟发效应及胃肠微生物屏障损伤的研究.

2.4.3 经口给药法: 大鼠经口给药的半数致死量为230 mg/kg. Shiota等[64]选用7周龄♂SD大鼠, 实验第5天给予5-FU 300 mg/kg灌胃后大鼠进食量和体质量急剧下降, 腹泻率为75%. 第8天处死后组织检查发现小肠绒毛呈不同程度萎缩、倒伏, 隐窝深度增加, 空肠黏膜IL-6和TNF-α mRNA表达降低. Saegusa等[65,66]给予Wistar大鼠连续5 d 50 mg/kg 5-FU灌胃, 测量发现胃黏膜粘蛋白含量下降57.6%, 空肠粘蛋白含量自化疗第1天开始显著下降, 最低降至43.9%, 第13天恢复正常. 胃和小肠PCNA含量第1天开始降低, 第7天增加至空白组的2倍. Kotani等[67]为研究5-FU化疗后胃的形态和功能变化, 给予SD大鼠同等剂量5-Fu(50 mg/kg, 连续5 d)灌胃, 与Saegusa结果不同的是, 肉眼和镜下均未见胃黏膜的明显改变, 改为100 mg/kg 5-Fu连续5 d灌胃后, 大鼠出现胃功能紊乱, 黏膜对酸等不良刺激的抵抗力降低. 病理可见胃黏膜高度减低, 上皮细胞基底层脱离. 上述变化说明胃黏膜对化疗的敏感性相对低于肠黏膜. Manzano等[68]以小型猪为实验对象, 每周给予5 d 12 mg/kg 5-FU口服, 持续4 wk, 成活率为100%. 模型组于化疗第1周后体质量呈显著下降趋势, 第2周表现出典型的化疗胃肠道反应(如呕吐和腹泻). 检测发现空肠和回肠重量明显降低, 空回肠所含蛋白质和DNA数量降低. 由于猪胃肠道的病理生理与人类非常相似, 因此该模型非常接近癌症患者化疗致GIM, 为评估新颖的抗黏膜毒性方法提供了一个有效途径.

以上非荷瘤模型价格低廉, 相比其他模型制作方法更为简便快速, 在一定程度上符合人类GIM形成的病理过程. 在成功的建立起化疗致GIM模型的前提下, 保证了科研资源的合理利用. 从实验的可操作性和研究目的来说, 不失为

化疗胃肠黏膜炎研究的有效方法, 值得借鉴.

3 结论

由于不同化疗药物引发的胃肠黏膜炎病理基础不同, 导致的病理学变化、损伤程度和恢复过程也不相同. 目前在建立化疗GIM模型方面尚无统一标准. 因此, 研究者在开展实验前必须明确实验设计上想要了解或研究的内容, 选择合适的造模方法. 在选用模型时, 除考虑药物种类外, 还应考虑药物剂量和干预时间. 原则上以能够引起胃肠道黏膜损伤, 而又远低于致死剂量为准[33]. 虽然动物模型只是一种间接反映人类疾病的手段和方法, 尚不能完全代表人类疾病. 但转基因、基因敲除等技术的发展以及与人类胃肠道病理生理相似的实验动物的广泛应用, 均为研究化疗致GIM的提供了新思路与新方法, 在化疗致GIM的机制研究、药物筛选和治疗方案确立过程中起到关键性作用.

4 参考文献

1 Rustum YM. Fluoropyrimidines in Cancer Therapy. Totowa: Humana Press, 2003: 249-259
2 Peterson DE, Bensadoun RJ, Roila F. Management of oral and gastrointestinal mucositis: ESMO Clinical Practice Guidelines. *Ann Oncol* 2011; 22 Suppl 6: vi78-vi84
3 Wells M, Donnan PT, Sharp L, Ackland C, Fletcher J, Dewar JA. A study to evaluate nurse-led on-treatment review for patients undergoing radiotherapy for head and neck cancer. *J Clin Nurs* 2008; 17: 1428-1439
4 Prisciandaro LD, Geier MS, Butler RN, Cummins AG, Howarth GS. Evidence supporting the use of probiotics for the prevention and treatment of chemotherapy-induced intestinal mucositis. *Crit Rev Food Sci Nutr* 2011; 51: 239-247
5 Leblond J, Le Pessot F, Hubert-Buron A, Duclos C, Vuichoud J, Faure M, Breuillé D, Déchelotte P, Coëffier M. Chemotherapy-induced mucositis is associated with changes in proteolytic pathways. *Exp Biol Med* (Maywood) 2008; 233: 219-228
6 Gibson RJ. Gut microbiome and intestinal mucositis: A new challenge for researchers. *Cancer Biol Ther* 2009; 8. *[Epub ahead of print]*
7 Sonis ST. Regimen-related gastrointestinal toxicities in cancer patients. *Curr Opin Support Palliat Care* 2010; 4: 26-30
8 Chipponi J, Huguier M, Pezet D, Basso N, Hay JM, Quandalle P, Jaeck D, Fagniez PL, Gainant A. Randomized trial of adjuvant chemotherapy after curative resection for gastric cancer. *Am J Surg* 2004; 187: 440-445
9 Gibson RJ, Keefe DM. Cancer chemotherapy-induced diarrhoea and constipation: mechanisms of damage and prevention strategies. *Support Care Cancer* 2006; 14: 890-900
10 Gibson RJ, Keefe DM, Clarke JM, Regester GO, Thompson FM, Goland GJ, Edwards BG, Cummins AG. The effect of keratinocyte growth factor on tumour growth and small intestinal mucositis after chemotherapy in the rat with breast cancer. *Cancer Chemother Pharmacol* 2002; 50: 53-58
11 Gibson RJ, Bowen JM, Keefe DM. Palifermin reduces diarrhea and increases survival following irinotecan treatment in tumor-bearing DA rats. *Int J Cancer* 2005; 116: 464-470
12 Kim KA, Kakitani M, Zhao J, Oshima T, Tang T, Binnerts M, Liu Y, Boyle B, Park E, Emtage P, Funk WD, Tomizuka K. Mitogenic influence of human R-spondin1 on the intestinal epithelium. *Science* 2005; 309: 1256-1259
13 Gibson RJ, Stringer AM, Bowen JM, Logan RM, Yeoh AS, Burns J, Alvarez E, Keefe DM. Velafermin improves gastrointestinal mucositis following irinotecan treatment in tumor-bearing DA rats. *Cancer Biol Ther* 2007; 6: 541-547
14 Letari O, Booth C, Bonazzi A, Garofalo P, Makovec F, Rovati LC, Caselli G. Efficacy of CR3294, a new benzamidine derivative, in the prevention of 5-fluorouracil-induced gastrointestinal mucositis and diarrhea in mice. *Cancer Chemother Pharmacol* 2010; 66: 819-827
15 Gibson RJ, Bowen JM, Alvarez E, Finnie J, Keefe DM. Establishment of a single-dose irinotecan model of gastrointestinal mucositis. *Chemotherapy* 2007; 53: 360-369
16 Gibson RJ, Keefe DM, Thompson FM, Clarke JM, Goland GJ, Cummins AG. Effect of interleukin-11 on ameliorating intestinal damage after methotrexate treatment of breast cancer in rats. *Dig Dis Sci* 2002; 47: 2751-2757
17 Leitão RF, Brito GA, Oriá RB, Braga-Neto MB, Bellaguarda EA, Silva JV, Gomes AS, Lima-Júnior RC, Siqueira FJ, Freire RS, Vale ML, Ribeiro RA. Role of inducible nitric oxide synthase pathway on methotrexate-induced intestinal mucositis in rodents. *BMC Gastroenterol* 2011; 11: 90
18 Kim JK, Takeuchi M, Yokota Y. Impairment of intestinal intraepithelial lymphocytes in Id2 deficient mice. *Gut* 2004; 53: 480-486
19 Kato S, Ito K, Kato Y, Wakayama T, Kubo Y, Iseki S, Tsuji A. Involvement of multidrug resistance-associated protein 1 in intestinal toxicity of methotrexate. *Pharm Res* 2009; 26: 1467-1476
20 Xian CJ, Cool JC, Howarth GS, Read LC. Effects of TGF-alpha gene knockout on epithelial cell kinetics and repair of methotrexate-induced damage in mouse small intestine. *J Cell Physiol* 2002; 191: 105-115
21 Tran CD, Sundar S, Howarth GS. Dietary zinc supplementation and methotrexate-induced small intestinal mucositis in metallothionein-knockout and wild-type mice. *Cancer Biol Ther* 2009; 8: 1662-1667
22 Tran CD, Howarth GS, Coyle P, Philcox JC, Rofe AM, Butler RN. Dietary supplementation with zinc and a growth factor extract derived from bovine cheese whey improves methotrexate-damaged rat intestine. *Am J Clin Nutr* 2003; 77: 1296-1303
23 Howarth GS, Francis GL, Cool JC, Xu X, Byard RW, Read LC. Milk growth factors enriched from cheese whey ameliorate intestinal damage by methotrexate when administered orally to rats. *J Nutr* 1996; 126: 2519-2530
24 Tucker JM, Davis C, Kitchens ME, Bunni MA, Priest DG, Spencer HT, Berger FG. Response to 5-fluorouracil chemotherapy is modified by dietary folic acid deficiency in Apc(Min/+) mice. *Cancer Lett*

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该篇综述检索系统全面, 论文撰写条理清晰, 内容对临床相关研究有一定指导意义.

2002; 187: 153-162
25 Soares PM, Lima-Junior RC, Mota JM, Justino PF, Brito GA, Ribeiro RA, Cunha FQ, Souza MH. Role of platelet-activating factor in the pathogenesis of 5-fluorouracil-induced intestinal mucositis in mice. *Cancer Chemother Pharmacol* 2011; 68: 713-720
26 Kang SJ, Popat R, Bragdon C, Odonnell K, Phelan S, Yuan J, Sonis ST. Caspase-11 is not necessary for chemotherapy-induced intestinal mucositis. *DNA Cell Biol* 2004; 23: 490-495
27 Beck PL, Wong JF, Li Y, Swaminathan S, Xavier RJ, Devaney KL, Podolsky DK. Chemotherapy- and radiotherapy-induced intestinal damage is regulated by intestinal trefoil factor. *Gastroenterology* 2004; 126: 796-808
28 Huang FS, Kemp CJ, Williams JL, Erwin CR, Warner BW. Role of epidermal growth factor and its receptor in chemotherapy-induced intestinal injury. *Am J Physiol Gastrointest Liver Physiol* 2002; 282: G432-G442
29 Soares PM, Mota JM, Gomes AS, Oliveira RB, Assreuy AM, Brito GA, Santos AA, Ribeiro RA, Souza MH. Gastrointestinal dysmotility in 5-fluorouracil-induced intestinal mucositis outlasts inflammatory process resolution. *Cancer Chemother Pharmacol* 2008; 63: 91-98
30 Stringer AM, Gibson RJ, Logan RM, Bowen JM, Yeoh AS, Hamilton J, Keefe DM. Gastrointestinal microflora and mucins may play a critical role in the development of 5-Fluorouracil-induced gastrointestinal mucositis. *Exp Biol Med* (Maywood) 2009; 234: 430-441
31 Torres DM, Tooley KL, Butler RN, Smith CL, Geier MS, Howarth GS. Lyprinol only partially improves indicators of small intestinal integrity in a rat model of 5-fluorouracil-induced mucositis. *Cancer Biol Ther* 2008; 7: 295-302
32 Cool JC, Dyer JL, Xian CJ, Butler RN, Geier MS, Howarth GS. Pre-treatment with insulin-like growth factor-I partially ameliorates 5-fluorouracil-induced intestinal mucositis in rats. *Growth Horm IGF Res* 2005; 15: 72-82
33 Wright TH, Yazbeck R, Lymn KA, Whitford EJ, Cheah KY, Butler RN, Feinle-Bisset C, Pilichiewicz AN, Mashtoub S, Howarth GS. The herbal extract, Iberogast, improves jejunal integrity in rats with 5-Fluorouracil (5-FU)-induced mucositis. *Cancer Biol Ther* 2009; 8: 923-929
34 Carneiro-Filho BA, Oriá RB, Wood Rea K, Brito GA, Fujii J, Obrig T, Lima AA, Guerrant RL. Alanyl-glutamine hastens morphologic recovery from 5-fluorouracil-induced mucositis in mice. *Nutrition* 2004; 20: 934-941
35 Pritchard DM, Bower L, Potten CS, Jackman AL, Hickman JA. The importance of p53-independent apoptosis in the intestinal toxicity induced by raltitrexed (ZD1694, Tomudex): genetic differences between BALB/c and DBA/2 mice. *Clin Cancer Res* 2000; 6: 4389-4395
36 Wu Z, Han X, Qin S, Zheng Q, Wang Z, Xiang D, Zhang J, Lu H, Wu M, Zhu S, Yu Y, Wang Y, Han W. Interleukin 1 receptor antagonist reduces lethality and intestinal toxicity of 5-fluorouracil in a mouse mucositis model. *Biomed Pharmacother* 2010; 64: 589-593
37 Smith CL, Geier MS, Yazbeck R, Torres DM, Butler RN, Howarth GS. Lactobacillus fermentum BR11 and fructo-oligosaccharide partially reduce jejunal inflammation in a model of intestinal mucositis in rats. *Nutr Cancer* 2008; 60: 757-767
38 Bonneville F, Bloch F, Kurys E, du Montcel ST, Welter ML, Bonnet AM, Agid Y, Dormont D, Houeto JL. Camptocormia and Parkinson's disease: MR imaging. *Eur Radiol* 2008; 18: 1710-1719
39 Han X, Wu Z, Di J, Pan Y, Zhang H, Du Y, Cheng Z, Jin Z, Wang Z, Zheng Q, Zhang P, Wang Y. CXCL9 attenuated chemotherapy-induced intestinal mucositis by inhibiting proliferation and reducing apoptosis. *Biomed Pharmacother* 2011; 65: 547-554
40 Jhun HJ, Cho SI, Park JT. Changes in job stress, musculoskeletal symptoms, and complaints of unfavorable working conditions among nurses after the adoption of a computerized order communication system. *Int Arch Occup Environ Health* 2004; 77: 363-367
41 Stringer AM, Gibson RJ, Logan RM, Bowen JM, Yeoh AS, Laurence J, Keefe DM. Irinotecan-induced mucositis is associated with changes in intestinal mucins. *Cancer Chemother Pharmacol* 2009; 64: 123-132
42 Logan RM, Gibson RJ, Bowen JM, Stringer AM, Sonis ST, Keefe DM. Characterisation of mucosal changes in the alimentary tract following administration of irinotecan: implications for the pathobiology of mucositis. *Cancer Chemother Pharmacol* 2008; 62: 33-41
43 Stringer AM, Gibson RJ, Logan RM, Bowen JM, Yeoh AS, Burns J, Keefe DM. Chemotherapy-induced diarrhea is associated with changes in the luminal environment in the DA rat. *Exp Biol Med* (Maywood) 2007; 232: 96-106
44 Bowen JM, Gibson RJ, Tsykin A, Stringer AM, Logan RM, Keefe DM. Gene expression analysis of multiple gastrointestinal regions reveals activation of common cell regulatory pathways following cytotoxic chemotherapy. *Int J Cancer* 2007; 121: 1847-1856
45 Al-Dasooqi N, Gibson RJ, Bowen JM, Logan RM, Stringer AM, Keefe DM. Matrix metalloproteinases are possible mediators for the development of alimentary tract mucositis in the dark agouti rat. *Exp Biol Med* (Maywood) 2010; 235: 1244-1256
46 Al-Dasooqi N, Bowen JM, Gibson RJ, Logan RM, Stringer AM, Keefe DM. Selection of housekeeping genes for gene expression studies in a rat model of irinotecan-induced mucositis. *Chemotherapy* 2011; 57: 43-53
47 Bowen JM, Gibson RJ, Stringer AM, Chan TW, Prabowo AS, Cummins AG, Keefe DM. Role of p53 in irinotecan-induced intestinal cell death and mucosal damage. *Anticancer Drugs* 2007; 18: 197-210
48 Bowen JM, Tsykin A, Stringer AM, Logan RM, Gibson RJ, Keefe DM. Kinetics and regional specificity of irinotecan-induced gene expression in the gastrointestinal tract. *Toxicology* 2010; 269: 1-12
49 Ramesh M, Ahlawat P, Srinivas NR. Irinotecan and its active metabolite, SN-38: review of bioanalytical methods and recent update from clinical pharmacology perspectives. *Biomed Chromatogr* 2010; 24: 104-123
50 Bowen JM, Stringer AM, Gibson RJ, Yeoh AS, Hannam S, Keefe DM. VSL#3 probiotic treatment reduces chemotherapy-induced diarrhea and weight loss. *Cancer Biol Ther* 2007; 6: 1449-1454
51 Gulgun M, Erdem O, Oztas E, Kesik V, Balamtekin N, Vurucu S, Kul M, Kismet E, Koseoglu V. Proan-

thocyanidin prevents methotrexate-induced intestinal damage and oxidative stress. *Exp Toxicol Pathol* 2010; 62: 109-115
52 Fijlstra M, Rings EH, Verkade HJ, van Dijk TH, Kamps WA, Tissing WJ. Lactose maldigestion during methotrexate-induced gastrointestinal mucositis in a rat model. *Am J Physiol Gastrointest Liver Physiol* 2011; 300: G283-G291
53 de Koning BA, van Dieren JM, Lindenbergh-Kortleve DJ, van der Sluis M, Matsumoto T, Yamaguchi K, Einerhand AW, Samsom JN, Pieters R, Nieuwenhuis EE. Contributions of mucosal immune cells to methotrexate-induced mucositis. *Int Immunol* 2006; 18: 941-949
54 Tsuji E, Hiki N, Nomura S, Fukushima R, Kojima J, Ogawa T, Mafune K, Mimura Y, Kaminishi M. Simultaneous onset of acute inflammatory response, sepsis-like symptoms and intestinal mucosal injury after cancer chemotherapy. *Int J Cancer* 2003; 107: 303-308
55 Murakami M, Sato N, Tashiro K, Nakamura T, Masunaga H. Effects of caloric intake on intestinal mucosal morphology and immune cells in rats treated with 5-Fluorouracil. *J Clin Biochem Nutr* 2009; 45: 74-81
56 Silecchia G, Guarino E, Sinibaldi-Vallebona P, Pierimarchi P, Restuccia A, Spaziani E, Bernard P, Tuthill C, Garaci E, Rasi G. Efficacy of repeated cycles of chemo-immunotherapy with thymosin alpha1 and interleukin-2 after intraperitoneal 5-fluorouracil delivery. *Cancer Immunol Immunother* 1999; 48: 172-178
57 Hirata K, Horie T. A prostaglandin E1 analog, OP-1206, alleviates 5-fluorouracil-induced injury of rat small intestine. *Res Commun Mol Pathol Pharmacol* 1999; 104: 243-251
58 Leblond J, Le Pessot F, Hubert-Buron A, Duclos C, Vuichoud J, Faure M, Breuillé D, Déchelotte P, Coëffier M. Chemotherapy-induced mucositis is associated with changes in proteolytic pathways. *Exp Biol Med* (Maywood) 2008; 233: 219-228
59 Alamir I, Boukhettala N, Aziz M, Breuillé D, Déchelotte P, Coëffier M. Beneficial effects of cathepsin inhibition to prevent chemotherapy-induced intestinal mucositis. *Clin Exp Immunol* 2010; 162: 298-305
60 Boukhettala N, Ibrahim A, Claeyssens S, Faure M, Le Pessot F, Vuichoud J, Lavoinne A, Breuillé D, Déchelotte P, Coëffier M. A diet containing whey protein, glutamine, and TGFbeta modulates gut protein metabolism during chemotherapy-induced mucositis in rats. *Dig Dis Sci* 2010; 55: 2172-2181
61 Soares PM, Lopes LO, Mota JM, Belarmino-Filho JN, Ribeiro RA, Souza MH. Methotrexate-induced intestinal mucositis delays gastric emptying and gastrointestinal transit of liquids in awake rats. Arq *Gastroenterol* 2011; 48: 80-85
62 Harsha WT, Kalandarova E, McNutt P, Irwin R, Noel J. Nutritional supplementation with transforming growth factor-beta, glutamine, and short chain fatty acids minimizes methotrexate-induced injury. *J Pediatr Gastroenterol Nutr* 2006; 42: 53-58
63 Sukhotnik I, Mogilner JG, Shteinberg D, Karry R, Lurie M, Ure BM, Shaoul R, Coran AG. Leptin accelerates enterocyte turnover during methotrexate-induced intestinal mucositis in a rat. *Cancer Biol Ther* 2009; 8: 899-906
64 Shiota A, Hada T, Baba T, Sato M, Yamanaka-Okumura H, Yamamoto H, Taketani Y, Takeda E. Protective effects of glycoglycerolipids extracted from spinach on 5-fluorouracil induced intestinal mucosal injury. *J Med Invest* 2010; 57: 314-320
65 Saegusa Y, Ichikawa T, Iwai T, Goso Y, Okayasu I, Ikezawa T, Shikama N, Saigenji K, Ishihara K. Changes in the mucus barrier of the rat during 5-fluorouracil-induced gastrointestinal mucositis. *Scand J Gastroenterol* 2008; 43: 59-65
66 Saegusa Y, Ichikawa T, Iwai T, Goso Y, Ikezawa T, Nakano M, Shikama N, Saigenji K, Ishihara K. Effects of acid antisecretory drugs on mucus barrier of the rat against 5-fluorouracil-induced gastrointestinal mucositis. *Scand J Gastroenterol* 2008; 43: 531-537
67 Kotani T, Nakagiri A, Murashima Y, Takeuchi K. Prophylactic effect of lafutidine against the adverse reaction induced in rat stomach by repeated administration of 5-fluorouracil. *Inflammopharmacology* 2007; 15: 203-208
68 Manzano M, Bueno P, Rueda R, Ramirez-Tortosa CL, Prieto PA, Lopez-Pedrosa JM. Intestinal toxicity induced by 5-fluorouracil in pigs: a new preclinical model. *Chemotherapy* 2007; 53: 344-355

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