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在线全文

电离辐射对肠道胆汁酸代谢的影响：甘氨熊脱氧胆酸辐射防护作用机制的探索*

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【摘要】 目的 放射性肠道损伤是肿瘤放射治疗过程中常见并发症，本研究旨在观察电离辐射对肠道胆汁酸短期变化的影响，并探索胆汁酸对肠道细胞辐射防护作用。**方法** 采用腹部每日照射2 Gy，连续照射4 d射线构建大鼠小肠损伤模型，并运用代谢组学技术对胆汁酸进行定量分析。将小肠上皮细胞IEC-6分为二甲基亚砜（dimethyl sulfoxide，DMSO）对照组（DMSO+0 Gy）、甘氨熊脱氧胆酸（glycoursodeoxycholic acid，GUDCA）实验组（GUDCA+0 Gy）、DMSO辐照组（DMSO+10 Gy）、GUDCA辐照组（GUDCA+10 Gy）。用CCK-8法检测细胞的存活率和细胞毒性；采用流式细胞术检测细胞的凋亡率；通过平板克隆形成实验检测细胞克隆形成率以及放射敏感性；利用Western blot检测与细胞死亡相关的蛋白表达水平。**结果** 大鼠小肠组织辐照后均出现典型放射性肠损伤表现，多种胆汁酸在辐照前后发生波动，其中GUDCA在辐照后3 d显著升高，而在辐照后7 d恢复至辐照前水平；与对照组相比较，20 μmol/L GUDCA作用24 h，辐照后细胞存活率高于DMSO组（P<0.05）；PARP、caspase-3、RIP、GSDMD蛋白表达量明显低于对照组（P<0.05）；20 μmol/L GUDCA作用24 h、48 h，辐照后细胞凋亡率低于DMSO组（P<0.05）；与DMSO对照组相比，GUDCA实验组在0、2、4和6 Gy剂量辐照下克隆形成能力均强于DMSO组（P<0.05），GUDCA组平均致死量D_0为6.374，DMSO组平均致死量D_0为4.572，与DMSO对照组相比，GUDCA药物组的D_0值增大，SER为0.717。**结论** 辐照大鼠腹部后，大鼠肠道胆汁酸代谢会产生显著变化，GUDCA可在一定程度上对肠道细胞产生辐射防护作用。

【关键词】 放射性肠炎 胆汁酸 甘氨熊脱氧胆酸 凋亡 辐射防护

Effects of Ionizing Radiation on Intestinal Bile Acid Metabolism: Mechanism of the Radioprotective Effect of Glycoursodeoxycholic Acid

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【Abstract】 Objective Radioactive intestinal injury is a common complication during radiotherapy of tumors. The aim of this study is to observe the effect of ionizing radiation on short-term changes in intestinal bile acids and to investigate the radioprotective effect of bile acids on intestinal cells. **Methods** A rat model of small intestinal injury was constructed by exposing the abdomen of the rats to daily irradiation at 2 Gy for 4 d in succession. The bile acids were quantified using metabolomics analysis. IEC-6 cells, a small intestinal epithelial cell line, were divided into a dimethyl sulfoxide (DMSO) control group receiving DMSO and 0 Gy irradiation, a glycoursodeoxycholic acid (GUDCA) experimental group receiving GUDCA and 0 Gy irradiation, a DMSO irradiation group receiving DMSO and 10 Gy irradiation, and a GUDCA irradiation group receiving GUDCA and 10 Gy irradiation. Cell viability and cytotoxicity was assessed by CCK-8 assay test. The apoptosis rate of cells was determined by flow cytometry. The colony formation rate and the radiosensitivity of the cells were determined by colony formation assay on solid media. The expression levels of proteins associated with cell death were determined using Western blot. **Results** After exposure to irradiation, the small intestine tissues of the rats showed typical radioactive intestinal injury. In addition, various bile acids showed fluctuation before and after irradiation. Among the bile acids, GUDCA increased significantly at 3 d after irradiation, but returned to the pre-irradiation level at 7 d after irradiation. Compared with the control group, after GUDCA treatment at 20 μmol/L for 24 h, the cell viability rate after irradiation was significantly higher than that of the DMSO group (P<0.05); the expression levels of the proteins, including PARP, caspase-3, RIP, and GSDMD, were significantly lower than those in the control group (P<0.05). After GUDCA treatment at 20 μmol/L for 24 h and 48 h, the cell apoptosis rate of the cells after irradiation was lower than that of the DMSO group (P<0.05). Compared with the DMSO control group, the colony formation ability of the GUDCA experimental group was stronger than that of the DMSO group after irradiation at 0, 2, 4,

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and 6 Gy (P<0.05). D_0, or the mean lethal dose, of the GUDCA group was 6.374, while that of the DMSO group was 4.572. Compared with the DMSO control group, the D_0 value of the GUDCA treatment group increased, and the sensitization enhancement ratio (SER) was 0.717. **Conclusion** After exposing the abdomen of rats to irradiation, the intestinal bile acid metabolism of the rats will change significantly, and GUDCA can produce radioprotective effects on intestinal cells to a certain extent.

【Key words】 Radiation enteritis Bile acids Glycoursodeoxycholic acid Apoptosis Radiation protection

癌症一直是人类面临的最大健康威胁之一，也是全球最主要的死亡原因之一[1]。放射疗法作为治疗癌症的3大主要手段之一，不仅可以在外科术前术后辅以杀死肿瘤细胞，降低转移风险，而且单独使用时也能治愈某些早期恶性肿瘤，如鼻咽癌、宫颈癌和前列腺癌等[2-6]。然而，放射疗法在杀死肿瘤细胞同时，健康细胞也可能受到损伤，从而导致相应并发症风险的增加，特别是由电离辐射造成的放射性肠道损伤受到了大家的关注[7]。

电离辐射可直接破坏DNA和蛋白质，损伤DNA双链并产生活性氧，引起脂质过氧化，导致组织损伤[8-10]。放射性肠道损伤是指高剂量放射线在治疗腹腔、盆腔肿瘤等时对靶组织附近的肠管的物理性损伤，分为急性和慢性两种类型。急性放射性肠道损伤在放疗期间或辐射暴露后的数小时至几周内发生，而慢性可能在放疗后的1～2年内出现，甚至潜伏期最长可达10年。放射性肠道损伤可导致肠道溃疡、狭窄甚至穿孔坏死等，严重时危及生命[11-12]。

尽管自发现X线以来，针对辐射损伤的对策研究已经开始，但由于缺乏特异性的检查指标和有效的治疗手段，导致我们对放射性肠道损伤的病理机制了解甚少。同时，放射性肠道损伤愈后效果仍然不尽如人意[13-14]。因此，深入探讨放射性肠道损伤发生和发展的机制，对于寻找有效的干预靶点和治疗药物具有重要意义。

胆汁酸是由肝脏中胆固醇合成的两性分子[15]。胆汁酸通过激活多种受体调节信号传导，促进脂质的乳化和吸收，调节体内代谢，维持肠道稳态。近10年研究表明，胆汁酸作为信号分子在调节炎症、癌症、心力衰竭、阿尔茨海默病和衰老等生理和病理过程中发挥重要作用[16-19]。这些研究表明，胆汁酸及其衍生物不仅在肝胆和消化系统中消化脂肪，也在其他系统中发挥作用。

射线可影响胆盐生物合成过程中的相关酶谱，导致肝脏中胆盐代谢的不确定性，炎症反应还可能引起回肠吸收不良，二者共同导致胆汁酸肠肝循环障碍，进而在患者结肠中产生过量胆汁盐，造成排便习惯改变并引发腹泻[20-22]。研究发现，肠腔内容物会加重肠道的辐射损伤，而单纯的胆汁混合食物会加剧这种损害，当识别出胆汁中相关有害成分时，采用排除或中和这些物质的治疗措施能够有效保护肠道免受辐射损伤[23]。我们前期研究表明，脱氧胆酸能有效治疗放疗引起的皮肤损伤，并证明了胆汁酸具有防治辐射损伤的作用[24]。基于这些发现，本研究进一步探索胆汁酸在肠道中的辐射防护作用，建立了大鼠放射性肠道损伤模型，分析胆汁酸代谢在其进展过程中的变化。

1 材料与方法

1.1 材料

1.1.1 实验动物和细胞

40只雄性SD大鼠，体质量200～210 g，购自四川大学实验动物中心〔生产许可证编号SCXK(川)2024-0026〕，本研究严格遵守徐州医科大学实验动物伦理委员会的要求(批准号：P20230417-001)；大鼠肠上皮细胞系IEC-6(上海中乔新舟生物)。

1.1.2 主要试剂

DMEM High Glucose培养基、胰酶(上海Viva Cell)；胎牛血清、青霉素-链霉素(美国Gibco)；甘氨熊脱氧胆酸(glycoursodeoxycholic acid, GUDCA)、二甲基亚砜(dimethyl sulfoxide, DMSO)均购自MCE公司；Cell Counting Kit-8试剂盒(美国APExBIO)；Annexin V-FITC/PI 细胞凋亡检测试剂盒、ECL化学发光超敏显色试剂盒(上海翌圣生物)；Tubulin、caspase-3、BAX、PARP、RIP、GSDMD抗体(美国Cell Signaling Technology)，HRP标记山羊兔二抗(英国Abcam)。

1.1.3 主要仪器

质谱仪、液相色谱仪(上海爱博才思)；X射线辐照仪(美国KUBTEC)、倒置显微镜(日本Olympus)；全波长酶标仪(美国Molecular Devices)、流式细胞仪(美国BD)。

1.2 实验方法

1.2.1 动物分组

18只大鼠随机分为对照组(0 Gy)、辐照组(8 Gy)，其中对照组6只，辐照组12只。

1.2.2 放射性肠道损伤动物模型构建

适应性喂养大鼠一周后进行辐照操作，大鼠麻醉后腹部辐照区域(4 cm×5 cm)暴露于射线，其他区域使用

3 cm厚的铅块屏蔽。使用辐照仪X射线直线加速器以1.7 Gy/min的固定剂量率对靶向区域进行8 Gy剂量的辐照(图1)。为了模拟临床放射治疗以及观察不同时间的组织学变化，采用每日辐照2 Gy，连续辐照4 d(Day 1至Day 4)的分割照射方案，并在Day 3、Day 7分别取6只大鼠小肠组织，部分用体积分数4%多聚甲醛固定进行组织病理学检查；部分用液相色谱-质谱联用(LC-MS)进行胆汁酸定量分析。对照组大鼠除不进行辐照外，其余处理方式与辐照组一致，在辐照前(Day 0)采集样品。

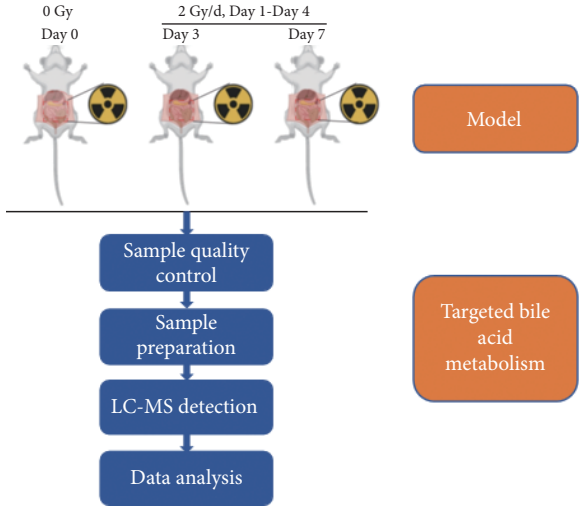

图 1　放射性肠道损伤动物模型构建方法

Fig 1　Establishment of the animal irradiation model

1.2.3　细胞培养和辐照条件

IEC-6细胞用含有10%胎牛血清、100 U/mL青霉素和100 μg/mL链霉素的DMEM培养基，在37 ℃、体积分数5%的CO_2培养箱中培养。采用科研专用X线辐照机照射细胞，直线加速器能量320 kV，源靶距为50 cm，射野大小为20 cm×20 cm，照射剂量为10 Gy，剂量率1.7 Gy/min。

1.2.4　细胞活性检测

选取对数生长期IEC-6细胞，以4×10^4 mL^{-1}接种到96孔板(100 μL/孔)。接种24 h后，加入浓度为1、5、10、20、40、60、80、100 μmol/L的GUDCA，以DMSO为对照组，每组6重复。培养24 h后分别用0 Gy和10 Gy剂量的X射线照射，照射24 h后每孔中加入10 μL CCK-8工作试剂，培养箱中孵育1 h后，在450 nm波长处测量光密度(optical density, OD)值，并以(实验组OD值−空白对照组OD值)/(对照组OD值−空白对照组OD值)×100%计算细胞存活率。

1.2.5　细胞凋亡检测

选取对数生长期IEC-6细胞，以4×10^4 mL^{-1}接种到6孔板中，2 mL/孔。培养24 h后弃培养基，分别加入含20 μmol/L GUDCA和20 μmol/L DMSO的细胞培养基，每组设3重复。培养24 h后分别用0 Gy和10 Gy剂量的X射线照射，分别在X射线处理后24 h、48 h用0.25%胰酶进行消化，4 ℃、800 r/min离心3 min，用PBS洗涤后将细胞重悬于100 μL结合缓冲液，用10 μL碘化丙啶和5 μL标记的膜联蛋白染色，室温避光孵育15 min后，用流式细胞仪检测细胞凋亡。

1.2.6　Western blot检测蛋白表达

使用RIPA裂解液提取细胞总蛋白，用BCA试剂盒对蛋白浓度进行定量。经SDS-PAGE凝胶电泳后转移至PVDF膜，5%脱脂奶粉室温封闭2 h后加入一抗caspase-3、BAX、PARP、RIP、GSDMD(1∶1 000)，4 ℃孵育过夜。加入山羊抗兔二抗(1∶10 000)，室温孵育2 h后用TBST溶液洗涤，以TUBULIN为内参。洗膜，用ECL化学发光超敏显色试剂盒曝光显影。使用Image J软件(美国NIH公司)对条带灰度值进行定量分析。

1.2.7　平板克隆形成实验

将对数生长期IEC-6细胞接种到6孔板中，细胞数量根据X射线照射剂量(0、2、4、6 Gy)分别为4 000、5 000、6 000、8 000细胞/孔。培养24 h后弃培养基，并分别加入含20 μmol/L GUDCA和DMSO的细胞培养基，每组3重复，24 h后分别用0、2、4、6 Gy剂量的X射线照射，并继续培养10 d。PBS清洗3次，用体积分数4%多聚甲醛固定15 min后，弃固定液，并用结晶紫染料染色30 min；PBS冲洗染色液后室温晾干，拍照并计算克隆形成率。并绘制“单击多靶模型”拟合细胞存活分数曲线图，计算放射增敏比(sensitization enhancement ratio, SER)，SER=DMSO对照组D_0/GUDCA药物组D_0。D_0为平均致死量。

1.3　统计学方法

采用SPSS 24.0软件进行统计学分析。所有实验重复至少重复3次，数据符合正态分布，定量数据以$\bar{x}\pm s$表示。两样本比较采用Dunnett-t检验，多样本比较采用单因素方差分析，P<0.05为差异有统计学意义。

2　结果

2.1　辐照对大鼠小肠组织形态以及胆汁酸的影响

与对照组大鼠小肠形态相比较，照射3 d后，大鼠小肠组织绒毛前端性出血坏死，正常结构遭到破坏，小肠腺体变圆且大规模增多，呈不规则排列(图2A、2B)；照射7 d后，大鼠小肠组织绒毛结构破坏散乱，大量细胞脱落，小肠腺体增多且不规则排列(图2C)。辐照组均出现典型的放射性肠损伤表现，表明放射性肠道损伤大鼠模型构建成功。对胆汁酸定量分析发现，多种胆汁酸在照射前后发生波动，其中GUDCA在照射后3 d显著升高，而在照射后7 d恢复至照射前水平(图2D)。结果表明，辐照能明显

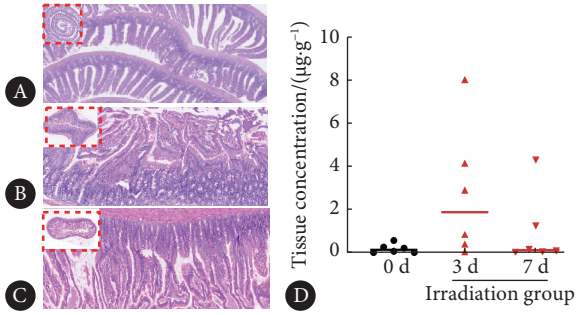

图 2 动物辐照模型照后小肠组织的形态变化和胆汁酸定量分析结果

Fig 2 Morphological changes in small intestinal tissues and quantitative analysis of bile acids after irradiation in an animal irradiation model

A, HE staining of the small intestine of unirradiated healthy rats (×100). B, HE staining of small intestine samples collected from rats 3 days after irradiation (×100). C, HE staining of small intestine samples collected from rats 7 days after irradiation (×100). D, Quantitative analysis of GUDCA metabolites by liquid chromatography-mass spectrometry (LC-MS) (n=6 per time piont; 0 d : control group).

增加GUDCA水平。接下来的实验将进一步研究GUDCA是否对小肠细胞具有辐射防护作用。

2.2 GUDCA对受辐射小肠上皮IEC-6细胞活性及损伤的保护作用

CCK-8检测结果显示，辐照前不同浓度GUDCA对IEC-6活性没有明显影响(P>0.05，图3A)；在10 Gy照射剂量下，1、5、10、20、40 μmol/L GUDCA对IEC-6具有一定辐射防护作用，而60、80、100 μmol/L GUDCA浓度组IEC-6活性明显降低(P<0.05，图3B)。根据以上实验结果，本研究选用20 μmol/L GUDCA进行后续实验。

2.3 GUDCA降低辐射导致的小肠上皮IEC-6细胞凋亡

与对照组相比较，辐照组细胞均出现明显细胞凋亡(P<0.05)，细胞经20 μmol/L GUDCA预处理后，辐照引起的细胞凋亡率明显降低(P<0.05)(图4)。

2.4 GUDCA对辐照小肠上皮IEC-6细胞死亡相关蛋白表达的影响

结果发现，辐照前后GUDCA组的PARP、BAX、RIP、caspase-3、GSDMD的表达水平均低于DMSO组(P<0.05)，且对照组上述蛋白在辐照后表达量明显增加，而GUDCA组辐照后表达量增加不明显(图5)。结果表明，GUDCA可能通过减少IEC-6细胞凋亡、坏死、焦亡等多种方式提高IEC-6细胞的辐射耐受性。

2.5 GUDCA对辐射小肠上皮IEC-6细胞克隆形成的影响

结果显示，DMSO对照组IEC-6细胞随着辐照剂量的增加，其克隆能力逐渐减弱；当IEC-6细胞接受20 μmol/L GUDCA处理后，其克隆形成能力显著增强(P<0.05，

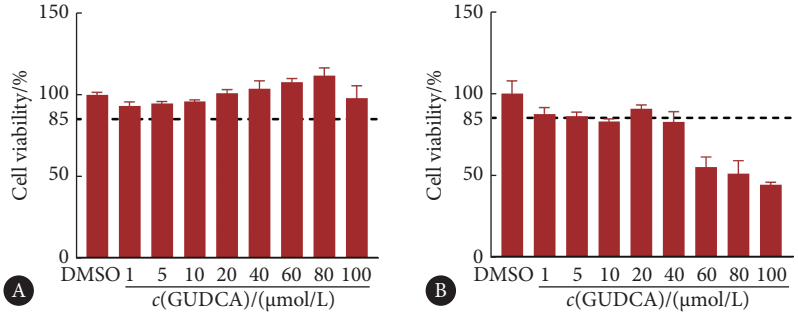

图 3 CCK-8检测GUDCA联合电离辐射对IEC-6细胞活性的影响

Fig 3 Effect of GUDCA combined with ionizing radiation on IEC-6 cell activity and cytotoxicity assessed by CCK-8 assay

A, Effect of GUDCA combined with 0 Gy irradiation on IEC-6 cell activity (n=6). B, Effect of GUDCA combined with 10 Gy irradiation on IEC-6 cell activity (n=6).

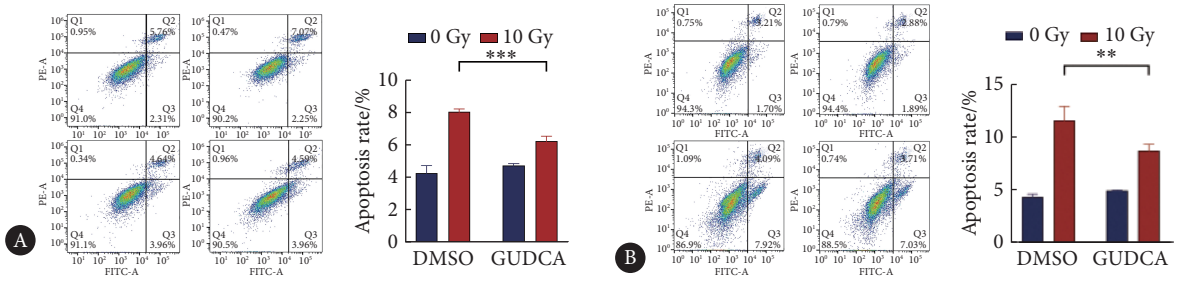

图 4 GUDCA联合电离辐射对小肠上皮IEC-6细胞凋亡水平影响

Fig 4 Effect of GUDCA combined with ionizing radiation on the apoptosis level of small intestinal epithelial IEC-6 cells

A, Flow cytometry was conducted to determine the apoptosis rate of IEC-6 cells under two drug treatments after 10 Gy X-ray irradiation for 24 h. B, Flow cytometry was conducted to determine the apoptosis rate of IEC-6 cells under two drug treatments after 10 Gy X-ray irradiation for 48 h. ** P<0.01, *** P<0.001. n=3.

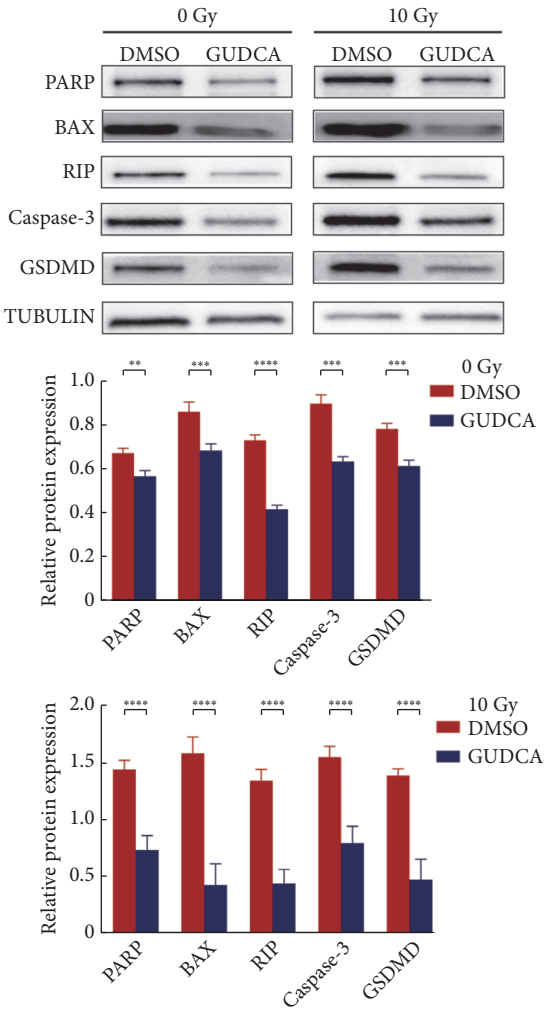

图 5　GUDCA联合X射线对IEC-6细胞死亡相关蛋白表达的影响

Fig 5　Effect of GUDCA combined with X-rays on the expression of IEC-6 cell death-related proteins

** P<0.01, **** P<0.001, **** P<0.000 1. n=3.

图6A）。“单击多靶模型”拟合细胞存活分数曲线图显示，GUDCA组平均致死量D_0为6.374，DMSO组平均致死量D_0为4.572。与DMSO对照组相比，GUDCA药物组的D_0值增大，SER为0.717（图6B）。

3　讨论

放射治疗是腹部和盆腔肿瘤的重要治疗手段之一，但其带来的副作用不可忽视[25-26]。放射性肠炎的发生涉及复杂的病理生理机制，包括肠道生理结构的损伤、肠道免疫机制的应激反应以及肠道微生物区系的变化和影响等[27]。肠道微生物及其代谢产物在放射性肠损伤中发挥重要作用，但目前可供选择的治疗方式仍然有限。因此，探寻新的治疗药物显得尤为重要。

本研究针对几种波动较大的胆汁酸进行了细胞层面的研究，经过一系列实验验证，发现GUDCA对肠道损伤具有一定的辐射防护作用。同时，研究表明GUDCA能促进肠道DNA损伤修复、抑制细胞凋亡、坏死及焦亡，进一步证实了GUDCA在辐射防护中的作用。

辐射不仅会破坏细胞内稳态，还可激活促炎细胞因子[28-29]。炎性小体在感受到细胞内压力变化时，会触发Caspase-1酶原的裂解，进而激活促炎细胞因子IL-1和IL-18[30-31]，并激活GSDMD以诱导焦亡[32]。基于此，笔者推测GUDCA可以改善炎症因子的释放，减轻炎性小体的激活，从而减缓细胞凋亡。同时GUDCA还可调节肠道菌群丰度，增加有益菌数量，并在一定程度上改变胆汁酸代谢谱，影响胆汁酸肝肠循环，减轻回肠胆汁酸盐蓄积压力，从而减轻肠道炎症[33]。

本实验存在一定的局限性。首先，尚缺乏对GUDCA具体保护机制的深入研究，未来可结合基因转录组学进一步探索。其次，在辐射诱导的正常组织损伤的背景下，细胞内胆汁酸水平和全身胆汁酸浓度之间的关系仍然不清楚，需要进行更深入的机制研究。另外，目前尚不清楚外源性游离胆汁酸是否影响内源性游离胆汁酸的表达和分泌，以及如何影响。这一问题对开发体外游离胆汁酸作为一种新型放射防护药物至关重要，课题组计划在今后的研究中开展药理和药效学实验。同时，由于缺乏临

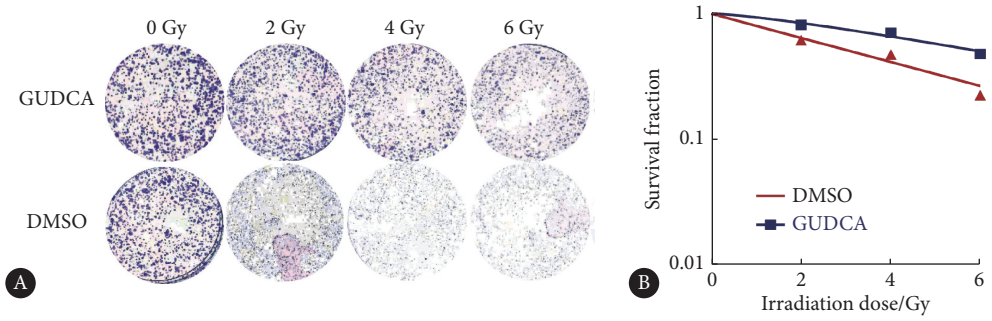

图 6　GUDCA联合电离辐射对IEC-6细胞克隆形成以及克隆形成率的影响

Fig 6　Effect of GUDCA combined with ionizing radiation on the colony formation as well as the colony formation rate of IEC-6 cells

A, Colony formation of IEC-6 cells under different irradiation dose conditions with two drug treatments. B, IEC-6 cell survival curves. n=3.

床试验数据,尚未在体内进行相关实验,因此游离胆汁酸作为辐射防护药物的最佳剂量仍未确定。计划在后续研究中对大鼠进行灌胃或者灌肠实验,以获得确切体内研究数据。尽管如此,本研究仍然为预防放射治疗的肠道副作用以及治疗意外辐射暴露的受害者提供了一种新的和有前途的治疗选择。

综上所述,本研究展示了大鼠肠道经辐射后各种胆汁酸的短期变化,通过细胞层面的研究证明了GUDCA具有一定的辐射防护作用,作为一种内源性产物,GUDCA有望在未来的临床中得到验证。

* * *

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Author Contribution DAI Jun is responsible for conceptualization, formal analysis, methodology, software, visualization, and writing--original draft. GAO Yi is responsible for investigation, project administration, and writing--review and editing. WANG Jian is responsible for resources and supervision. ZHANG Shuyu is responsible for data curation, conceptualization, and supervision. LIU Pengfei is responsible for conceptualization and funding acquisition. All authors consented to the submission of the article to the Journal. All authors approved the final version to be published and agreed to take responsibility for all aspects of the work.

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