论著·基础医学

SGLT-2表达随高糖腹膜透析液的浓度与时间递增而加重腹膜纤维化、炎症及血管病变

蔡青利[1],王可樊[2],贺媛媛[1],何智尧[2],罗亚东[1],陈 佳[2],蔡明玉[2] 陆军军医大学(第三军医大学)大坪医院:[1]战伤救治前沿技术研究室,[2]肾脏内科,重庆

[摘要] **目的** 腹膜透析(peritoneal dialysis,PD)是终末期肾脏病的重要替代治疗方式,但长期高糖腹透液暴露可诱发腹膜纤维化、炎症及血管病变,导致超滤衰竭。钠-葡萄糖协同转运蛋白2(sodium-glucose cotransporter 2,SGLT-2)在腹膜组织中表达,可能参与高糖诱导的腹膜损伤。本研究旨在观察SGLT-2在PD患者及高糖腹透液小鼠模型腹膜组织中的表达定位与变化规律,分析其与腹膜病理损伤的定量关系,为SGLT-2作为腹膜损伤潜在生物标志物及后续干预靶点研究提供实验依据。**方法** ①选取2024年12月至2025年12月于陆军军医大学大坪医院肾脏内科首次行腹膜透析置管术的终末期肾脏病患者25例,采用免疫组织化学染色和免疫荧光双染检测PD患者腹膜组织中SGLT-2的表达与定位。②选取6~8周龄SPF级C57BL/6雄性小鼠60只,体质量(22.5±1.5)g,构建7.00%葡萄糖腹透液诱导的腹膜损伤模型。取诱导1周小鼠的腹膜组织,采用免疫组织化学染色和免疫荧光双染检测SGLT-2的表达与定位。分别于第1、4、8、12周收集腹膜组织,采用HE染色评估腹膜病理损伤,免疫组织化学染色观察SGLT-2表达的时间依赖性变化。构建2.50%、4.25%和7.00%葡萄糖腹透液小鼠模型,干预12周后取材,采用HE染色评估腹膜病理损伤,免疫组织化学染色观察SGLT-2表达的浓度依赖性变化。Spearman相关分析SGLT-2表达与腹膜组织病理损伤程度(间皮下层厚度、急慢性炎症评分、血管病变评分)之间的相关性。③构建30 mmol/L高糖刺激下人腹膜间皮细胞株(human peritoneal mesothelial cells,HPMCs)和人脐静脉内皮细胞株(human umbilical vein endothelial cells,HUVECs)模型,RT-qPCR检测SGLT-2 mRNA表达。**结果** ①SGLT-2在PD患者腹膜组织中主要表达于腹膜间皮细胞和血管内皮细胞。②SGLT-2在PD小鼠腹膜组织中主要表达于腹膜间皮细胞和血管内皮细胞。7.00%高糖腹透液诱导显著上调小鼠腹膜组织SGLT-2表达,且随着诱导时间延长逐渐增加,SGLT-2表达量在12周时达到高峰,与对照组比较,8周组、12周组SGLT-2阳性细胞率均显著升高($P<0.000\ 1$),且12周组高于8周组($P=0.013\ 3$)。随着腹透液葡萄糖浓度的升高,小鼠腹膜组织SGLT-2表达水平逐渐上调,12周时7.00%高糖腹透液小鼠的腹膜组织SGLT-2表达水平较4.25%高糖腹透液显著升高($P<0.000\ 1$);HE染色显示腹膜间皮下层厚度、炎症及纤维化程度随浓度升高而加重。相关性分析显示,SGLT-2表达水平与间皮下层厚度($r=0.766\ 5$,$P<0.000\ 1$)、慢性炎症评分($r=0.921\ 0$,$P<0.000\ 1$)和血管病变评分($r=0.882\ 9$,$P<0.000\ 1$)均呈显著正相关,而与急性炎症评分无显著相关性($r=0.223\ 9$,$P=0.297\ 3$)。③体外实验表明高糖刺激可显著上调HPMCs与HUVECs中SGLT-2 mRNA及蛋白表达,24 h时HPMCs、HUVECs表达达到峰值($P<0.001$)。**结论** 高糖微环境可上调腹膜SGLT-2表达,其水平与腹膜炎症、纤维化及血管病变密切相关。SGLT-2可能参与高糖诱导的腹膜损伤过程,有望作为腹膜损伤评估的潜在生物标志物及干预靶点。

[关键词] 腹膜透析;钠-葡萄糖协同转运蛋白2;腹膜纤维化;炎症;高糖

[中图法分类号] R341;R459.5;R572.02 [文献标志码] A

[基金项目] 重庆市科卫联合医学科研项目面上项目(2026MSXM110)

[通信作者] 蔡明玉,E-mail:66597853@qq.com

2097-0927/Copyright © 2026, 陆军军医大学(第三军医大学)。这篇开放获取文章遵循 CC BY 许可协议 (https://creativecommons.org/licenses/by/4.0/)

引用格式:蔡青利,王可樊,贺媛媛,等.SGLT-2表达随高糖腹膜透析液的浓度与时间递增而加重腹膜纤维化、炎症及血管病变[J].陆军军医大学学报,2026,48(20):2897-2907.DOI:10.16016/j.2097-0927.202607051.

Citation:Cai Q L,Wang K F,He Y Y,*et al*. SGLT-2 expression increases with glucose concentration and duration of high-glucose peritoneal dialysis solution,exacerbating peritoneal fibrosis, inflammation, and vascular lesions [J]. J Army Med Univ, 2026, 48 (20) : 2897-2907. DOI: 10.16016/j.2097-0927.202607051.

SGLT-2 expression increases with glucose concentration and duration of high-glucose peritoneal dialysis solution, exacerbating peritoneal fibrosis, inflammation, and vascular lesions

Cai Qingli[1], Wang Kefan[2], He Yuanyuan[1], He Zhiyao[2], Luo Yadong[1], Chen Jia[2], Cai Mingyu[2] [1]Laboratory of Frontier Technology for Combat Casualty Care, [2]Department of Nephrology, Daping Hospital, Army Medical University (Third Military Medical University), Chongqing, China

[**Abstract**] Objective Peritoneal dialysis (PD) is an important renal replacement therapy for end-stage renal disease, but long-term exposure to high-glucose dialysate can induce peritoneal fibrosis, inflammation, and vascular lesions, leading to ultrafiltration failure. Sodium-glucose cotransporter 2 (SGLT-2) is expressed in peritoneal tissues and may participate in high glucose-induced peritoneal injury. This study aimed to investigate the expression, localization, and dynamic changes of SGLT-2 in peritoneal tissues from PD patients and a mouse model of high-glucose peritoneal dialysis solution, and to analyze the quantitative relationship between SGLT-2 expression and peritoneal pathological injury, thereby providing experimental evidence for SGLT-2 as a potential biomarker of peritoneal injury and for a subsequent intervention target. Methods ① Twenty-five patients with end-stage renal disease who underwent peritoneal dialysis catheterization for the first time in Department of Nephrology of our hospital between December 2024 and December 2025 were enrolled. Immunohistochemistry (IHC) and immunofluorescence double staining were used to detect the expression and localization of SGLT-2 in peritoneal tissues of PD patients. ② Sixty SPF male C57BL/6 mice [6 to 8 weeks old, weighing (22.5±1.5) g] were subjected to establish a peritoneal injury model induced by 7.00% glucose peritoneal dialysis solution. Peritoneal tissues from mice after 1 week of induction were collected, and IHC and immunofluorescence double staining were employed to detect the expression and localization of SGLT-2. Peritoneal tissues were harvested at weeks 1, 4, 8, and 12, respectively; HE staining was performed to evaluate peritoneal pathological injury, and IHC was applied to observe time-dependent changes in SGLT-2 expression. Mouse models treated with 2.50%, 4.25%, and 7.00% glucose peritoneal dialysis solutions were constructed. After 12 weeks of intervention, peritoneal tissue samples were collected; HE staining and IHC were carried out to observe peritoneal pathological injury and concentration-dependent changes in SGLT-2 expression. Spearman correlation analysis was utilized to analyze the correlation between SGLT-2 expression and the degree of peritoneal histopathological injury (submesothelial layer thickness, acute and chronic inflammation scores, and vascular lesion score). ③ Human peritoneal mesothelial cells (HPMCs) and human umbilical vein endothelial cells (HUVECs) stimulated with 30 mmol/L high glucose were established, and RT-qPCR was used to detect the mRNA expression of SGLT-2. Results ① SGLT-2 was mainly expressed in peritoneal mesothelial cells and vascular endothelial cells in peritoneal tissues of PD patients. ② SGLT-2 was mainly expressed in peritoneal mesothelial cells and vascular endothelial cells in peritoneal tissues of PD mice. Induction with 7.00% high-glucose peritoneal dialysis solution significantly upregulated SGLT-2 expression in mouse peritoneal tissues, which gradually increased with the prolongation of induction time and reached a peak at 12 weeks. Compared with the control group, the percentage of SGLT-2-positive cells was significantly increased in the 8- and 12-week groups (P<0.000 1), and was higher in the 12-week group than in the 8-week group (P=0.013 3). With the increase of glucose concentration in peritoneal dialysis solution, the expression level of SGLT-2 in mouse peritoneal tissue was gradually upregulated. At 12 weeks, SGLT-2 expression in the peritoneal tissue of mice treated with 7.00% high-glucose peritoneal dialysate was significantly higher than that in mice treated with 4.25% high-glucose peritoneal dialysate (P<0.000 1). HE staining showed that the thickness of the submesothelial layer, inflammation, and fibrosis of the peritoneum aggravated with the increase of concentration. Correlation

analysis revealed that the expression level of SGLT-2 was significantly positively correlated with submesothelial layer thickness (r=0.766 5, P<0.000 1), chronic inflammation score (r=0.921 0, P<0.000 1), and vascular lesion score (r=0.882 9, P<0.000 1), but not significantly correlated with acute inflammation score (r=0.223 9, P=0.297 3). ③ *In vitro* experiments demonstrated that high-glucose stimulation significantly upregulated the mRNA and protein expression of SGLT-2 in HPMCs and HUVECs, with peak expression at 24 h. **Conclusion** High-glucose microenvironment upregulates the expression of peritoneal SGLT-2, and its level is closely associated with peritoneal inflammation, fibrosis, and vascular lesions. SGLT-2 may be involved in the process of high-glucose-induced peritoneal injury and is expected to serve as a potential biomarker for peritoneal injury assessment and as a therapeutic target.

[**Key words**] peritoneal dialysis; sodium-glucose cotransporter 2; peritoneal fibrosis; inflammation; high glucose

Supported by the General Joint Medical Research Project of Chongqing Municipal Science and Technology Bureau and Chongqing Municipal Health Commission (2026MSXM110). Corresponding author: Cai Mingyu, E-mail: 66597853@qq.com

腹膜透析(peritoneal dialysis,PD)是终末期肾脏病(end-stage renal disease,ESRD)重要的肾脏替代治疗方式,具有保护残余肾功能、血流动力学稳定、操作简便和医疗成本较低等优势[1]。我国PD患者数量已位居全球首位,且在全球PD患者中的占比持续增长[2]。鉴于PD具有较高的经济可及性和可负担性,国际腹膜透析协会(International Society for Peritoneal Dialysis, ISPD)推荐将其作为一种可负担的生命维持肾脏替代治疗方案[3]。然而,长期暴露于高糖腹透液可诱发腹膜炎症、纤维化、血管新生及超滤功能衰竭,是导致PD技术失败的核心原因[1,4],亟需明确其分子机制并探索有效干预靶点。

钠-葡萄糖协同转运蛋白2(sodium-glucose cotransporter 2,SGLT-2)是介导肾脏近端小管葡萄糖重吸收的关键转运体。SGLT-2除表达于肾脏外,亦在腹膜间皮细胞及血管内皮细胞中表达,并参与局部葡萄糖代谢的调控[5]。Schricker等[6]在临床研究中证实PD患者腹膜SGLT-2表达随透析龄延长逐渐升高,包囊性腹膜硬化症患者SGLT-2表达显著增强。姚登湖等[7]综述了SGLT-2抑制剂在腹膜透析中的研究进展,指出SGLT-2在人腹膜间皮细胞中表达,可能参与腹膜纤维化与超滤衰竭的发生,并通过抑制炎症和氧化应激发挥腹膜保护作用;Minutolo等[8]概述了SGLT-2抑制剂在透析患者中的应用前景,并指出该类药物在腹膜损伤治疗中具有潜在价值。然而,SGLT-2在PD相关腹膜损伤中的时空表达特征、与多种病理损伤指标的定量关系及其在高糖诱导的腹膜间皮细胞和血管内皮细胞中的表达调控规律尚未完全阐明。尽管已有研究证实SGLT-2在腹膜组织中表达,且SGLT-2抑制剂在动物模型中显示出腹膜保护作用,但以下问题尚未解决:①SGLT-2在高糖腹膜损伤过程中表达的动态变化规律(时间依赖性与浓度依赖性)缺乏系统描述;②SGLT-2表达水平与腹膜多种病理损伤指标(间皮下层厚度、急慢性炎症、血管病变等)的定量关系尚未明确;③高糖对腹膜间皮细胞和血管内皮细胞SGLT-2表达的影响缺乏体外验证。本研究从临床标本、动物模型及体外细胞实验3个层面,系统阐明上述问题,为SGLT-2作为腹膜损伤评估的生物标志物及干预靶点提供了实验依据。

1 材料与方法

1.1 主要试剂与细胞

SGLT-2抗体和E-cadherin抗体购自英国Abcam公司;FITC标记山羊抗兔IgG(二抗)和Cy3标记山羊抗鼠IgG(二抗)购自碧云天生物技术有限公司;2.50%葡萄糖腹膜透析液购自百特医疗用品有限公司;50%葡萄糖注射液购自四川科伦药业股份有限公司;TRIzol试剂和SYBR Green qPCR Set购自葆光生物公司。人腹膜间皮细胞株(human peritoneal mesothelial cells,HPMCs)购自上海雅吉生物科技有限公司,人脐静脉内皮细胞株(human umbilical vein endothelial cells,HUVECs)购自赛百慷(上海)生物技术股份有限公司。

1.2 PD患者腹膜组织

选取2024年12月至2025年12月于陆军军医大学大坪医院肾脏内科首次行腹膜透析置管术的ESRD患者25例。纳入标准:①符合ESRD诊断标准且年龄>18岁;②首次行腹膜透析置管术。排除标准:①既往有腹部手术史者;②合并急性感染、恶性肿瘤或严重凝血功能障碍者;③术中活检组织取材不足或严重损伤者。本研究经陆军特色医学中心伦理委员会批准[医研伦审(2024)第237号]。所有患者由具有丰富经

验的腹膜透析置管术医师在常规手术操作下完成[9]。取下的腹膜组织立即用4%多聚甲醛溶液固定,常规脱水、石蜡包埋,3 μm厚连续切片,行免疫组织化学染色及免疫荧光双染检查。

1.3 动物实验

6~8周龄SPF级C57BL/6雄性小鼠60只,体质量(22.5±1.5)g,购自斯贝福(北京)生物技术有限公司。小鼠饲养于陆军特色医学中心动物实验中心,环境温度22~25 ℃,湿度50%~60%,昼夜节律12 h/12 h,自由摄食饮水,定期更换垫料和笼具。本研究经陆军军医大学实验动物福利伦理委员会审查批准(AMUWEC20237100),所有动物实验操作遵循机构实验动物福利伦理要求。

1.4 动物分组、模型建立及标本处理

采用随机数字表法,由不参与实验操作的人员生成随机序列,将60只小鼠按1∶1∶1∶3比例随机分为4组:对照组、2.50%PD组、4.25%PD组、7.00%PD组。其中,对照组、2.50%PD组和4.25%PD组小鼠各10只;7.00%PD组小鼠30只。对照组不予干预;2.50%、4.25%和7.00%PD组每日腹腔注射相应葡萄糖浓度腹透液0.1 mL/g;7.00%高糖腹透液由2.50%葡萄糖腹膜透析液(90.5 mL)与50%葡萄糖注射液(9.5 mL)混合配制,总体积为100 mL。本研究选用7.00%高糖腹透液建立小鼠模型[10-13],主要基于以下考虑:临床PD患者腹膜长期暴露于高糖环境,7.00%高糖浓度可在12周内快速诱导明显的腹膜纤维化与血管新生[14],便于观察SGLT-2的动态表达变化及后续干预效果。既往研究已证实,该浓度能有效改变腹膜通透性等功能。近年来,高糖腹透液诱导的腹膜损伤模型仍被广泛用于探索腹膜纤维化、炎症及血管病变的分子机制[10]。此外,7.00%PD组小鼠分别于建模后第1、4、8和12周麻醉后处死并取壁层腹膜组织,设定为对照组、1周组、4周组、8周组和12周组,每组各6只,对照组不予干预。壁层腹膜组织取1/2置于液氮中速冻,-80 ℃保存用于RT-qPCR;1/4经OCT包埋后液氮快速冷冻15 min,制备冰冻切片;其余1/4经4%多聚甲醛固定24 h,常规脱水处理后用石蜡包埋,用于HE染色、免疫组织化学染色及免疫荧光检测。

1.5 细胞培养与高糖刺激

HUVECs、HPMCs培养于含10%胎牛血清(VivaCell,重庆)及1%青霉素-链霉素双抗的DMEM培养基(Gibco,美国)中,置于37 ℃、5%CO_2恒温培养箱中培养。HPMCs和HUVECs均为永生化的细胞株,设定分组为:对照组、24 h组和48 h组。对照组不予干预,24 h组和48 h组给予30 mmol/L葡萄糖溶液刺激,该浓度的选择参考了既往高糖诱导腹膜间皮细胞及内皮细胞损伤的体外研究[11],可模拟PD患者腹腔内高糖微环境,并能有效诱导细胞SGLT-2表达变化,并分别刺激0、24和48 h收集细胞,提取总RNA用于后续检测。

1.6 实验方法

1.6.1 HE染色检测腹膜组织病理学改变及损伤评分 石蜡切片常规脱蜡至水,HE染色,中性树胶封片。光学显微镜下观察腹膜形态。采用数字病理阅片软件(深圳市生强科技有限公司,版本:DPVIEW V2.0.4.1118)测量腹膜厚度,每张切片随机选取5个高倍视野(high-power field,HPF;×400),并取均值。参照文献[15-16]的病理评分标准进行评估,具体如下。急性炎症按中性粒细胞浸润程度评分:0分为无中性粒细胞浸润;1分为1个/HPF;2分为2~5个/HPF;3分为>5个/HPF。慢性炎症按圆形细胞浸润程度评分:0分为无圆形细胞浸润;1分为1~5个/HPF;2分为6~20个/HPF;3分为>20个/HPF。血管病变评分标准为:0分为无玻璃样变血管病变;1分为内皮下玻璃样物质厚度≤7 μm;2分为内皮下玻璃样物质厚度>7 μm且无管腔变形或狭窄;3分为出现管腔变形或狭窄;4分为管腔闭塞。

1.6.2 免疫组织化学染色检测腹膜组织SGLT-2蛋白表达 石蜡切片脱蜡、水化,置于3%H_2O_2室温孵育20 min,以阻断内源性过氧化物酶的表达;随后采用柠檬酸盐缓冲液进行抗原修复,95 ℃孵育15 min;山羊血清封闭15 min后,滴加SGLT-2一抗(1∶200),4 ℃孵育过夜(16~18 h)。PBS洗涤后滴加Dako REAL EnVision HRP(Rabbit/Mouse)通用二抗(Agilent Dako,美国),室温孵育1 h;DAB显色,苏木素复染,常规脱水、透明、中性树胶封片。每张切片随机选取5个HPF(×400),计算SGLT-2阳性细胞率,公式如下:阳性细胞率=阳性细胞数/总细胞数×100%。

1.6.3 免疫荧光双染检测腹膜组织SGLT-2与E-cadherin共定位 石蜡切片经脱蜡、水化、抗原修复、封闭后,滴加SGLT-2(1∶200)与E-cadherin(1∶100)混合一抗,4 ℃孵育过夜(16~18 h)。PBS洗涤后滴加FITC/CY3标记二抗(1∶500),室温避光孵育1 h;DAPI染核,甘油封片,荧光显微镜观察并采集图像。

1.6.4 RT-qPCR检测腹膜组织SGLT-2 mRNA表达 采用TRIzol法提取腹膜组织总RNA,测定RNA浓度

及纯度后,使用葆光生物公司的逆转录试剂盒,进行逆转录合成cDNA。RT-qPCR反应体系总体积为20 μL,包括:cDNA 2 μL、上游引物0.5 μL、下游引物0.5 μL、SYBR Green 10 μL和ddH_2O 7 μL。引物由生工生物工程(上海)股份有限公司合成,引物序列如下。SGLT-2:上游5′-GGTCTTCAGTCTCCGGCATAG-3′,下游5′-CCTGGGGCTCATTCATCTCC-3′;GDPAH:上游5′-CTTTTGCGTCGCCAGCCGAG-3′,下游5′-GGCGCCC-AATACGACCAAATCC-3’。反应条件为:95 ℃预变性3 min;95 ℃变性10 s,60 ℃退火/延伸30 s,共40个循环。采用$2^{-\Delta\Delta Ct}$法计算目标基因的相对表达量,并以GAPDH为内参基因进行归一化。

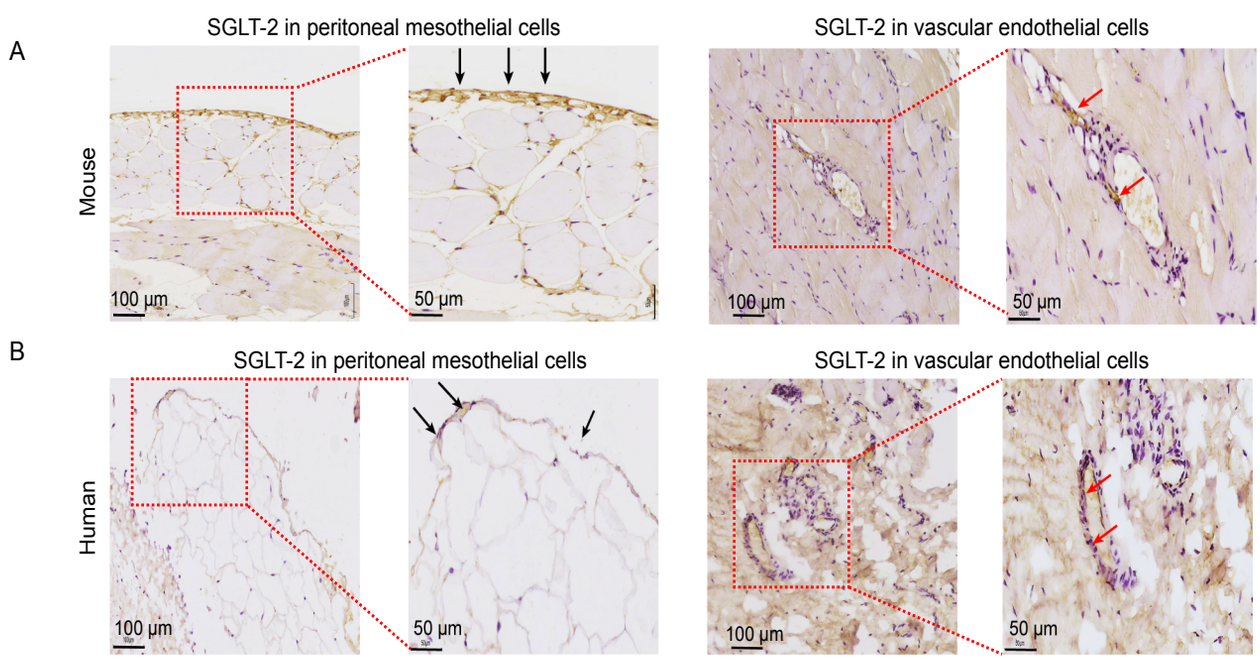
1.7　统计学分析

采用GraphPad Prism软件(11.0.0)进行统计分析。独立样本间的差异采用单因素方差分析(one-way ANOVA)进行比较;当总体差异具有统计学意义时,采用Tukey多重比较检验进行组间两两比较。SGLT-2表达量与病理损伤评分之间的单因素相关性采用Spearman秩相关分析,并在GraphPad Prism软件中完成。进一步采用R软件ppcor包进行偏Spearman相关分析,以评估控制其他病理损伤评分后SGLT-2表达量与目标病理损伤评分之间的相关性。所有检验为双侧检验,以$P<0.05$为差异具有统计学意义。

2　结果

2.1　SGLT-2主要定位于PD小鼠和患者腹膜间皮细胞及血管内皮细胞

为明确SGLT-2在腹膜组织中的表达部位,本研究对PD小鼠及患者腹膜组织进行免疫组织化学染色,阳性染色呈棕黄色。结果显示,SGLT-2在两种腹膜组织中均有表达,主要位于腹膜间皮细胞的细胞膜和细胞质,血管内皮细胞胞质中亦可见明显表达(图1A、B)。进一步采用免疫荧光双染对其细胞定位进行验证,SGLT-2用绿色荧光(FITC)标记,腹膜间皮细胞标志物E-cadherin和血管内皮细胞标志物CD31用红色荧光(Cy3)标记。结果显示,SGLT-2绿色荧光信号与间皮细胞标志物E-cadherin红色荧光信号共定位,同时与血管内皮细胞标志物CD31红色荧光信号亦呈共定位(图1C、D)。上述结果提示,SGLT-2在腹膜组织中主要表达于腹膜间皮细胞和血管内皮细胞,说明其可能参与腹膜间皮细胞及微血管内皮相关的病理生理过程。

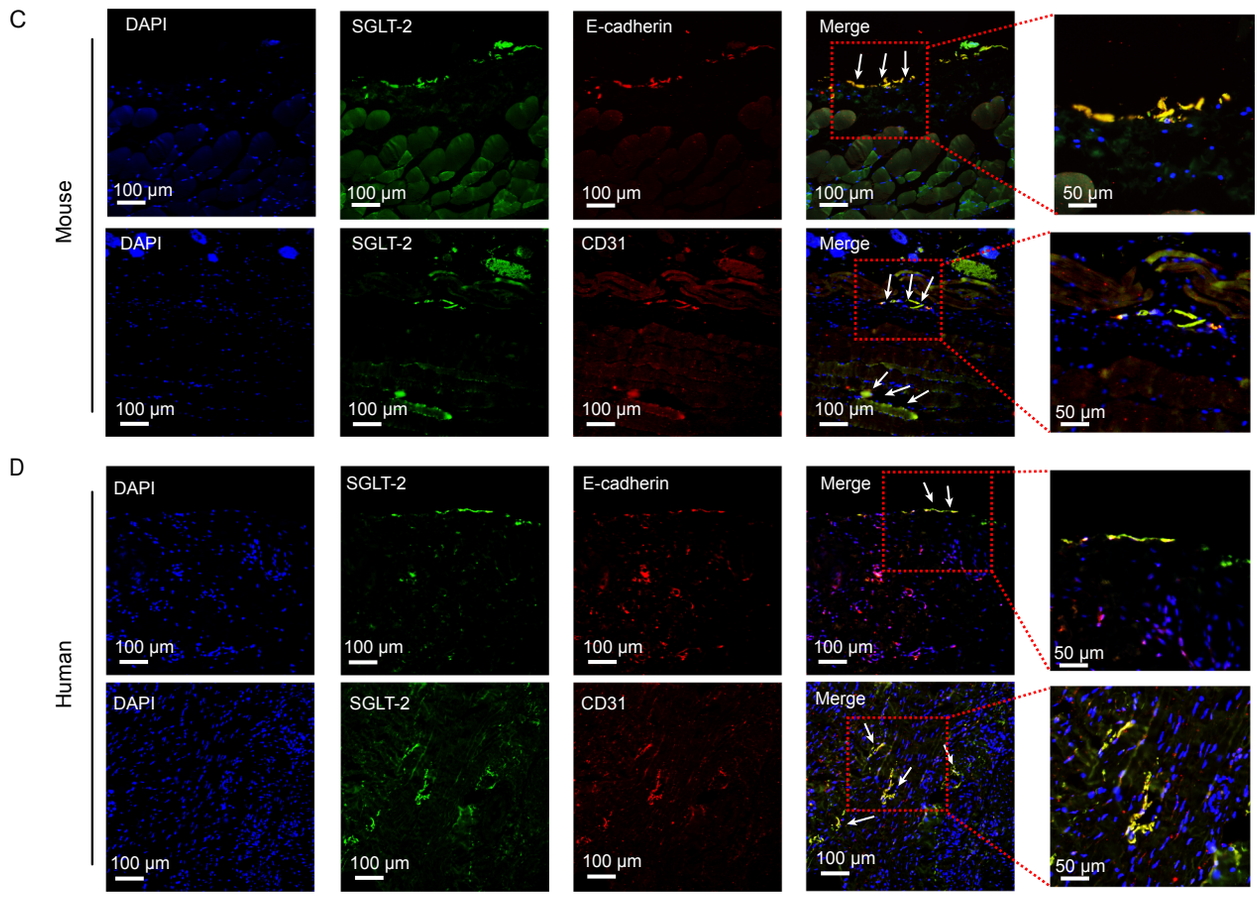


A and B: Representative images of immunohistochemistry (IHC) of SGLT-2 expression in peritoneal tissues of PD mice (A) and patients (B), with black arrows indicating mesothelial cells and red arrows indicating vascular endothelial cells

图1　SGLT-2在PD小鼠和患者腹膜组织中的表达定位

Figure 1　Expression and localization of SGLT-2 in peritoneal tissues of PD mice and patients

(图1C、D续下页)



C and D: Representative images of immunofluorescence double staining verifying colocalization of SGLT-2 with cellular markers in peritoneal tissues of PD mice (C) and patients (D), with white arrows indicating yellow signals representing the colocalization of SGLT-2 with E-cadherin or CD31

续图1 SGLT-2在PD小鼠和患者腹膜组织中的表达定位

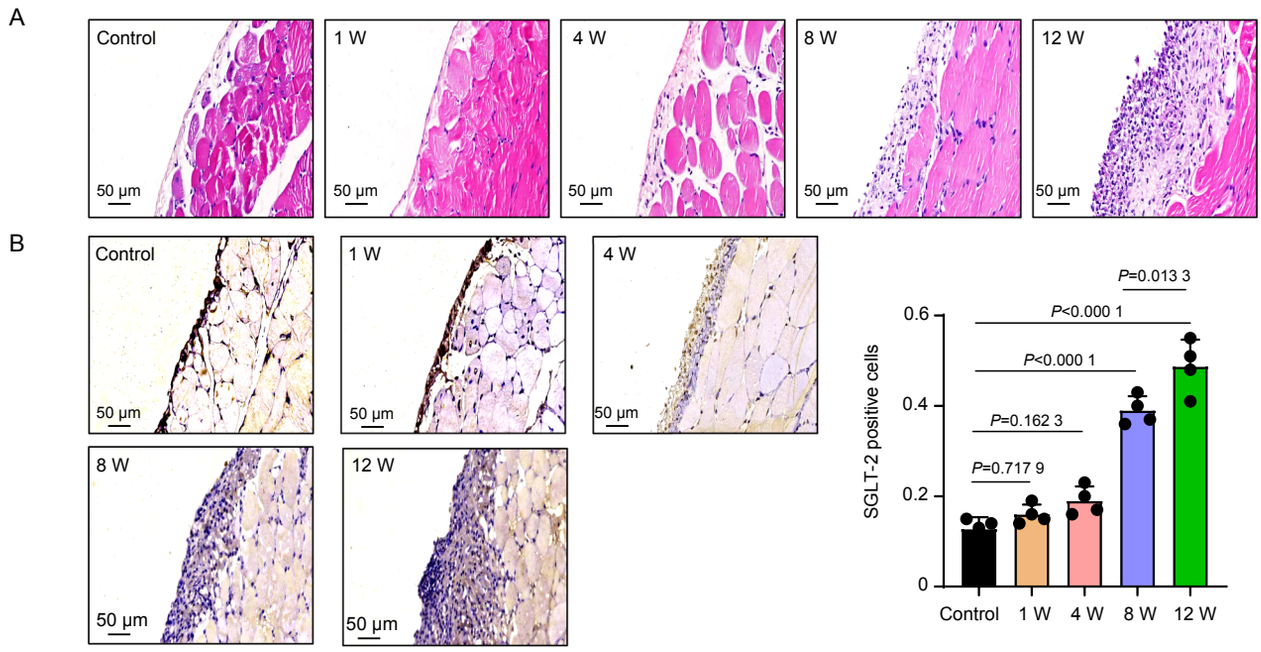
Figure 1(continued) Expression and localization of SGLT-2 in peritoneal tissues of PD mice and patients

2.2 高糖腹透液诱导SGLT-2表达呈时间依赖性上调

为观察高糖腹透液诱导时长对腹膜结构及SGLT-2表达的影响,采用7.00%高糖腹透液对小鼠进行1~12周干预。HE染色结果显示,随干预时间延长,小鼠腹膜间皮细胞脱落、间皮下层厚度增厚、炎症细胞浸润及呈现纤维化样改变,且上述病理改变随着高糖干预时间延长逐渐加重(图2A)。其中12周时上述病理改变最为显著,故后续浓度依赖性实验选择12周作为观察时间点。免疫组织化学染色显示,SGLT-2阳性细胞呈棕黄色,对照组腹膜组织中SGLT-2表达较低;随着高糖腹透液干预时间延长,SGLT-2阳性信号逐渐增多(图2B)。半定量分析结果显示,与对照组相比,8周组和12周组SGLT-2阳性细胞率显著升高(P<0.000 1);且12周组SGLT-2阳性细胞率高于8周组(P=0.013 3),达到高峰;而1周组和4周组SGLT-2阳性细胞率与对照组相比差异无统计学意义(图2B)。上述结果提示,SGLT-2表达随着高糖腹透液诱导时间延长逐渐增加,呈现出一定的时间依赖性。

2.3 高糖腹透液诱导SGLT-2表达呈浓度依赖性上调

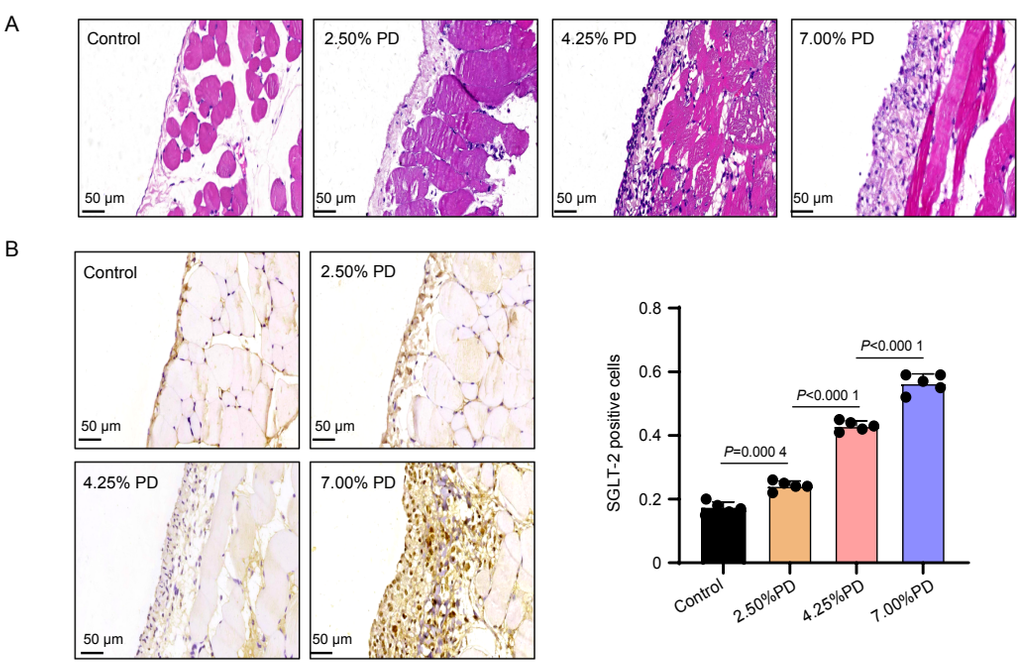
基于上述时间依赖性结果,为探讨不同浓度高糖腹透液对SGLT-2表达水平的影响,本研究采用2.50%、4.25%和7.00%葡萄糖浓度腹透液连续干预小鼠12周。HE染色结果显示,随着腹透液葡萄糖浓度升高,小鼠腹膜间皮细胞覆盖率逐渐降低,间皮下层厚度逐渐增厚,炎症细胞浸润程度逐渐加重,腹膜纤维化程度加重(图3A)。同时免疫组化染色结果显示,SGLT-2阳性表达随葡萄糖浓度升高而逐渐增强(图3B)。半定量分析结果显示,与对照组相比,2.50%PD组SGLT-2阳性细胞率升高(P=0.000 4);与2.50%PD组相比,4.25%PD组SGLT-2阳性细胞率进一步升高(P<0.000 1);与4.25%PD组相比,7.00%PD组SGLT-2阳性细胞率继续升高(P<0.000 1,图3B)。上述结果提示,SGLT-2表达随腹透液糖浓度升高逐渐增加,具有糖浓度依赖性。



A: Representative HE staining images of mouse peritoneal tissues after intervention with high-glucose dialysis solution for control, 1, 4, 8, and 12 weeks; B: Representative IHC images of SGLT-2 and semi-quantitative analysis of positive cell rates in mouse peritoneal tissues after intervention with high-glucose dialysis solution for 1, 4, 8 and 12 weeks

图2 7.00%高糖腹透液不同干预时间对小鼠腹膜组织病理改变及SGLT-2表达的影响

Figure 2 Effects of different intervention durations of 7.00% high-glucose peritoneal dialysis solution on pathological changes of peritoneal tissues and SGLT-2 expression in mice



A: Representative HE staining images of mouse peritoneal tissues after 12 weeks of intervention with control, 2.50%, 4.25% and 7.00% glucose dialysis solution; B: Representative IHC images of SGLT-2 and semi-quantitative analysis of positive cell rates in mouse peritoneal tissues after 12 weeks of intervention with control, 2.50%, 4.25% and 7.00% glucose dialysis solution

图3 不同葡萄糖浓度的高糖腹透液干预12周对小鼠腹膜病理改变及SGLT-2表达的影响

Figure 3 Effects of 12-week intervention with high-glucose peritoneal dialysis solutions at different glucose concentrations on peritoneal pathological changes and SGLT-2 expression in mice

2.4　SGLT-2表达与腹膜慢性炎症及血管病变密切相关，以与慢性炎症关联更独立

为进一步探讨SGLT-2表达在腹膜损伤进展中的潜在意义，本研究分析了SGLT-2表达水平与小鼠腹膜病理指标之间的相关性。Spearman相关分析显示，SGLT-2表达水平与间皮下层厚度（r=0.766 5，P<0.000 1）、慢性炎症评分（r=0.921 0，P<0.000 1）和血管病变评分（r=0.882 9，P<0.000 1）均呈显著正相关，而与急性炎症评分无显著相关性（r=0.223 9，P=0.297 3）。图中红色实线表示线性拟合趋势线（图4）。上述结果表明SGLT-2的表达变化可能主要与腹膜的慢性病理性改变相关，而非急性炎症反应。由于慢性炎症评分与血管病变评分之间亦高度相关（r=0.905，P<0.000 1），提示二者之间可能存在相互关联或共同反映腹膜慢性损伤程度，故进一步采用基于秩转换的偏相关分析。结果显示，在控制血管病变评分后，SGLT-2表达与慢性炎症评分仍呈显著正相关（partial r=0.586，P=0.003）；在控制慢性炎症评分后，SGLT-2表达与血管病变评分的相关性不再显著（partial r=0.306，P=0.155）。上述结果提示，SGLT-2表达与腹膜慢性炎症之间存在相对独立的关联，而其与血管病变的相关性可能主要由慢性炎症所影响。

2.5　高糖刺激诱导体外细胞SGLT-2表达上调

为观察高糖刺激对腹膜相关细胞SGLT-2表达的影响，采用30 mmol/L葡萄糖分别刺激HPMCs和HUVECs 24、48 h。RT-qPCR结果显示，在HPMCs中，高糖刺激24 h后SGLT-2 mRNA表达水平较对照组显著升高（P=0.000 2）；48 h时虽较24 h有所下降，但仍高于对照组（P=0.008 0）。在HUVECs中，高糖刺激24 h后SGLT-2 mRNA表达水平亦显著升高（P<0.000 1），而48 h时较24 h明显下降，且与对照组相比差异无统计学意义（P=0.641 5，图5A）。免疫荧光染色结果显示，SGLT-2蛋白主要分布于HPMCs和HUVECs的细胞质及细胞膜。在HPMCs中，高糖刺激24 h后SGLT-2荧光信号明显增强，荧光强度显著高于对照组（P<0.000 1）；48 h时荧光信号较24 h明显减弱，且与对照组相比差异无统计学意义（P=0.821 9，图5B、C）。在HUVECs中，高糖刺激24 h后SGLT-2荧光信号同样明显增强（P<0.000 1）；48 h时虽较24 h显著下降，但仍高于对照组（P=0.029 2，图5D、E）。上述结果表明，高糖刺激可诱导HPMCs和HUVECs中SGLT-2表达上调。

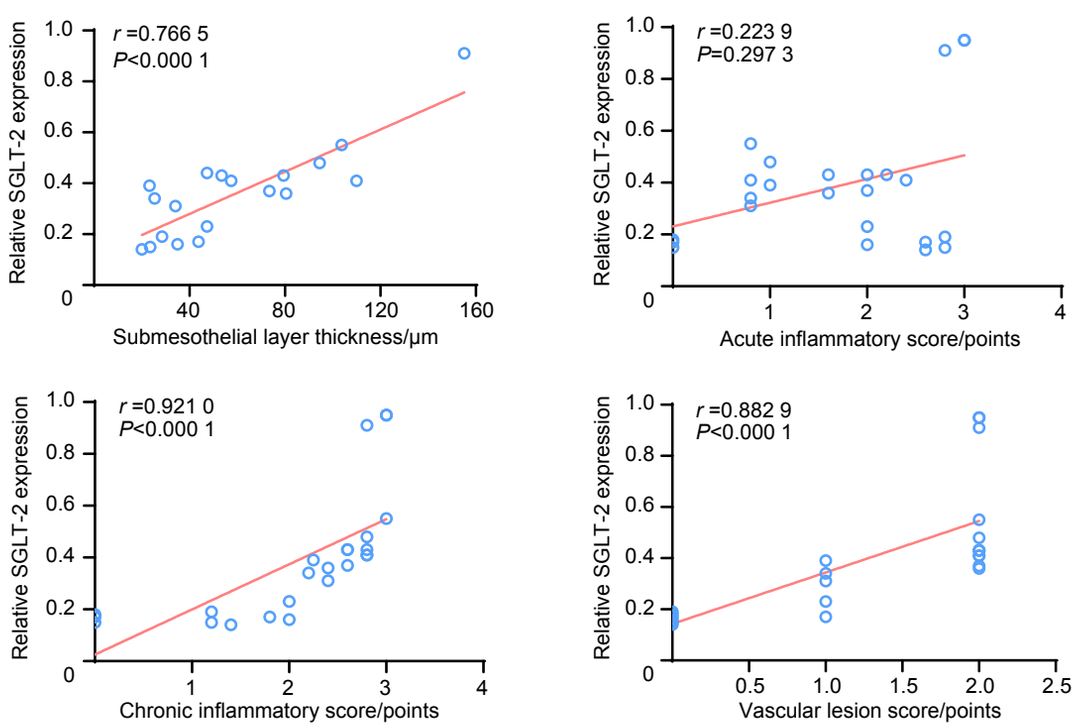
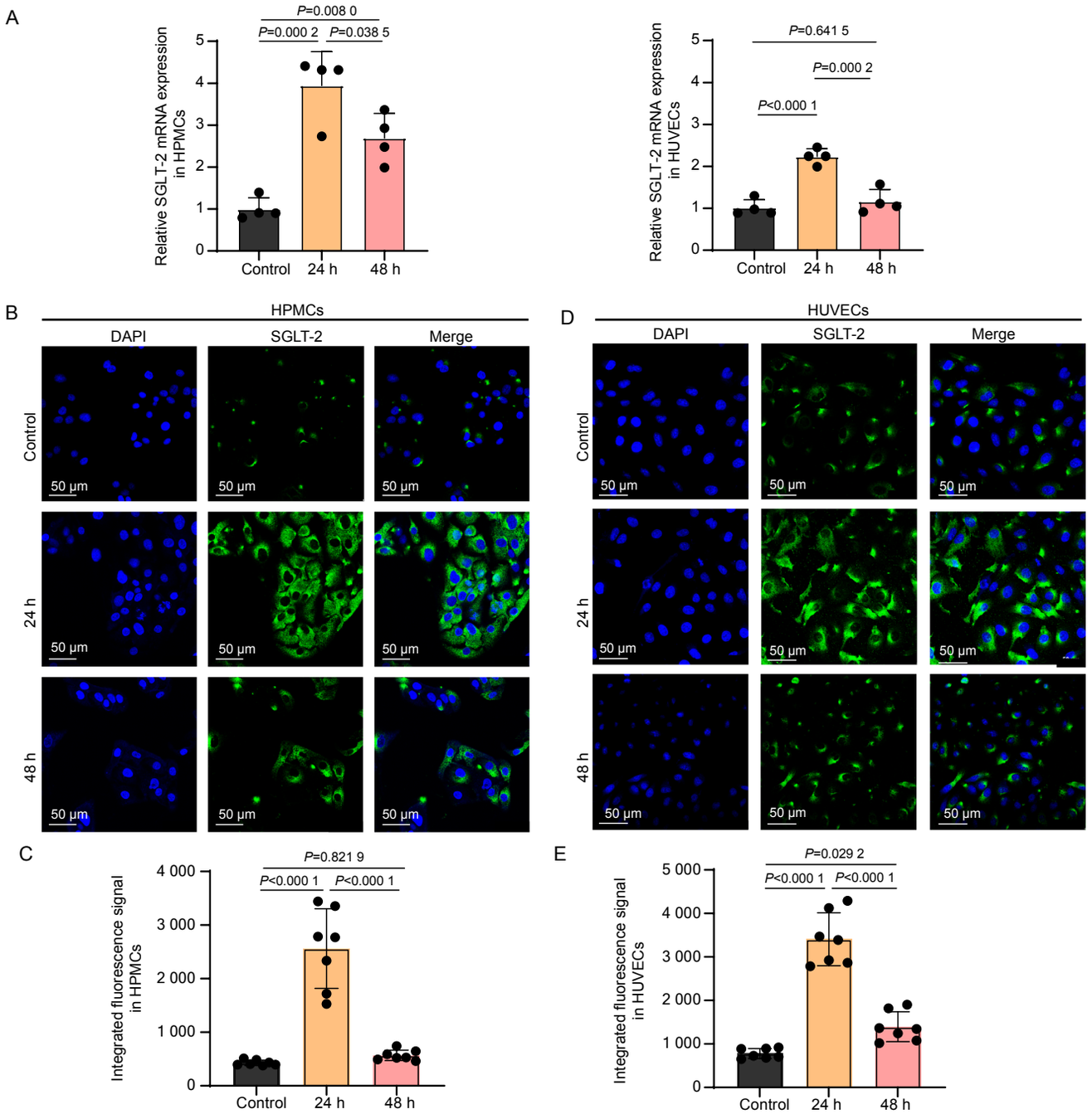


图4　SGLT-2表达水平与腹膜病理指标的相关性分析

Figure 4　Correlation analysis between SGLT-2 expression level and peritoneal pathological indicators



A: RT-qPCR of SGLT-2 mRNA expression levels in HPMCs and HUVECs after 24 and 48 h of 30 mmol/L glucose stimulation; B: Immunofluorescence assay showing SGLT-2 protein expression in HPMCs after 24 and 48 h of 30 mmol/L glucose stimulation; C: Quantitative analysis of integrated fluorescence signals of SGLT-2 in HPMCs; D: Immunofluorescence assay displaying SGLT-2 protein expression in HUVECs after 24 and 48 h of 30 mmol/L glucose stimulation; E: Quantitative analysis of integrated fluorescence signals of SGLT-2 in HUVECs

图5 高糖刺激(30 mmol/L)对HPMCs和HUVECs中SGLT-2表达的影响

Figure 5 Effects of high-glucose stimulation (30 mmol/L) on SGLT-2 expression in HPMCs and HUVECs

3 讨论

本研究系统观察了高糖腹膜损伤过程中SGLT-2的表达变化及其与病理指标的关系。结果证实,SGLT-2在高糖刺激下呈时间及浓度依赖性上调,且其表达水平与间皮下层厚度、炎症评分及血管病变评分等病理指标密切相关。这些发现提示SGLT-2可能参与高糖诱导的腹膜局部病理重塑过程,为后续机制研

究和干预策略提供了研究基础。

3.1 SGLT-2主要定位于腹膜间皮细胞和血管内皮细胞

本研究通过免疫组织化学染色与免疫荧光双染验证了SGLT-2在腹膜间皮细胞与血管内皮细胞间的特异性定位。这与Schricker等[6]的临床观察一致。在此基础上,本研究进一步在动物模型中揭示了SGLT-2表达随高糖刺激时间和浓度递增的规律,并通过体外实验验证了高糖对间皮细胞和内皮细胞SGLT-2的直接诱导作用。与Balzer等[12]采用达格列净干预的研究不同,本研究聚焦于表达调控与病理损伤的定量关联,为后续干预研究提供了剂量-效应基线。

3.2 高糖上调SGLT-2表达呈时间与浓度依赖性

动物实验中,SGLT-2表达在显著形态学损伤出现前已升高,并随暴露时间延长而持续上升;而体外细胞中其表达呈先升后降的时相变化。这一差异可能源于体内持续重复的葡萄糖刺激及细胞间旁分泌交互作用[12],提示体内微环境对SGLT-2的维持性调控更为复杂。尽管时相不尽相同,体内外结果均支持高糖是SGLT-2上调的直接驱动因素。在浓度依赖性实验中,从2.50%到7.00%的葡萄糖浓度梯度,SGLT-2表达呈阶梯式上升,提示SGLT-2对葡萄糖浓度的响应具有高度敏感性,这为临床上控制腹透液糖负荷提供了分子层面的理论支持。

既往研究已证实,高糖腹透液可显著增加腹膜组织中SGLT-1和SGLT-2的表达[13],且PD患者腹膜SGLT-2蛋白表达随透析龄延长而逐渐升高[6]。机制上,有研究发现TGF-β1通过Smad3磷酸化上调SGLT-2表达[17],而高糖经SGLT-2-ERK通路激活TGF-β1/Smad3信号[18],并在纤维化模型中观察到SGLT-2表达与TGF-β1和p-Smad3共升高[19]。本研究中SGLT-2表达与慢性炎症评分的强相关性与此类机制报道一致,提示其可能通过促纤维化和促炎信号参与腹膜损伤。

3.3 SGLT-2表达与腹膜慢性病理损伤密切相关

本研究的核心发现之一是SGLT-2表达水平与腹膜间皮下层厚度、慢性炎症评分及血管病变评分均呈显著正相关,而与急性炎症评分无显著相关性。SGLT-2表达增加可能增强细胞对葡萄糖的摄取,加重代谢应激,进而激活NF-κB、MAPK和TGF-β等通路[10, 20-21]。结合其定位及与各病理指标的相关性,可推测高糖首先诱导间皮细胞和内皮细胞SGLT-2上调,促进局部葡萄糖内流,触发炎症信号,最终导致间皮下增厚和血管病变。

3.4 SGLT-2是腹膜损伤的潜在干预靶点

SGLT-2抑制剂的心血管和肾脏保护作用已得到广泛认可[22]。本研究的发现将其应用于腹膜保护提供理论依据:局部高表达的SGLT-2可直接被抑制剂靶向,从而减少局部葡萄糖摄取、减轻氧化应激、抑制炎症纤维化,并且保护作用不依赖全身降糖效应。动物研究显示,达格列净可减轻高糖腹透液诱导的小鼠腹膜纤维化和超滤衰竭[18],且临床药代动力学证实其在PD患者中安全性可控[23]。

综上所述,本研究主要基于动物及细胞模型研究,发现高糖微环境可上调腹膜组织SGLT-2表达,其表达水平与腹膜炎症、纤维化及血管病变密切相关。但上述研究结果仍需要在PD患者中进一步验证;此外,目前还缺乏干预SGLT-2对腹膜组织损伤及腹膜功能影响的研究,后续拟通过构建SLC5A2基因过表达/敲除动物和细胞模型进行研究,并采用SGLT-2抑制剂进行干预,旨在为减轻腹膜损伤和保护腹膜功能提供潜在的有效方法。

利益冲突 本文所有作者声明不存在利益冲突

参考文献:

[1] Mehrotra R, Devuyst O, Davies S J, *et al*. The current state of peritoneal dialysis[J]. J Am Soc Nephrol, 2016, 27(11): 3238-3252. DOI:10.1681/ASN.2016010112.

[2] 《中国腹膜透析管理现状白皮书》项目组. 中国腹膜透析管理现状白皮书[J]. 中华肾脏病杂志, 2022, 38(12): 1076-1104. DOI: 10.3760/cma.j.cn441217-20220418-00158.
Project Group of "White paper on the status of peritoneal dialysis management in China". White paper on the current status of peritoneal dialysis management in China[J]. Chin J Nephrol, 2022, 38(12): 1076-1104. DOI: 10.3760/cma.j.cn441217-20220418-00158.

[3] 温雯,李月红.2016年国际腹膜透析协会腹膜炎预防和治疗推荐指南解读[J].临床内科杂志, 2017, 34(1): 70-72. DOI:10.3969/j.issn.1001-9057.2017.01.026.
Wen W, Li Y H. Interpretation of 2016 recommended guidelines for prevention and treatment of peritonitis of international peritoneal dialysis association[J]. J Clin Intern Med, 2017, 34(1): 70-72. DOI: 10.3969/j.issn.1001-9057.2017.01.026.

[4] Krediet R T, Parikova A. Relative contributions of pseudohypoxia and inflammation to peritoneal alterations with long-term peritoneal dialysis patients[J]. Clin J Am Soc Nephrol, 2022, 17(8): 1259-1266. DOI: 10.2215/CJN.15371121.

[5] 包满辰, 杨晓晓, 张琳, 等. 钠-葡萄糖协同转运蛋白1、2在腹膜透析患者腹膜中的表达[J]. 中华肾脏病杂志,

2020, 36(12): 942-947. DOI: 10.3760/cma.j.cn441217-20200521-00163.
Bao M C, Yang X X, Zhang L, *et al*. Expression of Na^+-dependent glucose transporter 1 and 2 in peritoneum of peritoneal dialysis patients[J]. Chin J Nephrol, 2020, 36(12): 942-947. DOI: 10.3760/cma.j.cn441217-20200521-00163.

[6] Schricker S, Oberacker T, Fritz P, *et al*. Peritoneal expression of SGLT-2, GLUT1, and GLUT3 in peritoneal dialysis patients[J]. Kidney Blood Press Res, 2022, 47(2): 125-134. DOI:10.1159/000520894.

[7] 姚登湖, 张明霞. 钠-葡萄糖协同转运蛋白2抑制剂在腹膜透析中作用的研究进展[J]. 中国医药, 2023, 18(9): 1427-1431. DOI:10.3760/j.issn.1673-4777.2023.09.033.
Yao D H, Zhang M X. Research progress on the role of sodium-glucose cotransporter 2 inhibitors in peritoneal dialysis[J]. China Med, 2023, 18(9): 1427-1431. DOI:10.3760/j.issn.1673-4777.2023.09.033.

[8] Minutolo R, Ruotolo C, Conte G, *et al*. SGLT2 inhibitors in hemodialysis or peritoneal dialysis patients: rationale and state-of-the art[J]. Clin Kidney J, 2025, 19(1): sfaf350. DOI: 10.1093/ckj/sfaf350.

[9] 中国腹膜透析置管专家组. 中国腹膜透析置管指南[J]. 中华肾脏病杂志, 2016, 32(11): 867-871. DOI: 10.3760/cma.j.issn.1001-7097.2016.11.014.
China of Peritoneal Dialysis Catheterization Expert Group. Guide to peritoneal dialysis catheterization in China[J]. Chin J Nephrol, 2016, 32(11): 867-871. DOI: 10.3760/cma.j.issn.1001-7097.2016.11.014.

[10] 方吕贵, 饶向荣. 腹膜透析相关动物模型的研究进展[J]. 中国血液净化, 2023, 22(11): 850-852.
Fang L G, Rao X R. Research progresses in peritoneal dialysis related animal models[J]. Chin J Blood Purif, 2023, 22(11): 850-852.

[11] Liu J H, Xu X X, Zhang L J, *et al*. Dapagliflozin ameliorates high glucose-induced peritoneal fibrosis through downregulation of ENKUR/PI3K/AKT signaling pathway[J]. Sci Rep, 2025, 15: 38334. DOI: 10.1038/s41598-025-22195-9.

[12] Balzer M S, Rong S, Nordlohne J, *et al*. SGLT2 inhibition by intraperitoneal dapagliflozin mitigates peritoneal fibrosis and ultrafiltration failure in a mouse model of chronic peritoneal exposure to high-glucose dialysate[J]. Biomolecules, 2020, 10(11): 1573. DOI: 10.3390/biom10111573.

[13] Shi Y Y, Jiang Z, Zhang L J, *et al*. Sotagliflozin reduces glucose absorption and improves ultrafiltration in a rat model of chronic peritoneal exposure to high-glucose dialysate[J]. Blood Purif, 2025, 54(12): 751-763. DOI: 10.1159/000547528.

[14] Lotfollahzadeh S, Vazirani A, Sellinger I E, *et al*. Aryl hydrocarbon receptor pathway augments peritoneal fibrosis in a murine CKD model exposed to peritoneal dialysate[J]. Kidney360, 2024, 5(9): 1238-1250. DOI: 10.34067/KID.0000000000000516.

[15] Yang J, Cai M Y, Wan J F, *et al*. Effluent decoy receptor 2 as a novel biomarker of peritoneal fibrosis in peritoneal dialysis patients[J]. Perit Dial Int, 2022, 42(6): 631-639. DOI:10.1177/08968608211067866.

[16] Honda K, Hamada C, Nakayama M, *et al*. Impact of uremia, diabetes, and peritoneal dialysis itself on the pathogenesis of peritoneal sclerosis: a quantitative study of peritoneal membrane morphology[J]. Clin J Am Soc Nephrol, 2008, 3(3): 720-728. DOI:10.2215/CJN.03630807.

[17] Panchapakesan U, Pegg K, Gross S, *et al*. Effects of SGLT2 inhibition in human kidney proximal tubular cells: renoprotection in diabetic nephropathy?[J]. PLoS One, 2013, 8(2): e54442. DOI:10.1371/journal.pone.0054442.

[18] Pan X L, Phanish M K, Baines D L, *et al*. High glucose-induced Smad3 linker phosphorylation and CCN2 expression are inhibited by dapagliflozin in a diabetic tubule epithelial cell model[J]. Biosci Rep, 2021, 41(6): BSR20203947. DOI:10.1042/BSR20203947.

[19] Shentu Y P, Li Y Y, Xie S C, *et al*. Empagliflozin, a sodium glucose cotransporter-2 inhibitor, ameliorates peritoneal fibrosis *via* suppressing TGF-β/Smad signaling[J]. Int Immunopharmacol, 2021, 93: 107374. DOI: 10.1016/j.intimp.2021.107374.

[20] Nataatmadja M S, Johnson D W, Pascoe E M, *et al*. Associations between peritoneal glucose exposure, glucose degradation product exposure, and peritoneal membrane transport characteristics in peritoneal dialysis patients: secondary analysis of the *bal*ANZ trial[J]. Perit Dial Int, 2018, 38(5): 349-355. DOI:10.3747/pdi.2017.00223.

[21] Shi X, Zou W, Li X H, *et al*. SGLT2 inhibition attenuates diabetic tubulopathy by suppressing SGK1-mediated pyroptosis[J]. Front Endocrinol, 2025, 16: 1620230. DOI: 10.3389/fendo.2025.1620230.

[22] Wang Y Q, Wang Y Q, He X J, *et al*. Sodium-glucose transporter 2 inhibitors and cardiovascular-kidney-metabolic syndrome: a narrative review[J]. Front Endocrinol, 2025, 16: 1554637. DOI:10.3389/fendo.2025.1554637.

[23] Barreto J, Borges C, Rodrigues T B, *et al*. Pharmacokinetic properties of dapagliflozin in hemodialysis and peritoneal dialysis patients[J]. Clin J Am Soc Nephrol, 2023, 18(8): 1051-1058. DOI:10.2215/CJN.0000000000000196.

(收稿:2026-07-14;修回:2026-09-07)
(编辑 黄 晟)