·基础研究·

木犀草素通过 SLC7A11/GPX4 信号通路调控铁死亡缓解血管平滑肌细胞衰老

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【摘 要】 目的 探讨木犀草素(Lut)通过溶质载体家族7成员11(SLC7A11)/谷胱甘肽过氧化物酶4(GPX4)信号通路调控铁死亡进而缓解血管平滑肌细胞(VSMCs)衰老的分子机制,为血管衰老相关疾病的防治提供新思路。**方法** 使用小鼠主动脉血管平滑肌细胞进行体外实验,设置空白对照组(Con组)、木犀草素组(Lut组,5 μmol/L Lut处理24 h)、多柔比星组(DOX组,1 μmol/L DOX处理24 h)和联合处理组(DOX+Lut组,5 μmol/L Lut预处理24 h后加入DOX)。使用β-半乳糖苷酶(SA-β-gal)染色试剂盒和细胞计数试剂盒-8(CCK-8)评价细胞衰老与活力,Western blot检测衰老蛋白(P53、P21、P16)及铁死亡通路蛋白(SLC7A11、GPX4),流式细胞术检测活性氧(ROS)水平,脂质过氧化荧光探针和FerroOrang亚铁离子荧光探针分别检测脂质过氧化和细胞内Fe^{2+},同时测定细胞裂解液内谷胱甘肽(GSH)和丙二醛(MDA)含量。通过SLC7A11抑制剂Erastin干预铁死亡观察衰老表型变化。采用GraphPad Prism 10.0软件进行数据分析,多组间比较采用单因素方差分析,结合Tukey事后检验;两组间比较采用双尾独立样本t检验。**结果** 与Con组相比,DOX组细胞活力显著下降,IC_{50}值为1.799 μmol/L,SA-β-gal阳性衰老细胞比例显著升高至63%($P<0.05$);同时伴随衰老蛋白(P53、P21、P16)表达上调,ROS及脂质过氧化水平显著增加,Fe^{2+}发生明显蓄积,GSH含量降低,SLC7A11和GPX4蛋白表达显著下调($P<0.05$)。与DOX组相比,DOX+Lut组上述指标均有明显改善,IC_{50}值提升至2.192 μmol/L,衰老细胞比例降至约38%,且SLC7A11与GPX4的表达明显恢复($P<0.05$)。**结论** Lut激活SLC7A11/GPX4信号,可有效抑制DOX诱导的铁死亡并缓解VSMCs衰老,可为防治血管衰老相关疾病提供新的理论依据。

【关键词】 木犀草素;铁死亡;血管平滑肌细胞衰老;溶质载体7成员11

【中图分类号】 R543 **【文献标志码】** A **【DOI】** 10.11915/j.issn.1671-5403.2026.03.045

Luteolin attenuates vascular smooth muscle cell senescence by regulating ferroptosis through SLC7A11/GPX4 signaling pathway

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【Abstract】 Objective To investigate the molecular mechanism by which luteolin (Lut) alleviates vascular smooth muscle cells (VSMCs) senescence by regulating ferroptosis *via* the solute carrier family 7 member 11 (SLC7A11)/glutathione peroxidase 4 (GPX4) signaling pathway, thereby providing novel insights for the prevention and treatment of vascular aging-related diseases. **Methods** Mouse vascular smooth muscle cells (MOVAS) were subjected and randomly divided into blank control group (Con group), Lut group (5 μmol/L Lut for 24 h), doxorubicin group (DOX group, 1 μmol/L DOX for 24 h), and combined treatment group (DOX+Lut group, pretreatment of 5 μmol/L Lut for 24 h followed by DOX treatment). Cell senescence and viability were evaluated using senescence-associated β-galactosidase (SA-β-gal) staining and cell counting kit-8 (CCK-8) assay, respectively. The expression of senescence-related proteins (P53, P21, P16) and ferroptosis pathway proteins (SLC7A11, GPX4) was detected by Western blot. Reactive oxygen species (ROS) production was measured by flow cytometry. Lipid peroxidation and intracellular ferrous iron (Fe^{2+}) levels were detected using lipid peroxidation fluorescent probes and FerroOrange fluorescent probe, respectively. Additionally, glutathione (GSH) and malondialdehyde (MDA) contents in cell lysates were measured. SLC7A11 inhibitor Erastin was used to intervene ferroptosis

收稿日期: 2025-08-29; **接受日期**: 2025-10-24

基金项目: 国家重点研发计划(2022YFC3602400)

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to observe the changes in senescence phenotypes. GraphPad Prism 10.0 software was employed for data analysis. Multiple-group comparison was performed using one-way ANOVA followed by Tukey's post hoc test, and intergroup comparison was applied using a two-tailed independent sample *t* test. **Results** Compared with the Con group, the DOX group exhibited significantly decreased cell viability (IC_{50} = 1.799 μmol/L) and an obviously increased proportion of SA-β-gal-positive senescent cells (approximately 63%, P< 0.05), accompanied with upregulated senescence proteins (P53, P21, P16), elevated ROS and lipid peroxidation levels, marked accumulation of Fe^{2+}, reduced GSH content, and notably downregulated expression of SLC7A11 and GPX4 proteins (P<0.05). The addition of Lut pretreatment remarkably improved the aforementioned indicators, such as the IC_{50} value increasing to 2.192 μmol/L, the proportion of senescent cells decreasing to approximately 38%, and restored protein levels of SLC7A11 and GPX4 when compared with the levels in the DOX group (P<0.05). **Conclusion** Lut effectively inhibits DOX-induced ferroptosis and alleviates VSMC senescence by activating the SLC7A11/GPX4 signaling pathway, providing a theoretical basis for the treatment of vascular aging-related diseases.

【Key words】 luteolin; ferroptosis; vascular smooth muscle cell senescence; solute carrier family 7 member 11

This work was supported by the National Key Research and Development Program of China (2022YFC3602400).

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随着人口老龄化不断加剧,心血管系统的衰老问题逐渐凸显,成为动脉粥样硬化、高血压及其他心血管疾病发生与进展的重要基础[1,2]。血管平滑肌细胞(vascular smooth muscle cells, VSMCs)是血管中层的主要细胞成分,在维持血管弹性、结构稳定和收缩功能中起关键作用[3,4]。大量研究表明,VSMCs 衰老不仅导致其增殖与迁移能力下降,还伴随炎症因子和基质金属蛋白酶的分泌升高,加速血管壁硬化[5,6]。因此,探索延缓 VSMCs 衰老的有效策略对心血管疾病的防治具有重要意义。

细胞衰老是指细胞在经历氧化应激、DNA 损伤或化学药物刺激等压力后进入一种不可逆的细胞周期停滞状态[7]。其生物学特征包括形态改变、β-半乳糖苷酶(senescence-associated β-galactosidase, SA-β-gal)活性增强及细胞周期抑制因子(如 P21、P53 等)表达上调[8]。近年来,铁死亡作为一种以铁依赖性脂质过氧化为标志的程序性细胞死亡方式,参与多种年龄相关疾病的发病机制[7]。

溶质载体 7 成员 11(solute carrier family 7 member 11,SLC7A11)是胱氨酸/谷氨酸逆向转运体-复合体的关键亚单位,负责将胞外半胱氨酸转运入细胞,促进谷胱甘肽(glutathione,GSH)合成,从而维持细胞内氧化还原平衡[9]。谷胱甘肽过氧化物酶 4(glutathione peroxidase 4,GPX4)利用 GSH 清除脂质过氧化物,是抑制铁死亡的关键[10]。SLC7A11/GPX4 轴是调控铁死亡的核心通路,其功能受损会导致脂质过氧化物蓄积和氧化应激升高,进而诱导细胞功能衰退和衰老[11]。因此,靶向 SLC7A11/GPX4 轴可能为调控 VSMCs 衰老提供新的策略。

木犀草素(luteolin,Lut)是一种天然类黄酮物质,广泛存在于芹菜、洋甘菊和青橘等植物中,具有抗氧化、抗炎、抗凋亡等多重生物学活性[12]。研究表明,Lut 可通过多条信号通路发挥细胞保护作用,尤其在神经退行性疾病和代谢性疾病模型中表现出对铁死亡的调控潜力[13,14]。然而,目前尚无明确证据表明其是否通过 SLC7A11/GPX4 通路介导铁死亡,从而发挥抗血管平滑肌细胞衰老的作用。本研究旨在探讨 Lut 延缓血管平滑肌细胞衰老的作用以及潜在分子机制。

1 材料与方法

1.1 主要实验材料与试剂

小鼠血管平滑肌细胞(mouse vascular smooth muscle cells,MOVAS,YC-A023)购于广州源井生物公司;DMEM 高糖培养基购于美国 Gibco 公司;Lut 购于上海麦克林生化科技有限公司;兔单克隆抗体 GPX4、SLC7A11 购于上海艾比玛特公司;兔单克隆抗体 P16、P21、P53 购于美国艾博抗公司;BCA 蛋白浓度测定试剂盒、细胞衰老 SA-β-gal 染色试剂盒、活性氧(reactive oxygen species,ROS)检测试剂盒、丙二醛(malondialdehyde,MDA)检测试剂盒购于上海碧云天生物公司;GSH 检测试剂盒购于北京索莱宝科技公司;脂质过氧化荧光探针 C11 BODIPY 581/591 购于上海宏叶生物科技公司;亚铁离子荧光探针 FerroOrange 购于日本同仁化学研究所。

1.2 方法

1.2.1 细胞培养 MOVAS 于 37℃、5% CO_2 湿润培养箱中培养,培养基为高糖 DMEM,内含 10%胎牛血清及 1%青霉素-链霉素混合液。细胞传代至第 4 代后,用含 1 μmol/L 多柔比星(doxorubicin,DOX)的培养基处理 24 h,以诱导细胞衰老。

1.2.2 细胞计数试剂盒-8 检测细胞活力 取第 4 代对数生长期细胞,以 5×10^3 个/孔接种于 96 孔板中,贴壁过夜后分别进行以下处理。(1)DOX 处理实验:分别加入 0.0,0.1,0.5,1.0,2.0,5.0 μmol/L

的DOX处理24 h,评估DOX对血管平滑肌细胞活力的抑制作用。(2)Lut处理实验:分别加入0.0,0.1,1.0,5.0,10.0,50.0,100.0 μmol/L的Lut孵育24 h,评估其对细胞活力的影响。(3)DOX+Lut联合处理实验:Lut预处理后,加入不同浓度DOX,共同孵育24 h,评估Lut对DOX诱导细胞损伤的影响。处理结束后,每孔加入细胞计数试剂盒-8(cell counting kit-8,CCK8)工作液,37°C孵育30 min,使用酶标仪在450 nm波长下测定吸光度($A_{450\,nm}$)。

1.2.3 Western blot检测 检测衰老相关蛋白P16、P21、P53,GPX4,SLC7A11及内参β-肌动蛋白等的表达水平。分别收集不同处理条件下的MOVAS,使用含苯甲基磺酰氟的RIPA裂解液提取细胞内总蛋白,用BCA试剂盒测定蛋白含量。各组分别取20 μg蛋白样品行Western blot实验。用Image J软件分析相应条带灰度值,以β-肌动蛋白标化蛋白表达。

1.2.4 细胞SA-β-gal染色 细胞用磷酸盐缓冲液洗涤后,固定于4%多聚甲醛(室温,15 min),随后加入含X-gal底物的染色液(pH 6.0),37℃避光孵育过夜。光学显微镜下拍照记录蓝色染色阳性细胞。

1.2.5 细胞内ROS水平检测 使用DCHF-DA染色试剂盒检测细胞内ROS水平。细胞经处理后用胰酶消化,收集后加入DCHF-DA工作液,37℃避光染色30 min。染色结束后离心,弃上清液后用磷酸盐缓冲液重悬细胞,制备成单细胞悬液。使用流式细胞仪进行检测,采集FITC通道荧光信号,评估细胞内ROS水平变化。

1.2.6 细胞内亚铁离子(Fe^{2+})水平检测 采用FerroOrange荧光探针检测细胞内亚铁离子水平。处理后的细胞用Hank's平衡盐溶液缓冲液洗涤,加入染色液,37℃避光孵育30 min。孵育结束后吸弃染色液,加入含DAPI的抗荧光淬灭封片液进行封片。随后使用奥林巴斯共聚焦激光扫描显微镜进行观察。

1.2.7 脂质过氧化水平检测 采用C11 BODIPY 581/591荧光探针检测细胞内脂质过氧化水平。细胞处理结束后用磷酸盐缓冲液洗涤,加入荧光探针,最终浓度为1 μmol/L,37℃孵育30 min。孵育后,用磷酸盐缓冲液洗涤细胞2次,去除未结合的探针。使用Olympus共聚焦激光扫描显微镜(激发:488 nm;发射:561 nm)观察细胞的绿色和红色荧光。

1.2.8 GSH和MDA含量检测 MOVAS处理结束后,收集细胞,遵循GSH、MDA检测试剂盒说明书的操作步骤,用酶标仪设定不同波长(GSH:412 nm;MDA:532 nm),读取各孔的吸光度值。

1.3 统计学处理

采用GraphPad Prism 10.0软件进行统计学分析。所有实验均独立重复至少3次($n=3$)。计量资料以均数±标准差($\bar{x}\pm s$)表示,多组间比较采用单因素方差分析,并结合Tukey事后检验进行两两比较;两组间比较采用双尾独立样本t检验。$P<0.05$为差异有统计学意义。

2 结 果

2.1 DOX处理对血管平滑肌细胞的影响

随着DOX浓度的升高,MOVAS细胞活力逐渐下降。与0.0 μmol/L组相比,0.5,1.0,2.0和5.0 μmol/L DOX组细胞活力均显著降低($P<0.05$;图1A)。1.0 μmol/L组与0.5 μmol/L组相比,细胞活力下降幅度相对较小,未引起明显毒性。与此同时,1.0 μmol/L DOX处理可显著上调P53和P21表达($P<0.05$;图1B~D),提示细胞出现典型衰老表型。因此,本研究选取1.0 μmol/L DOX作为建立MOVAS衰老模型的适宜剂量。

2.2 Lut对DOX诱导的衰老血管平滑肌细胞模型的影响

将MOVAS分为空白对照组(Con组)、Lut组(5.0 μmol/L Lut 24 h)、DOX组(1.0 μmol/L DOX 24 h)及Lut+DOX组(5.0 μmol/L Lut预处理24 h+1.0 μmol/L DOX 24 h)。结果显示,0.1~10.0 μmol/L Lut对细胞活力无显著影响,而50.0 μmol/L及100.0 μmol/L显著抑制细胞活力,差异有统计学意义($P<0.05$;图2A)。Lut对DOX诱导细胞毒性的影响见图2B,结果显示,Lut处理后MOVAS对DOX的耐受性提高,IC_{50}由1.799 μmol/L升至2.192 μmol/L,提示Lut可减轻DOX的毒性作用。进一步检测衰老标志物P53、P21、P16的表达水平,如图2C所示,DOX组中衰老相关蛋白表达显著升高,而Dox+Lut组与Dox组相比,P53、P21、P16的表达显著降低,差异均有统计学意义($P<0.05$;图2C~F)。为验证衰老表型,采用SA-β-gal染色法检测细胞衰老水平(图2G),DOX组可见大量蓝色阳性细胞,Dox+Lut组阳性细胞明显减少,差异具有统计学意义($P<0.05$;图2H),与蛋白表达结果一致,提示Lut可缓解DOX诱导的VSMCs衰老。

2.3 Lut对DOX诱导的细胞脂质过氧化和铁死亡抑制蛋白表达的影响

为评估DOX及Lut对细胞脂质过氧化的影响,本研究采用C11 BODIPY 581/591探针检测脂质过氧化水平(图3A)。结果显示,Con组细胞呈现明显

的红色荧光,绿色荧光较弱;DOX 组绿色荧光显著增强、红色荧光减弱,提示氧化应激水平升高;DOX+Lut 组可见绿色荧光强度明显降低,红色荧光有所恢复,差异均有统计学意义($P<0.05$;图 3B)。进一步通过 Western blot 实验检测 SLC7A11/GPX4 通路相关蛋白(图 3C),发现 DOX 明显抑制 SLC7A11 与 GPX4 表达,而 Lut 干预可明显恢复其水平,差异均有统计学意义($P<0.05$;图 3D~E)。

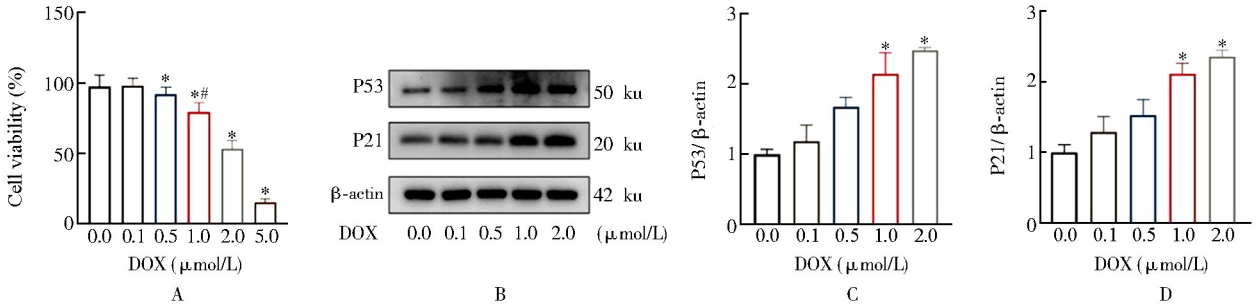


图 1 DOX 处理对血管平滑肌细胞的影响

Figure 1 Effects of DOX treatment on vascular smooth muscle cells

A: cell viability of MOVAS cells under different concentrations of DOX; B: expression of P53 and P21 by Western blotting; C-D: quantitative analysis of P53 and P21 expression. DOX: doxorubicin. Compared with 0.0 μmol/L group, $^{*}P<0.05$; compared with 0.5 μmol/L DOX group, $^{\#}P<0.05$.

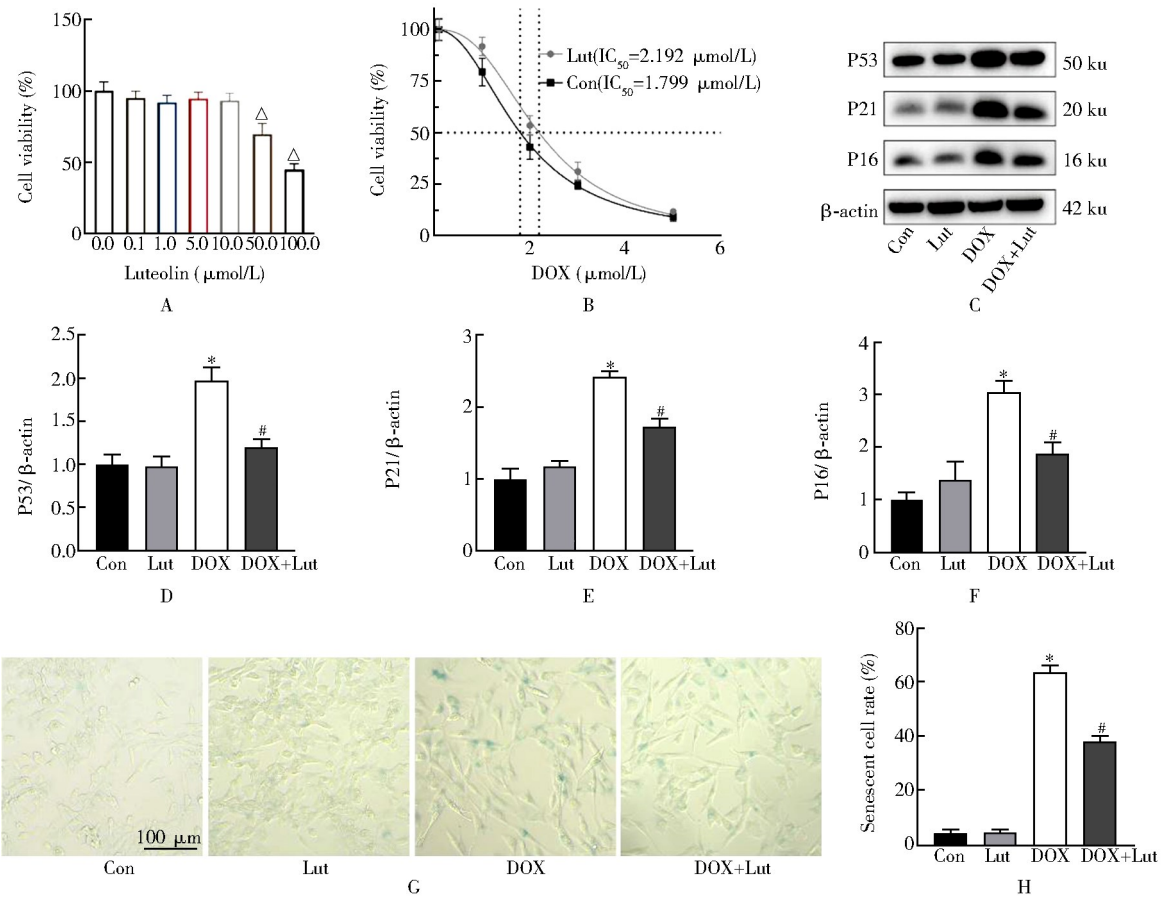


图 2 Lut 对 DOX 诱导的衰老血管平滑肌细胞模型的影响

Figure 2 Effects of Lut on a DOX-induced senescent vascular smooth muscle cell model

A: MOVAS cell viability at different concentrations of Lut; B: IC_{50} values of cell viability measured by CCK-8 assay; C: expression of P53, P21 and P16 by Western blotting; D-F: quantification of P53, P21, and P16 levels; G: SA-β-gal staining and quantification of MOVAS cells (scale bar=100 μm); H: quantification of SA-β-gal positive cells. Con: control; Lut: luteolin; DOX: doxorubicin; VSMCs: vascular smooth muscle cells. Compared with Con group, $^{*}P<0.05$; compared with DOX group, $^{\#}P<0.05$; compared with 10.0 μmol/L Lut group, $^{\triangle}P<0.05$.

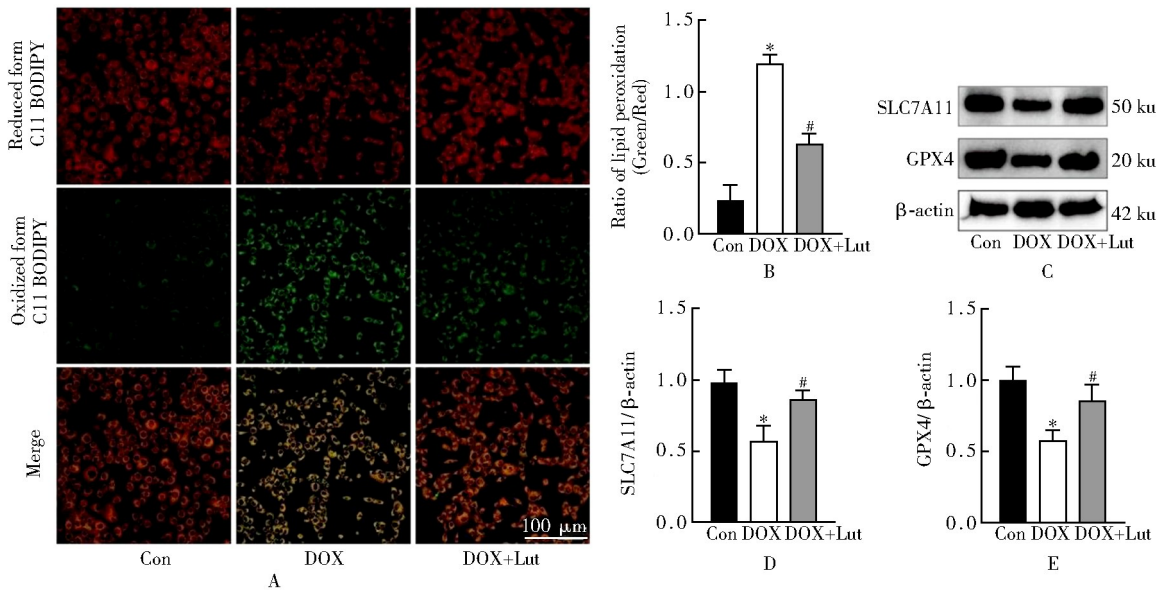


图3 Lut对DOX诱导的细胞脂质过氧化和铁死亡抑制蛋白表达的影响

Figure 3 Effects of Lut on DOX-induced lipid peroxidation and ferroptosis-inhibitory protein expression

A: C11 BODIPY 581/591 staining, showing intracellular lipid peroxidation levels in each group; B: quantitative analysis of ratio of oxidized to reduced lipids in each group; C: expression of SLC7A11 and GPX4 by Western blotting; D-E: quantification of SLC7A11 and GPX4 expression. Con: control; DOX: doxorubicin; Lut: luteolin; GPX4: glutathione peroxidase 4; SLC7A11: solute carrier family 7 member 11. Compared with Con group, $^{*}P<0.05$; compared with DOX group, $^{\#}P<0.05$.

2.4 Lut对DOX引起的氧化应激和铁死亡标志物的影响

进一步检测氧化应激相关指标及细胞内Fe^{2+}水平,结果显示,与Con组相比,DOX处理显著升高细胞内ROS水平($P<0.05$;图4A,B),显著增加MDA含量($P<0.05$;图4C),并显著降低GSH水平($P<0.05$;图4D),提示DOX明显诱导氧化应激和脂质过氧化反应增强。并且,与DOX组相比,Lut预处理可显著降低ROS水平和MDA含量,并部分恢复GSH水平($P<0.05$;图4B,C)。此外,FerroOrange荧光检测结果表明(图4E),DOX处理显著诱导细胞内Fe^{2+}积累,而Lut预处理可显著降低Fe^{2+}含量,差异有统计学意义($P<0.05$;图4F)。

2.5 Erastin处理对Lut在血管平滑肌细胞中抗铁死亡及抗衰老作用的影响

SLC7A11、GPX4和衰老相关蛋白的表达水平见图5A。与DOX组相比,Lut+DOX组中SLC7A11、GPX4蛋白的表达水平上调,差异有统计学意义($P<0.05$;图5B,C)。加入SLC7A11特异性抑制剂Erastin后,相比于Lut+DOX组,DOX+Lut+Erastin组中SLC7A11和GPX4表达均下降,且DOX+Lut+Erastin组的衰老相关蛋白P53和P21表达水平升高,差异均有统计学意义($P<0.05$;图5B~E)。

3 讨 论

本研究结果显示,Lut可减轻DOX诱导的血管平滑肌细胞铁死亡和细胞衰老,其作用可能与SLC7A11/GPX4信号通路的调控有关。本研究中,Lut可显著减轻DOX诱导的脂质过氧化、氧化应激及亚铁离子积累,并抑制衰老相关标志物P53、P21和P16的表达,提示Lut在DOX诱导的VSMCs衰老过程中具有明显的保护作用。本研究为Lut通过抑制铁死亡延缓血管衰老提供了新的实验证据。

Lut作为一种天然类黄酮,其在心血管疾病中的保护作用已被广泛研究[12]。既往研究发现,Lut能够改善心肌梗死[15]、缺血再灌注损伤[13]及动脉粥样硬化[16]等多种心血管疾病,其主要通过抗氧化、抗炎、促进自噬及抑制细胞凋亡等途径发挥作用[17,18]。目前大多数研究主要关注Lut的抗氧化和抗炎特性,关于其是否涉及铁死亡这一调控机制,尤其是在血管衰老模型中的作用,尚需进一步探讨。因此,本研究旨在从铁死亡的角度,初步探索Lut延缓血管平滑肌细胞衰老的可能机制。

铁死亡作为一种新型的细胞程序性死亡形式,因其独特的铁依赖脂质过氧化机制逐渐引起关注[7]。近年来的研究提示,铁死亡可能参与了血管

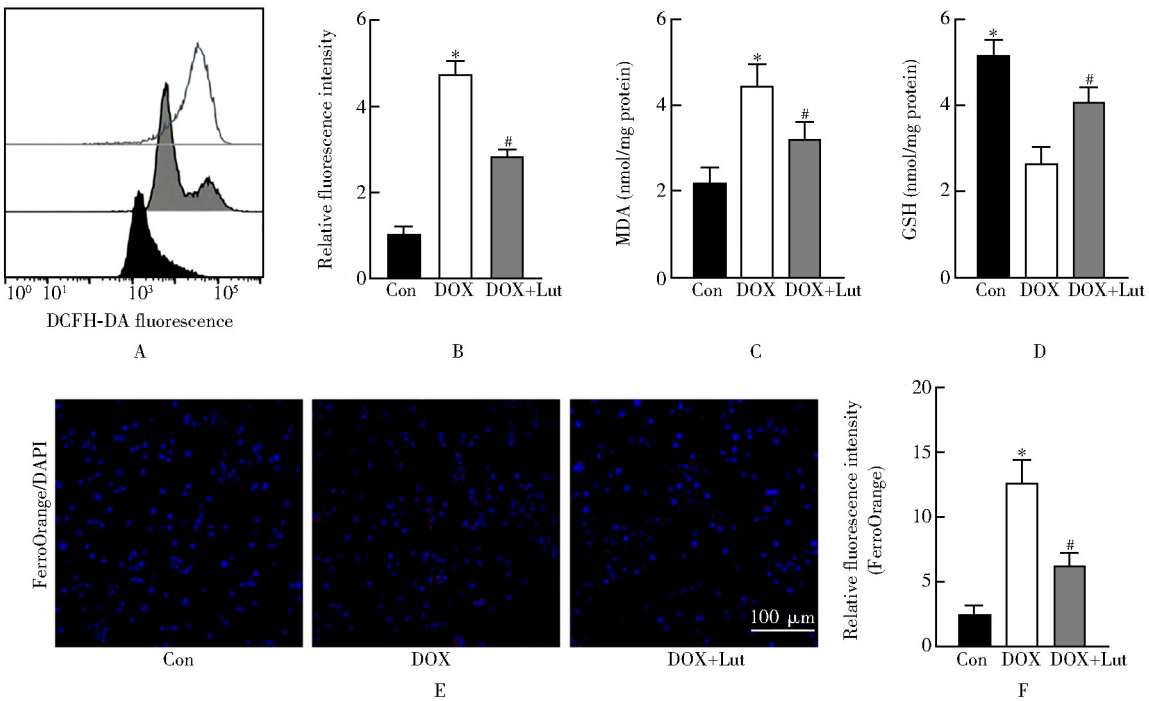


图 4　Lut 对 DOX 引起的氧化应激和铁死亡标志物的影响

Figure 4　Effects of Lut on DOX-induced oxidative stress and ferroptosis markers

A: flow cytometry plots of intracellular ROS levels detected by DCFH-DA probe in each group; B: quantitative analysis of ROS levels in each group; C: quantification of MDA levels in cell lysates; D: quantification of GSH levels in cell lysates; E: fluorescence images of intracellular Fe^{2+} detected by FerroOrange probe; F: quantitative analysis of intracellular Fe^{2+} levels. Con: control; Lut: luteolin; DOX: doxorubicin; ROS: reactive oxygen species; MDA: malondialdehyde; GSH: glutathione. Compared with Con group, $^{*}P<0.05$; compared with DOX group, $^{\#}P<0.05$.

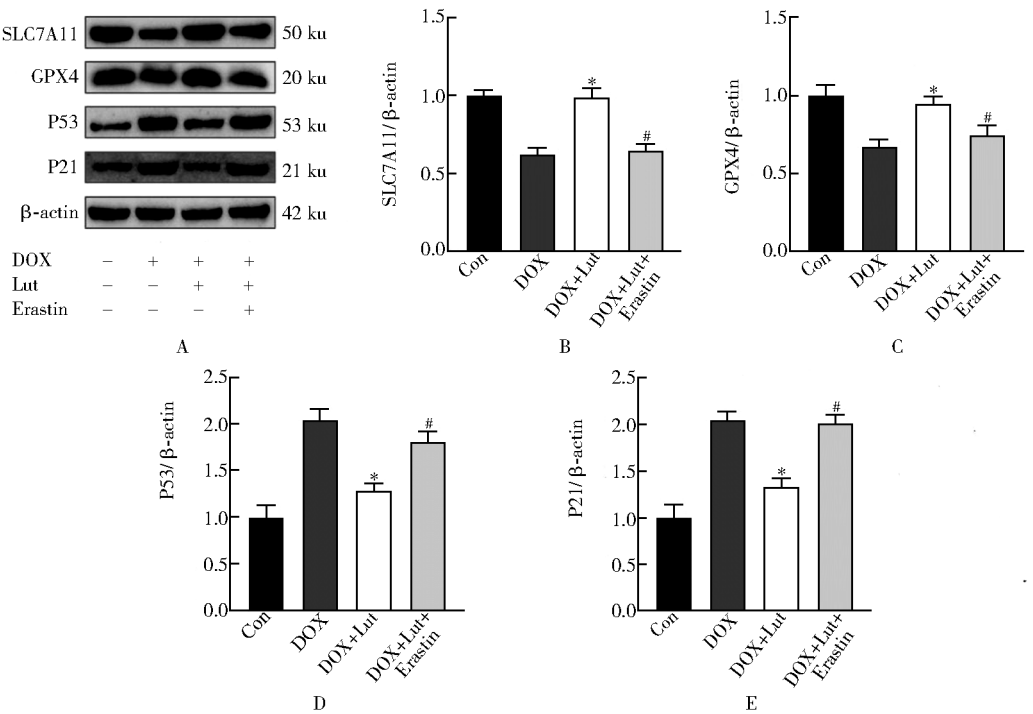


图 5　Erastin 处理对 Lut 在血管平滑肌细胞中抗铁死亡及抗衰老作用的影响

Figure 5　Effect of Erastin treatment on anti-ferroptotic and anti-senescence effects of luteolin in VSMCs

A: expression of SLC7A11, GPX4, P53, and P21 by Western blotting; B-E: Quantitative analysis of SLC7A11, GPX4, P53, and P21 expression. SLC7A11: solute carrier family 7 member 11; GPX4: glutathione peroxidase 4; Con: control; DOX: doxorubicin; ROS: reactive oxygen species; Lut: luteolin. Compared with DOX group, $^{*}P<0.05$; compared with DOX+Lut group, $^{\#}P<0.05$.

衰老的病理过程[19,20]。本研究建立的DOX诱导VSMCs衰老模型中,观察到了与铁死亡相关的特征性改变,包括脂质ROS水平升高、MDA含量增加以及细胞内亚铁离子的积聚。经Lut处理后,上述铁死亡相关指标均有所改善。这一结果提示,抑制铁死亡可能是Lut减轻DOX诱导的VSMCs衰老的机制之一。

为进一步了解其分子机制,本研究关注了SLC7A11/GPX4信号通路。SLC7A11/GPX4信号通路是目前公认的铁死亡调控核心机制之一[21]。SLC7A11主要负责细胞内胱氨酸的转运,后续胱氨酸被还原为半胱氨酸用于GSH的合成,从而维持GPX4活性,而GPX4是脂质过氧化物清除过程中关键的抗氧化酶[22]。实验结果显示DOX处理导致VSMCs中SLC7A11和GPX4的表达下降,而Lut预处理则部分恢复了这两种蛋白的表达水平。此外,在使用SLC7A11抑制剂Erastin后,Lut对衰老表型的改善作用受到了明显的抑制。这些数据表明,SLC7A11/GPX4信号通路的激活可能介导了Lut在VSMCs中的抗铁死亡及抗衰老效应。虽然Lut调控铁死亡的作用在其他疾病模型中已有报道[23],但其在心血管系统中的作用尚未明确。

本研究尚存在一定的局限性。首先,本研究主要基于体外细胞模型,难以完全模拟体内复杂的血管微环境及整体生理状态,因此后续有必要开展动物实验进行体内验证。其次,本研究主要聚焦于SLC7A11/GPX4通路,至于Lut是否同时也影响其他铁稳态相关蛋白(如铁蛋白、转铁蛋白受体1)或协同激活其他抗氧化信号通路,仍待进一步探索。此外,Lut对VSMCs衰老的长期效应及其剂量-反应关系也值得深入研究。

综上所述,本研究证实了Lut通过激活SLC7A11/GPX4信号通路抑制铁死亡,进而延缓DOX诱导的VSMCs衰老。未来的研究应利用动物模型进一步探讨Lut对血管衰老的整体效应,并评估其长期安全性及疗效。此外,鉴于血管衰老在动脉粥样硬化及高血压等多种心血管疾病中的关键作用,亟需在这些疾病模型中系统评估Lut的潜在疗效,从而为其临床应用提供更充分、可靠的理论依据。

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(编辑:郑真真)