蓝萼乙素通过抑制Prdx I/ROS/p53通路诱导肺腺癌细胞衰老

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摘要: 探寻细胞衰老诱导剂是筛选抗肿瘤活性先导化合物的途径之一, 蓝萼乙素是否具有诱导细胞衰老的作用有待阐明。本研究旨在探讨蓝萼乙素诱导肺腺癌细胞A549衰老的作用及其分子机制。2和5 μmol·L^{-1}蓝萼乙素均能诱导A549细胞发生衰老, 具体表现为蓝萼乙素显著上调A549细胞中细胞周期依赖性蛋白激酶抑制因子1A (cyclin-dependent kinase inhibitor 1A, p21) 蛋白的表达水平和衰老相关*β*-半乳糖苷酶 (senescence-associated *β*-galactosidase, SA-*β*-gal) 染色阳性细胞占比; 蓝萼乙素对A549细胞中过氧化还原酶I (peroxiredoxin I, Prdx I) 蛋白表达水平无明显影响, 但可显著抑制其酶活性; 敲低*Prdx I*可诱导A549细胞发生衰老; 蓝萼乙素抑制Prdx I酶活性进而引起活性氧 (reactive oxygen species, ROS) 增加, 而活性氧清除剂*N*-乙酰半胱氨酸可减弱蓝萼乙素诱导的A549细胞衰老; 蓝萼乙素或敲低*Prdx I*均可明显上调A549细胞中肿瘤蛋白p53蛋白表达水平, 而敲低*p53*能明显抑制蓝萼乙素诱导的A549细胞衰老。综上所述, 蓝萼乙素可通过抑制Prdx I/ROS/p53通路诱导肺腺癌细胞发生衰老, 这可能是其抑制肿瘤的作用机制之一。

关键词: 蓝萼香茶菜; 蓝萼乙素; 肺腺癌; 细胞衰老; 过氧化还原酶I; 活性氧

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Glaucocalyxin B triggers the senescence of lung adenocarcinoma cells *via* the inhibition of Prdx I/ROS/p53 pathway

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Abstract: Exploring cellular senescence inducers is one of the approaches to screen anti-tumor active lead compounds. Whether glaucocalyxin B induces cellular senescence remains to be elucidated. This study aims to investigate the effect and mechanism of glaucocalyxin B on the senescence of lung adenocarcinoma A549 cells. 2 and 5 μmol·L^{-1} of glaucocalyxin B induced senescence in A549 cells. Glaucocalyxin B significantly increased the levels of cyclin-dependent kinase inhibitor 1A (p21) and the proportion of *β*-galactosidase staining-positive cells in A549 cells. Glaucocalyxin B had no significant effect on the levels of peroxiredoxin I (Prdx I) protein in A549 cells but significantly inhibited its enzymatic activity. Knockdown of *Prdx I* induced senescence in A549 cells. Glaucocalyxin B inhibited the enzyme activity of Prdx I, leading to the increase of reactive oxygen species (ROS), and the ROS scavenger *N*-acetylcysteine attenuated glaucocalyxin B-induced the senescence of A549 cells. Either glaucocalyxin B or *Prdx I* knockdown significantly upregulated the levels of tumor protein p53 in A549 cells, while knockdown of p53 significantly inhibited glaucocalyxin B-induced the senescence of A549 cells. In conclusion, glaucocalyxin B can induce senescence in lung adenocarcinoma cells by inhibiting the Prdx I/ROS/p53 pathway, which might be one of its anti-tumor mechanisms.

Key words: *Rabdosia japonica*; glaucocalyxin B; lung adenocarcinoma; cellular senescence; peroxiredoxin I;

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reactive oxygen species

细胞衰老是一种永久的细胞周期阻滞状态, 与恶性肿瘤的发生发展密切相关[1,2]。诱导肿瘤细胞衰老的先导化合物发现是替代传统细胞毒疗法的潜在策略, 基于细胞衰老生物标志物 [如细胞内活性氧 (reactive oxygen species, ROS)、细胞衰老相关半乳糖苷酶 (senescence-associated β-galactosidase, SA-β-gal)、细胞衰老相关标志蛋白] 的抗肿瘤先导化合物探寻, 是研发低毒、持久的抗肿瘤疗法的关注方向[3]。

ROS积累是细胞衰老的主要特征之一[4], 其可通过激活肿瘤蛋白p53 (tumor protein p53, p53)/细胞周期依赖性蛋白激酶抑制因子1A (cyclin-dependent kinase inhibitor 1A, p21) 通路发挥作用是细胞衰老的调控机制之一[5]。靶向ROS平衡是调控细胞衰老策略的重要途径[6,7], 而过氧化还原酶I (peroxiredoxin I, Prdx I) 是清除过氧化氢等ROS的关键抗氧化酶, 具有维持细胞氧化还原稳态的功能[8]。高表达Prdx I会增强肿瘤细胞抗凋亡能力, 进而促进肺腺癌的发展[9]。然而Prdx I调控ROS是否与肺腺癌细胞衰老存在关联仍有待阐释。

蓝萼乙素是从唇形科香茶菜属提取分离的一种贝壳杉烯型二萜类化合物, 可通过诱导肿瘤细胞凋亡、阻滞细胞周期、抑制血管生成、激活细胞自噬等途径发挥抗宫颈癌、胃癌、卵巢癌等活性[10-12]。然而, 蓝萼乙素是否具有诱导细胞衰老的活性仍不清楚。本研究基于肺腺癌细胞探讨蓝萼乙素诱导细胞衰老的活性及其可能的分子机制。

材料与方法

药物与试剂 蓝萼乙素 (HY-N2113) 购自上海MedChemExpress (MCE) 公司; *N*-乙酰半胱氨酸 (ST1546-2g)、SA-β-gal染色试剂盒 (C0602)、2',7'-二氯二氢荧光素二乙酸酯 (2',7'-dichlorodihydrofluorescein diacetate, DCFH-DA) 活性氧检测试剂盒 (S0033S)、Hoechst 33342 (C1022)、辣根过氧化物酶标记山羊抗小鼠IgG (H+L) (货号A0216)、辣根过氧化物酶标记山羊抗兔IgG (H+L) (货号A0208) 均购自海门碧云天生物技术有限公司; 一抗信息如下: p21 (27296-1-AP)、Prdx I (15816-1-AP)、p53 (10442-1-AP)、GAPDH (60004-1-Ig) 均购自武汉三鹰生物技术有限公司; Prdx I siRNAs (AGAUAUCAGCCUGUCUGAC; CUGCCAAGUGA-UUGGUGCU), p53 siRNAs (AAAGACCUAUGGAAA-CUACUU) 和 negative control (NC) siRNAs 均由苏州吉玛基因股份有限公司合成。

仪器 二氧化碳细胞培养箱 (美国赛默飞世尔科技公司, 型号BB150); 细胞培养生物安全柜 (苏州安泰科技有限公司, 型号BSC-06IIB2); 化学发光显影仪 (上海天能生物科技有限公司, 型号Tanon-5200); 荧光倒置显微镜 (日本奥林巴斯公司, 型号X71); 全波长酶标仪 (瑞士帝肯集团有限公司, 型号: Spark); 小型电泳装置及电泳胶转膜装置系统 (美国伯乐生命医学产品有限公司, 型号Mini-PROTEAN Tetra)。

细胞培养 人肺腺癌细胞株A549细胞 (中国科学院分子细胞科学卓越创新中心细胞库) 在10 mL含10%胎牛血清的F12培养基中置于37 ℃、5% CO_2的细胞培养箱中培养。取对数生长期细胞, 按每毫升6×10^4个细胞密度接种在6孔板中; 次日, 细胞分为3组, 分别为对照组、蓝萼乙素 (2和5 μmol·L^{-1}) 组, 给药48 h后, 细胞根据实验目的进行处理。

蛋白免疫印迹实验 制备的细胞蛋白样品采用SDS-PAGE胶进行分离, 电泳结束后样品转移至PVDF膜, 然后使用5%脱脂牛奶封闭膜1 h, TBST清洗后加入相应的一抗孵育过夜; 次日, 回收一抗, 并使用TBST洗膜3次, 孵育对应的二抗1 h后, 将PVDF膜放入TBST中清洗3次, 每次10 min; 接着加入适量显影液在膜表面, 放入化学发光显影仪读取膜信息; 最后使用Image J软件对蛋白印迹图片进行灰度分析。

细胞SA-β-gal染色 细胞培养至指定时间后, 弃去培养基, 加入1 mL预冷PBS清洗3次后加入800 μL固定液固定15 min, 弃去固定液, PBS清洗3次后加入700 μL染色工作液, 并用封口膜密封细胞培养板, 37 ℃恒温烘箱中放置16 h; 次日, 弃去染色液, 使用适量预冷PBS清洗3次后在倒置显微镜下观察拍照。

细胞转染 细胞融合达到80%时转染, 阴性对照siRNA和目的基因siRNA各转染3个组; 各配置3份转染复合物, 600 μL Opti-MEM培养基与24 μL转染试剂, 静置5 min; 300 μL Opti-MEM培养基与15 μL 20 μmol·L^{-1} NC siRNA和目的基因的siRNA溶液混合加入上述转染试剂复合物中, 静置15 min; 最后每孔加入800 μL完全培养基和200 μL转染混合物, 培养箱中放置6 h后分皿, 次日根据实验目的进行相应处理。

重组Prdx I酶活力测定 采用标准Trx/Trx还原酶 (TrxR) /NADPH直接偶联分光光度法测定过氧化物酶Prdx I的活性。使用96孔板配制反应体系, 每孔反应体系的总体积为180 μL, 含0.1 U Trx, Prdx I重组

蛋白的终浓度为640 nmol·L^{-1}, 使用HEPES缓冲液配制体系。向反应孔中加入一定量的蓝萼乙素 (每个孔的蓝萼乙素浓度分别为0、5 μmol·L^{-1}), 反应底物为180 μmol·L^{-1} H_2O_2 10 μL (在反应体系中的终浓度为10 μmol·L^{-1})。使用全波长酶标仪分别检测反应体系在室温下反应20 min时340 nm处的吸光度。

活性氧检测 使用F12细胞培养基配制DCFH-DA (1∶100) 溶液和Hoechst (1∶2 000) 染液, 每份细胞中加入PBS清洗2次后, 先加入200 μL DCFH-DA溶液, 置37 ℃孵育10 min后再加200 μL Hoechst染液, 继续在37 ℃细胞培养箱中孵育15 min, 后使用PBS清洗3次, 最后加入300 μL F12培养基在荧光倒置显微镜下观察拍照, 在观察前所有操作都在避光条件下进行。

统计学分析 本研究数据均采用了3次生物学重复实验数据 ($\bar{x} \pm s$), 采用基于one-way ANOVA的 t 检验进行显著性差异分析, 用GraphPad Prism软件 (v10) 绘制统计图。$P < 0.05$表明结果具有统计学显著性。

结果

1 蓝萼乙素诱导肺腺癌细胞衰老

为探讨蓝萼乙素是否能诱导人肺腺癌细胞A549细胞衰老, 本研究采用蛋白免疫印迹法和SA-β-gal染色法测定不同浓度对人肺腺癌细胞的影响。结果如图1所示, 与对照组相比, 2和5 μmol·L^{-1}蓝萼乙素处理的A549细胞中p21蛋白水平明显上升, 且SA-β-gal染色阳性细胞比例显著增加, 上述结果提示, 蓝萼乙素可诱导肺腺癌细胞衰老。

2 蓝萼乙素诱导肺腺癌细胞中ROS增加

ROS是诱导细胞衰老的重要因素之一。为探索蓝萼乙素是否影响肺腺癌细胞中的ROS变化情况, 使用DCFH-DA荧光探针染色法检测了蓝萼乙素处理A549细胞后的ROS水平, 如图2所示, 与对照组相比, 5 μmol·L^{-1}蓝萼乙素处理的A549细胞中细胞内ROS明显增加, 提示蓝萼乙素可能通过增加肺腺癌细胞中的ROS水平诱导肺腺癌细胞衰老。

3 ROS参与蓝萼乙素诱导肺腺癌细胞衰老过程

为了确证ROS的异常增加参与了蓝萼乙素诱导肺腺癌细胞衰老过程, 应用ROS清除剂*N*-乙酰半胱氨酸处理蓝萼乙素诱导的肺腺癌细胞, 结果如图3所示, *N*-乙酰半胱氨酸能明显下调蓝萼乙素所致肺腺癌细胞中p21蛋白水平的增加, 且能明显降低蓝萼乙素所致SA-β-gal染色阳性细胞占比。上述结果提示, ROS的确参与了蓝萼乙素诱导的肺腺癌细胞衰老过程。

4 蓝萼乙素抑制肺腺癌细胞中Prdx I酶活性

Prdx I作为过氧化还原酶家族的重要一员, 在细胞ROS平衡中发挥重要作用。为了探索Prdx I在蓝萼乙素诱导肺腺癌细胞衰老中的作用, 首先应用Western blot检测了蓝萼乙素对肺腺癌细胞中Prdx I蛋白表达水平的影响, 如图4A所示, 5 μmol·L^{-1}蓝萼乙素对肺腺癌细胞中Prdx I蛋白表达水平无明显影响; 但蓝萼乙素明显抑制了Prdx I酶活性 (图4B)。上述结果表明, 蓝萼乙素可通过抑制Prdx I酶活性引起肺腺癌细胞中ROS水平的异常增加。

5 敲低*Prdx I*诱导肺腺癌细胞衰老

采用细胞转染*Prdx I* siRNA的方法来确证敲低

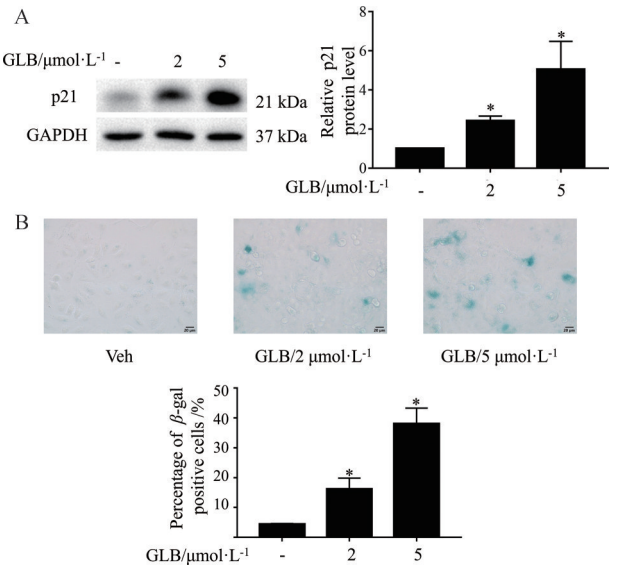


Figure 1 GLB induces the senescence of lung adenocarcinoma cells. A: A549 cells were treated with GLB at 2 and 5 μmol·L^{-1} for 48 h, and the levels of p21 protein expression were determined by Western blot analysis; B: A549 cells were treated with GLB at 2 and 5 μmol·L^{-1} for 48 h, and the percentage of senescent cells was measured by senescence-associated β-galactosidase (SA-β-gal) staining method. Scale bar: 20 μm, ×200. $n = 3$, $\bar{x} \pm s$. $^*P < 0.05$ *vs* control group. Veh: Vehicle; GLB: Glaucocalyxin B

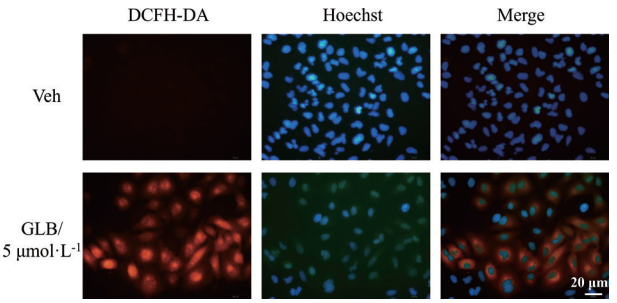


Figure 2 GLB induced the increase of ROS in lung adenocarcinoma cells. Immunofluorescence staining of intracellular ROS (red) after 5 μmol·L^{-1} GLB treatment for 48 h using 2',7'-dichlorodihydrofluorescein diacetate (DCFH-DA) probe staining method. Scale bar: 20 μm, ×200

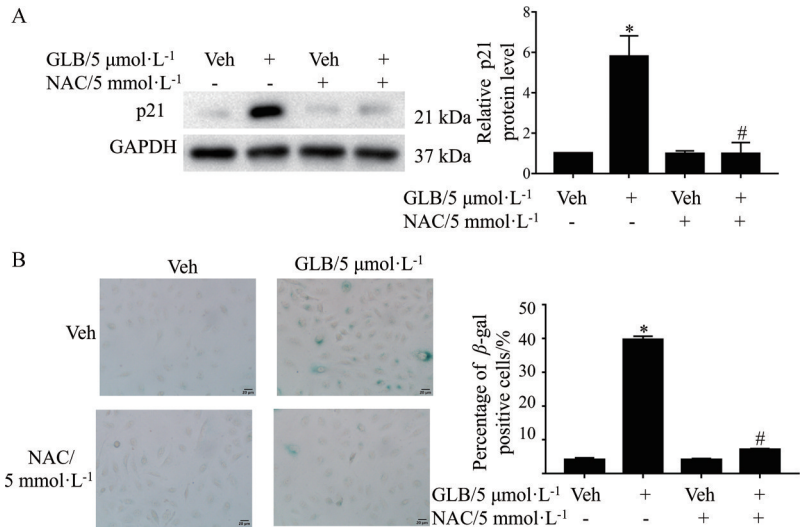


Figure 3 ROS is necessary for GLB-induced the senescence of lung adenocarcinoma cells. A: A549 cells were treated with 5 μmol·L^{-1} GLB and/or 5 mmol·L^{-1} *N*-acetylcysteine (NAC) for 48 h, and the levels of p21 and GAPDH protein were determined by Western blot analysis; B: A549 cells were treated with 5 μmol·L^{-1} GLB and/or 5 mmol·L^{-1} NAC for 48 h, and the percentage of senescent cells was measured by SA-β-gal staining method. Scale bar: 20 μm, ×200. $n = 3$, $\bar{x} \pm s$. $^{*}P < 0.05$ *vs* control group; $^{\#}P < 0.05$ *vs* GLB group

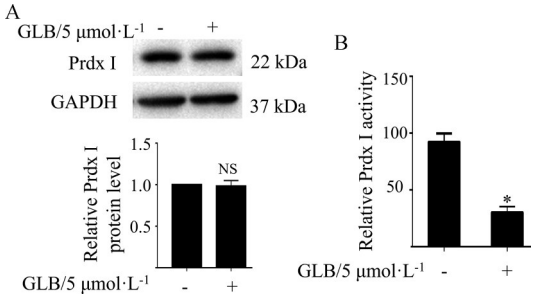


Figure 4 GLB repressed the peroxidase activity of peroxiredoxin (Prdx I) in human lung adenocarcinoma cells. A: A549 cells were treated with 5 μmol·L^{-1} GLB for 48 h, and the levels of Prdx I protein were determined by immunoblotting; B: The relative peroxidase activity of recombination human Prdx I with or without 5 μmol·L^{-1} GLB in H_2O_2 reduction assay. Scale bar: 20 μm, ×200. $n = 3$, $\bar{x} \pm s$. $^{*}P < 0.05$ *vs* control group; NS: No significance

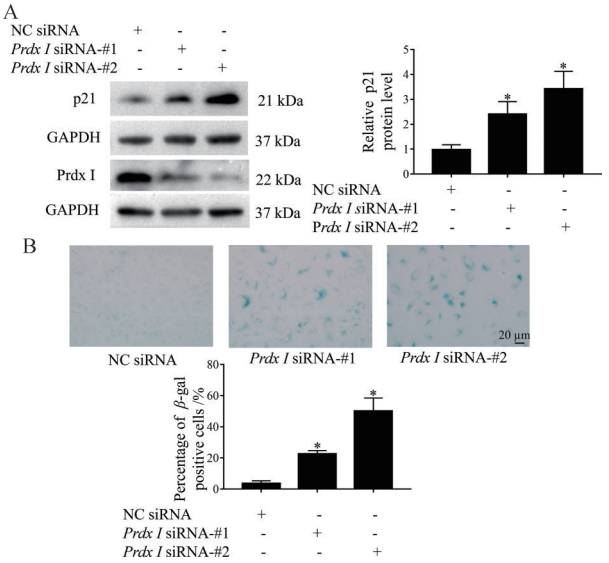


Figure 5 Knockdown of *Prdx I* induced the senescence of lung adenocarcinoma cells. A: A549 cells were transfected with *Prdx I* siRNA for 48 h, and the levels of p21 and GAPDH protein expression were determined by Western blot analysis; B: A549 cells were transfected with *Prdx I* siRNA for 48 h, and the percentage of senescent cells was measured by SA-β-gal staining method. Scale bar: 20 μm, ×200. $n = 3$, $\bar{x} \pm s$. $^{*}P < 0.05$ *vs* NC siRNA group

*Prdx I*是否能诱导肺腺癌细胞衰老。如图5所示, 与对照组相比, 敲低*Prdx I*后的A549细胞中p21蛋白水平明显上升, 且SA-β-gal染色阳性细胞比例显著增加。结果提示, 抑制Prdx I能诱导肺腺癌细胞衰老。

6 p53调控蓝萼乙素诱导的肺腺癌细胞衰老

为了探索ROS信号下游分子p53是否参与蓝萼乙素诱导的肺腺癌细胞衰老过程, 首先使用Western blot检测5 μmol·L^{-1}蓝萼乙素或敲低*Prdx I*对肺腺癌细胞中p53蛋白表达水平的影响, 如图6A所示, 与对照组相比, 5 μmol·L^{-1}蓝萼乙素或敲低*Prdx I*能显著上调A549细胞中p53蛋白表达水平。进一步, 为确证p53是否参与蓝萼乙素诱导肺腺癌细胞衰老过程, 联合应用蓝萼乙素和p53 siRNA处理A549细胞, 结果表明, 敲低*p53*可抑制蓝萼乙素诱导的A549细胞中p21蛋白水平上升和SA-β-gal染色阳性细胞增加 (图6B、C)。结果提示, p53的确参与了蓝萼乙素诱导的肺腺癌细胞衰老。

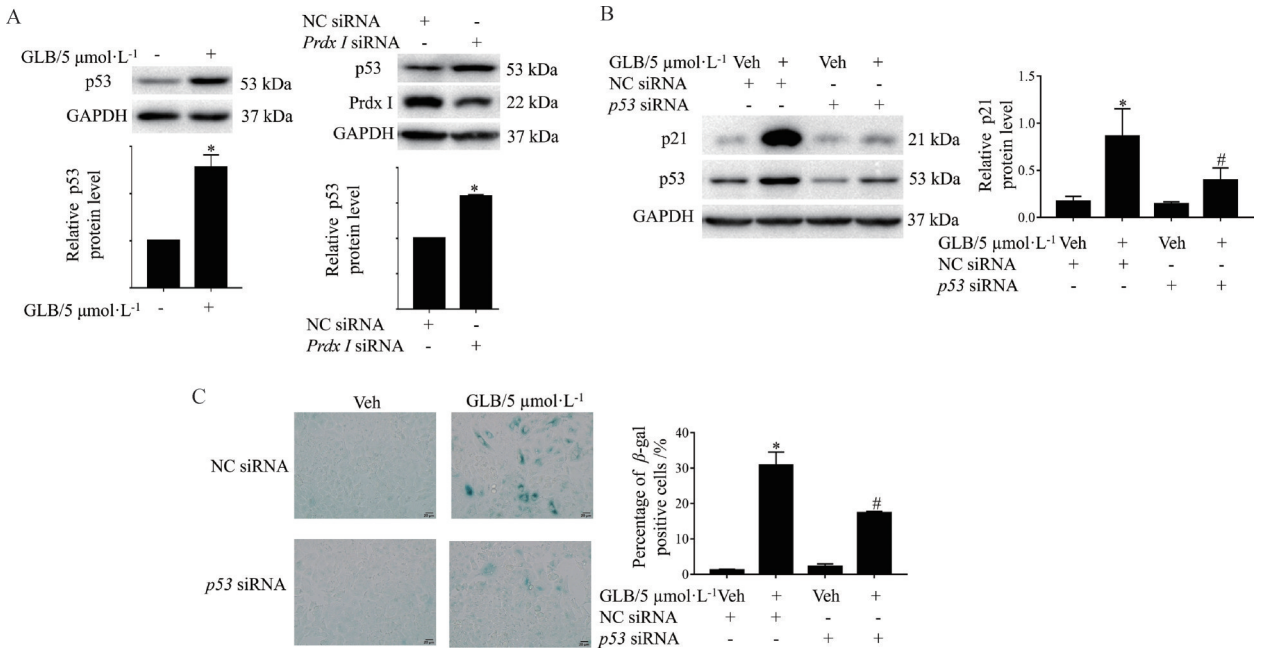


Figure 6 p53 is essential in GLB-induced the senescence of lung adenocarcinoma cells. A: A549 cells were treated with 5 μmol·L^{-1} GLB or transfection with *Prdx I* siRNA for 48 h, and the level of p53 protein were measured by immunoblotting; B: A549 cells were treated with 5 μmol·L^{-1} GLB and/or *p53* knockdown for 48 h, and the levels of p21 and GAPDH protein were determined by Western blot analysis; C: A549 cells were treated with 5 μmol·L^{-1} GLB and/or *p53* knockdown for 48 h, and the percentage of senescent cells was measured by SA-*β*-gal staining method. Scale bar: 20 μm, ×200. $n = 3$, $\bar{x} \pm s$. $^{*}P < 0.05$ *vs* NC siRNA group; $^{\#}P < 0.05$ *vs* NC siRNA + GLB group

讨论

细胞衰老是由内在和/或外在应激因素诱导的不可逆的细胞周期阻滞状态, 能阻抑潜在恶性细胞过度增殖, 对组织内稳态和肿瘤抑制具有重要作用[13]。目前, 单凭细胞死亡并不能充分阐释抗肿瘤药物的治疗作用, 从侧面凸显了细胞衰老作为癌症治疗中关键抗恶性肿瘤细胞增殖机制的重要作用。尽管细胞衰老发生的机制仍未阐明, 但通过促进或消除衰老细胞或调节衰老相关分泌表型来靶向细胞衰老发挥抗肿瘤作用已有较为丰富的研究[14,15], 是抗肿瘤药物发现领域一种具有前景的策略[16]。

蓝萼乙素是中药蓝萼香茶菜的特征成分之一, 然而有关蓝萼乙素生物活性的研究仍处于起步阶段[17]。目前, 已知的蓝萼乙素药理作用机制主要与炎症通路、氧化应激通路相关[18-22], 如核因子-*κ*B信号通路、核因子相关因子2通路等, 但它是否具有诱导细胞衰老的作用有待阐释。本研究以肺腺癌细胞为研究对象, 发现蓝萼乙素能够诱导肺腺癌细胞衰老。

研究表明, ROS异常增加是细胞衰老的已知关键特点和表现之一[23-25]。本研究结果观察到蓝萼乙素处理的肺腺癌细胞中ROS水平明显上升; 而应用ROS清除剂能逆转蓝萼乙素诱导肺腺癌细胞衰老的作用。这表明, ROS介导了蓝萼乙素诱导肺腺癌细胞衰老的作用。

过氧化物还原酶 (peroxiredoxin, Prx/Prdx) 是生物体内普遍存在的抗氧化系统的关键组成部分, 其可以保护细胞抵御生理或病理产生的ROS所引发的氧化应激[8]。另一方面, 肺癌患者中异常表达的过氧化物还原酶主要为Prdx I、Prdx IV、Prdx VI这三个亚类, 且目前主要对Prdx I的功能开展了深入研究[26]。有鉴于此, 本研究从Prdx I着手, 结果发现蓝萼乙素能明显抑制Prdx I过氧化酶的功能而影响肺腺癌细胞内ROS平衡; 同时单独敲低*Prdx I*也可诱导肺腺癌细胞衰老。这些数据提示, Prdx I-ROS与蓝萼乙素诱导肺腺癌细胞衰老密切相关。

ROS的下游信号分子p53是已知的细胞衰老驱动因子之一[27,28]。本研究发现, 蓝萼乙素或敲低*Prdx I*均能显著上调肺腺癌细胞中的p53蛋白表达水平; 进一步, 敲低*p53*的确能逆转蓝萼乙素诱导肺腺癌细胞衰老的作用。以上结果表明, p53参与了蓝萼乙素引起的肺腺癌细胞衰老过程。

综上所述, 本研究发现蓝萼乙素能诱导肺腺癌细胞衰老, 至少部分与蓝萼乙素下调Prdx I-ROS-p53信号轴的作用有关。

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利益冲突: 本文所有作者声明不存在利益冲突关系。

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