

曲古抑菌素A对慢性髓细胞白血病细胞增殖与凋亡的作用及机制研究

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摘要 该文研究了去乙酰化酶抑制剂曲古抑菌素A(trichostatin A, TSA)对慢性髓细胞白血病(chronic myeloid leukemia, CML)细胞株K562及K562/G01增殖和凋亡的影响及机制。采用不同浓度TSA处理K562及K562/G01细胞, CCK8和克隆形成实验检测细胞增殖能力; 流式细胞术、蛋白印迹法和DAPI染色检测细胞凋亡; 蛋白印迹法检测细胞自噬相关蛋白及BCR-ABL/STAT5/c-Myc信号轴蛋白水平。结果显示, TSA显著抑制K562及K562/G01细胞的增殖; 明显促进K562及K562/G01细胞的凋亡; TSA与伊马替尼(imatinib, IM)联用可更有效地杀伤CML细胞。TSA可抑制BCR-ABL/STAT5/c-Myc信号轴, 降低c-Myc蛋白水平; 增强CML细胞自噬, 自噬抑制剂氯喹(chloroquine, CQ)可部分回复TSA引起的凋亡。综上, TSA通过抑制STAT5信号通路, 降低c-Myc蛋白水平, 抑制CML细胞增殖; 增强CML细胞自噬, 促进其凋亡。

关键词 慢性髓细胞白血病; 曲古抑菌素A; 伊马替尼; 增殖; 凋亡; 自噬

The Effect and Mechanism of Trichostatin A on Proliferation and Apoptosis of Chronic Myeloid Leukemia Cells

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Abstract In this paper, the effects of TSA (trichostatin A) and the possible mechanisms on proliferation and apoptosis of CML (chronic myeloid leukemia) cells K562 and K562/G01 were investigated. Different concentrations of TSA were used to treat K562 and K562/G01 cells. CCK8 and clone formation assay were used to detect the effect of TSA on cell proliferation. FCM (flow cytometry analysis), Western blot and DAPI staining were used to detect apoptosis; Western blot was used to detect the autophagy levels of cells and the levels of BCR-ABL/STAT5/c-Myc signal axis proteins after treated with TSA. The results showed that TSA could effectively inhibit the proliferation of K562 and K562/G01 cells, and significantly promote the apoptosis of K562 and K562/G01 cells. The combination of TSA and IM (imatinib) could more effectively kill CML cells. TSA inhibited the BCR-ABL/STAT5/c-Myc signal axis and reduced the c-Myc protein level. TSA enhanced the autophagy of CML cells. The autophagy inhibitor CQ (chloroquine) partially rescued the apoptosis caused by TSA. Those results indicated that TSA inhibited the proliferation of CML cells by suppressing the STAT5 signaling pathway and reducing the level of

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c-Myc protein. Moreover, TSA enhanced CML cell autophagy and promoted cells apoptosis.

Keywords chronic myeloid leukemia; trichostatin A; imatinib; proliferation; apoptosis; autophagy

慢性髓细胞白血病(chronic myeloid leukemia, CML), 是一类起源于造血干祖细胞的恶性克隆性肿瘤, 其特征性的染色体异常为t(9;22)(q34;q11), 即Ph染色体, 形成BCR-ABL融合基因并编码BCR-ABL致癌蛋白; BCR-ABL通过其异常高表达的酪氨酸激酶活性持续激活包括JAK2/STAT5在内的下游多条信号通路, 促进血液细胞恶性转化、异常增殖, 导致CML发生发展^[1-3]。酪氨酸激酶抑制剂(tyrosine kinase inhibitors, TKIs)伊马替尼(imatinib, IM)作为治疗CML的一线药物, 可有效延长患者生存期⁴, 但仍有约25%患者发生TKIs耐药, 且尚无有效治疗对策⁵。因此, 亟需寻找新的CML治疗靶点, 以克服TKIs耐药问题。

组蛋白去乙酰化酶抑制剂(histone deacetylase inhibitor, HDACi)是一类去乙酰化酶抑制剂, 近些年在肿瘤治疗研究中颇受关注⁶, 其在三阴性乳腺癌⁷、胃癌⁸、急性髓细胞白血病⁹、T细胞淋巴瘤¹⁰及CML¹¹等肿瘤中均被发现对肿瘤细胞有不同程度的杀伤作用。许多研究已表明, HDACi成员曲古抑菌素A(trichostatin A, TSA), 是针对组蛋白去乙酰化酶类型I和II(HDAC class I/II)的抑制剂¹², 它可以促进胃癌细胞¹³、结肠癌细胞¹⁴、乳腺癌细胞¹⁵及骨肉瘤细胞¹⁶的自噬, 从而诱导肿瘤细胞凋亡。TSA能否通过促进自噬影响CML急变期细胞系K562及IM耐药细胞株K562/G01的增殖和凋亡尚未有报道。因此, 本研究着眼于TSA对K562及K562/G01细胞增殖及凋亡的影响及可能的机制, 旨在为CML的治疗提供新的思路。

1 材料与方法

1.1 材料

1.1.1 细胞株 人慢性髓细胞白血病急变期细胞系K562、IM耐药细胞株K562/G01由重庆医科大学临床检验诊断学教育部重点实验室保存。

1.1.2 主要试剂及抗体 曲古抑菌素A(TSA)、氯喹(chloroquine, CQ)购自上海陶素生化科技有限公司; 伊马替尼(IM)购自瑞士诺华制药有限公司; 胎牛血清和细胞培养基RPMI-1640购自美国Gibco公司; CCK8试剂盒购自索莱宝科技有限公司; DAPI试剂

盒、蛋白质提取试剂及BCA蛋白浓度测定试剂盒购自上海碧云天生物技术有限公司; PARP、Caspase3、p-BCR-ABL、BCR-ABL、p-STAT5、STAT5、P21抗体购自美国Cell Signaling Technology公司; LC3、P62抗体购自美国Bimake公司; β -actin抗体购自北京中杉金桥生物技术有限公司; IgG-HRP标记的山羊抗兔多克隆二抗、山羊抗鼠多克隆抗体购自杭州联科生物技术公司。

1.2 方法

1.2.1 细胞培养 人慢性髓细胞白血病细胞系K562、K562/G01均用含10%胎牛血清的RPMI-1640培养基在37 °C、5% CO₂的饱和湿度培养箱中培养, 当细胞密度达90%时传代。

1.2.2 CCK8实验 细胞以3 000个/孔的密度接种于96孔板, 每孔总体积为100 μ L。每组3复孔, 空白组为100 μ L RPMI-1640完全培养基, 处理组分别用0、0.032 5、0.062 5、0.125、0.25、0.5、1、2 μ mol/L的TSA进行处理, 分别于0 h、24 h、48 h、72 h、96 h时加入10 μ L CCK8试剂, 置于37 °C、5% CO₂恒温培养箱中避光孵育3 h, 在酶标仪波长为450 nm处读取各孔的吸光度(D)值。

1.2.3 克隆形成实验 细胞以100个/孔的密度接种于96孔板, 每孔总体积100 μ L, 每组3复孔, 分别用0、0.032 5 μ mol/L TSA进行处理, 置于37 °C、5% CO₂恒温培养箱培养7天, 于倒置显微镜下计数集落数量, 观察集落大小并拍照。

1.2.4 Western blot 收集各处理组细胞, 用蛋白裂解液(RIPA:PMSF:NaF:Na₃VO₄=100:1:1:1)裂解细胞, 冰上放置30 min, 每5 min剧烈涡旋15 s, 4 °C、13 300 r/min离心30 min提取总蛋白, BCA法测定蛋白浓度。每孔加样40 μ g蛋白质后, 再经10%的SDS-PAGE分离, 在210 mA恒流条件下湿转至PVDF膜上, 用含5%脱脂奶粉的TBST溶液室温封闭2 h, 加入相应一抗(稀释比例1:1 000)4 °C孵育过夜, 次日用TBST洗涤3次(5 min/次), 加入二抗(稀释比例1:5 000)室温孵育1 h, TBST洗涤3次(5 min/次), 采用ECL化学发光法检测目的蛋白表达情况。

1.2.5 DAPI染色 将1 \times 10⁶个细胞接种于2 mL体系的6孔板中, 不同浓度TSA处理24 h或48 h后收集细

胞, 涂片自然晾干, 用4%多聚甲醛于室温固定15 min, PBS洗涤3次(5 min/次); 加入DAPI(1:1 000 PBS稀释) 37 °C孵育15 min, PBS洗涤3次(5 min/次); 自然干燥, 甘油封片, 正置荧光显微镜下观察并拍照。

1.2.6 流式细胞术检测细胞凋亡 1 000 r/min离心5 min收集各处理组细胞, PBS洗涤3次(5 min/次), 再次在1 000 r/min条件下离心5 min, 最后用PBS重悬转移至EP管, 送凋亡测定。

1.2.7 统计学分析 各实验均独立重复3次, 使用GraphPad Prism 5.0软件进行统计学分析。计量资料使用均数±标准差($\bar{x}\pm s$)表示, 组间两两比较使用 t 检验分析, 多组间比较使用单因素方差分析, $P<0.05$ 表示差异有统计学意义。

2 结果

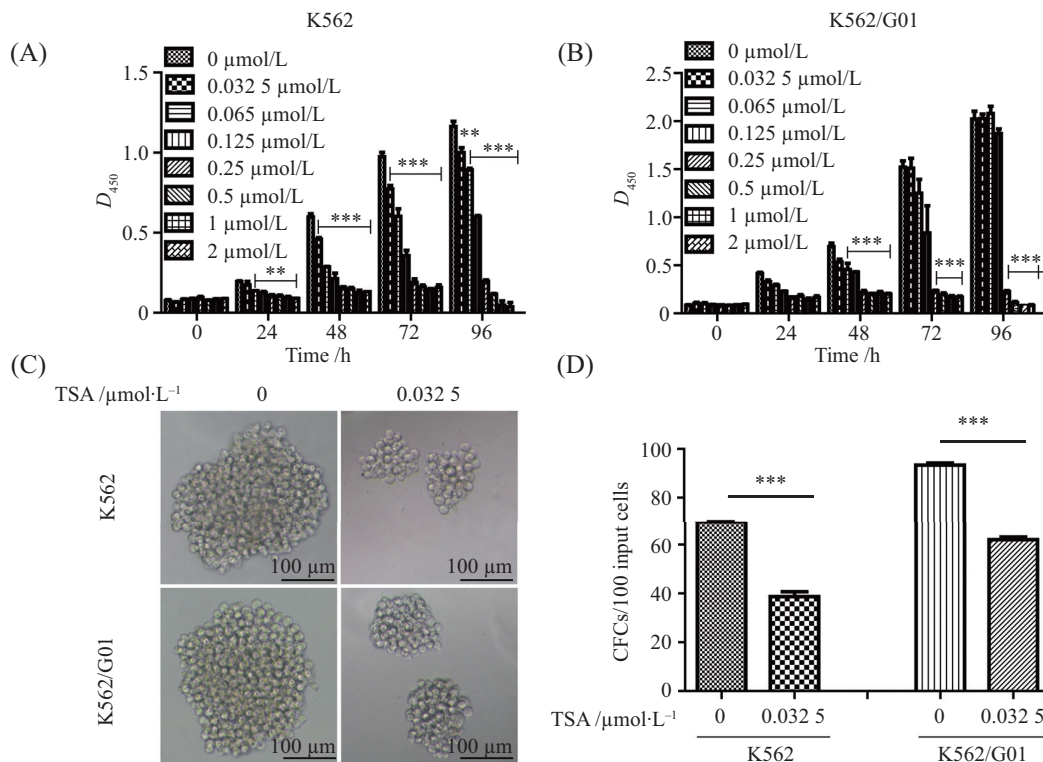
2.1 TSA抑制CML细胞的增殖和克隆形成能力

为了探究TSA对CML细胞增殖能力的影响,

用不同浓度TSA处理CML细胞K562和K562/G01, CCK8实验检测细胞增殖情况。结果显示, K562和K562/G01细胞增殖能力受到TSA时间和剂量依赖性抑制, TSA处理K562细胞24 h($P<0.01$), K562/G01细胞48 h时增殖差异具有统计学意义($P<0.001$)(图1A和图1B), 因此后续实验处理时间为K562细胞24 h, K562/G01细胞48 h。K562和K562/G01细胞经过低浓度TSA处理, 克隆形成实验显示, TSA处理组的克隆数量[K562(38.70 ± 3.51)、K562/G01(62.00 ± 2.00)]明显少于对照组[K562(69.33 ± 1.16)、K562/G01(93.33 ± 1.53)](图1D), 克隆形态显著小于对照组(图1C), 差异均具有统计学意义($P<0.001$)。以上实验均说明, TSA处理对CML细胞的增殖具有显著的抑制效果。

2.2 TSA促进CML细胞的凋亡

为了证实TSA对CML细胞凋亡的影响, 采用不同浓度TSA分别处理K562细胞(24 h)、K562/G01



A: CCK8检测不同浓度TSA对K562细胞增殖影响的柱状图; B: CCK8检测不同浓度TSA对K562/G01细胞增殖影响的柱状图; C: 使用TSA后K562和K562/G01细胞克隆形态; D: 使用TSA后K562和K562/G01细胞克隆数量。*** $P<0.001$, ** $P<0.01$, 与相应的0 $\mu\text{mol/L}$ TSA组比较。

A: the histogram of the effect on proliferation of K562 cells treated with different concentrations of TSA detected by CCK8 assay; B: the histogram of the effect on proliferation of K562/G01 cells treated with different concentrations of TSA detected by CCK8 assay; C: cell clone results of K562 cells and K562/G01 cells treated with TSA; D: the clone numbers of K562 cells and K562/G01 cells treated with TSA. *** $P<0.001$, ** $P<0.01$ vs the corresponding 0 $\mu\text{mol/L}$ TSA group.

图1 TSA对K562和K562/G01细胞增殖的影响

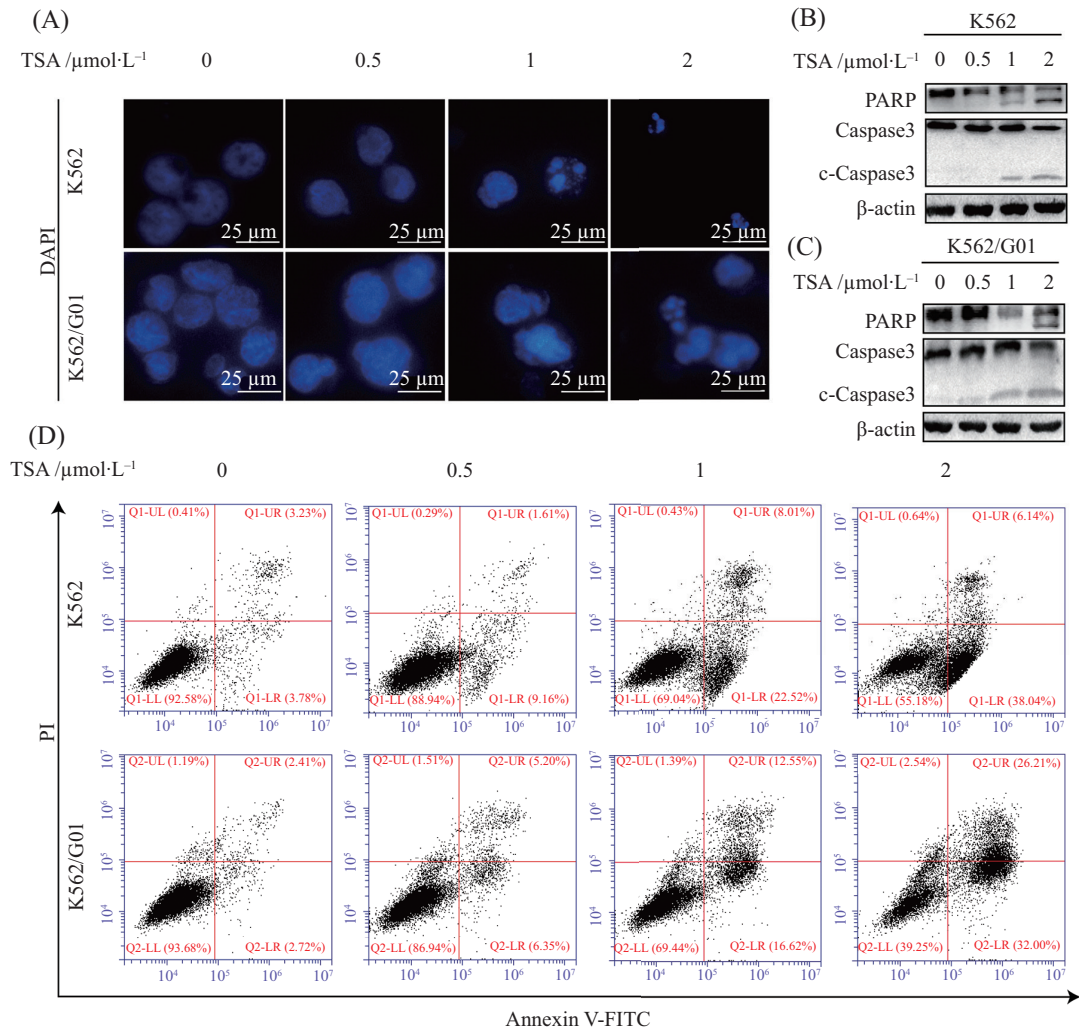
Fig.1 Effects of TSA on proliferation of K562 and K562/G01 cells

细胞(48 h), 利用流式细胞术、Western blot检测凋亡分子(PARP剪切体和Caspase3剪切体)及DAPI染色分析K562和K562/G01细胞的凋亡情况。流式细胞术结果显示, 1 $\mu\text{mol/L}$ 和2 $\mu\text{mol/L}$ 处理组凋亡率为30.53%、44.17%(K562细胞组), 29.17%、58.22%(K562/G01细胞组)。与对照组相比, TSA处理组K562和K562/G01细胞的凋亡明显增加, 且随着TSA浓度增高, 晚期凋亡细胞逐渐增多(图2D)。Western blot结果表明, 随着TSA浓度升高, K562和K562/G01处理组细胞逐渐出现PARP剪切体和Caspase3剪切体(图2B和图2C), 说明K562和K562/G01细胞发生凋亡。同时, DAPI染色显示, 与对照组相比,

TSA处理组K562和K562/G01细胞随着药物浓度增高, 核形态逐渐变形、皱缩至碎裂(图2A)。以上结果说明, TSA处理对CML细胞凋亡具有显著促进作用。

2.3 TSA和IM联用可以进一步促进CML凋亡

流式细胞术结果显示, 与对照组相比, 单独IM处理凋亡率为24.4%(K562细胞组)、15.7%(K562/G01细胞组); 单独TSA处理组凋亡率为39.9%(K562细胞组)、19.0%(K562/G01细胞组); 联合用药组凋亡率为56.9%(K562细胞组)、47.4%(K562/G01细胞组)(图3A和图3B)。Western blot结果显示, TSA处理组较IM处理组凋亡更明显(图3E和图3F)。以上结果

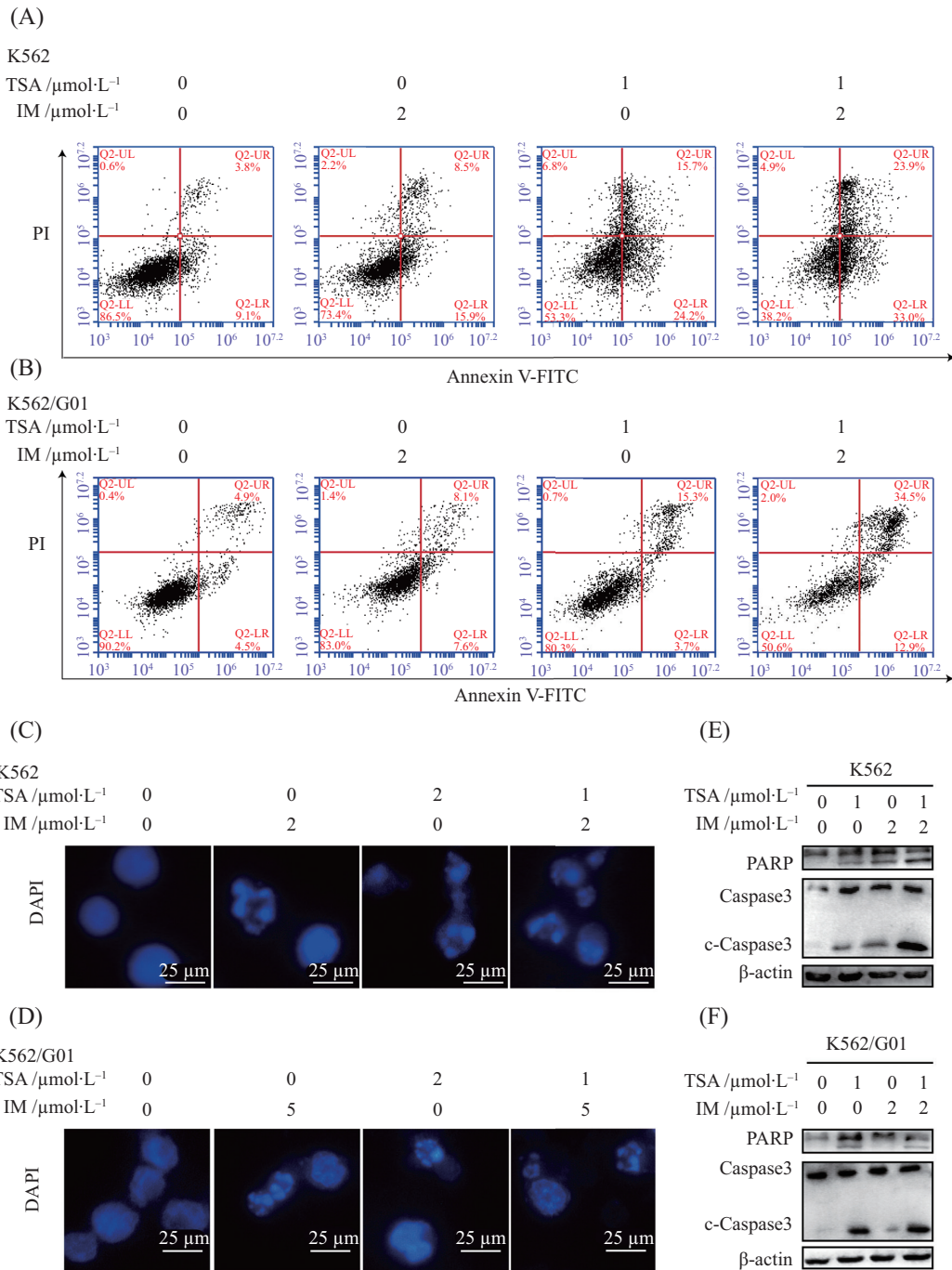


A: DAPI染色观察TSA处理K562(24 h)、K562/G01(48 h)后细胞核形态变化; B、C: Western blot检测TSA处理K562(24 h)、K562/G01(48 h)后细胞的凋亡情况; D: 流式细胞术检测TSA处理K562(24 h)、K562/G01(48 h)后细胞的凋亡情况。

A: the nucleus morphological changes of K562 (24 h) and K562/G01 (48 h) cells treated with TSA were detected by DAPI staining; B,C: the apoptosis of K562(24 h) and K562/G01 (48 h) cells treated with TSA was detected by Western blot; D: the apoptosis of K562 (24 h) and K562/G01 (48 h) cells treated with TSA was detected by Flow cytometry.

图2 TSA对K562和K562/G01细胞凋亡的影响

Fig.2 Effects of TSA on apoptosis of K562 and K562/G01 cells



A,B: 流式细胞术检测TSA、IM单独或联用处理K562(24 h)、K562/G01(48 h)后细胞的凋亡情况; C,D: DAPI染色观察TSA、IM单独或联用处理细胞K562(24 h)、K562/G01(48 h)后细胞核形态变化; E,F: Western blot检测TSA、IM单独或联用处理细胞K562(24 h)、K562/G01(48 h)后凋亡相关蛋白的表达。

A,B: the apoptosis of K562 (24 h) and K562/G01 (48 h) cells treated with TSA, IM alone and TSA combined with IM was detected by Flow cytometry; C,D: the nucleus morphological changes of K562 (24 h) and K562/G01 (48 h) cells treated with TSA, IM alone and TSA combined with IM was detected by DAPI staining; E,F: the expression of apoptosis-related proteins in K562 and K562/G01 cells treated with TSA, IM alone and TSA combined with IM was detected by Western blot.

图3 TSA与IM联用对K562和K562/G01细胞凋亡的影响

Fig.3 Effects of TSA combined with IM on proliferation and apoptosis of K562 and K562/G01 cells

表明, TSA对CML细胞凋亡的促进作用优于IM, 联合用药可以促进细胞凋亡的发生, 以细胞晚期凋亡更显著(图3)。

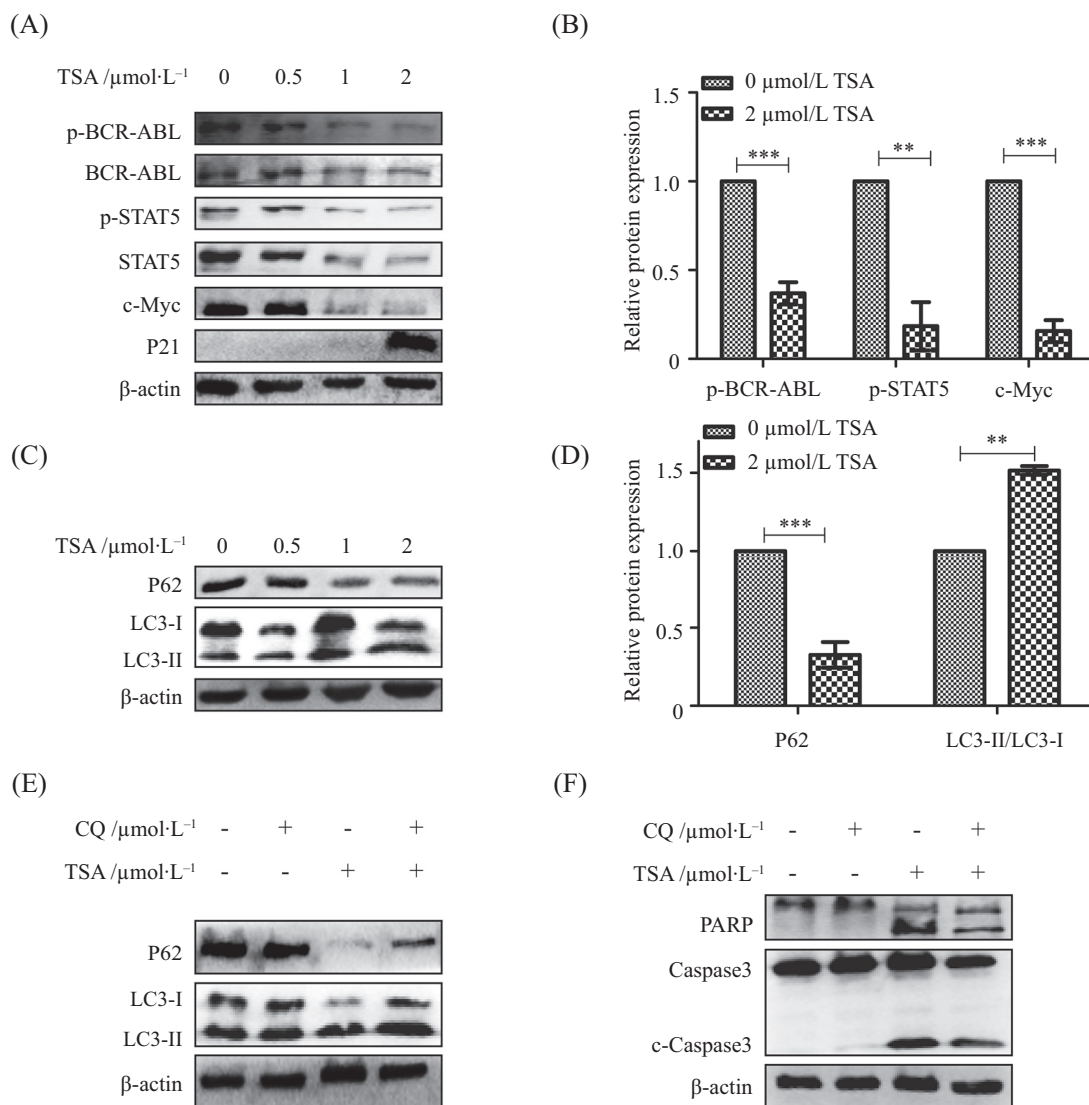
2.4 TSA减少BCR-ABL表达, 抑制下游STAT5信号通路

为探究TSA抑制CML细胞恶性增殖的机制, 我

们检测了TSA处理后BCR-ABL及其下游STAT5信号通路相关蛋白水平,发现p-BCR-ABL和p-STAT5蛋白水平降低,BCR-ABL、STAT5及c-Myc总蛋白水平降低(图4B)。结果提示TSA通过抑制BCR-ABL/STAT5信号通路,降低c-Myc蛋白水平而抑制CML细胞的增殖能力。

2.5 TSA通过增强CML细胞自噬促进其凋亡

相关研究发现,TSA可以增强部分肿瘤细胞的自噬促进其凋亡^[13-16],为探讨TSA能否通过增强K562细胞自噬促进其凋亡,K562细胞经不同浓度TSA处理24 h后,Western blot检测自噬底物P62蛋白和自噬产物LC3蛋白含量判断细胞自噬水平变化。



A: Western blot检测TSA处理K562细胞24 h后BCR-ABL通路相关蛋白水平; B: Western blot检测TSA处理K562细胞24 h后BCR-ABL通路相关蛋白量化图; C: Western blot检测TSA处理K562细胞24 h后自噬相关蛋白水平; D: Western blot检测TSA处理K562细胞24 h后自噬相关蛋白量化图; E: Western blot检测TSA和CQ处理K562细胞24 h后自噬相关蛋白水平; F: Western blot检测TSA和CQ处理K562细胞24 h后自噬相关蛋白量化图。
P<0.01, *P<0.001。

A: Western blot was used to detect the BCR-ABL pathway related proteins in K562 cells treated with TSA for 24 h; B: the relative level of BCR-ABL pathway related proteins in K562 cells treated with TSA for 24 h; C: Western blot was used to detect autophagy-related proteins in K562 cells treated with TSA for 24 h; D: the autophagy-related proteins relative protein level in K562 cells treated with TSA for 24 h; E: Western blot was used to detect autophagy-related proteins in K562 cells treated with TSA and CQ; F: Western blot was used to detect apoptosis-related proteins in K562 cells treated with TSA and CQ for 24 h. **P<0.01, ***P<0.001.

图4 Western blot检测不同浓度TSA处理K562细胞24 h后BCR-ABL通路相关蛋白水平及自噬相关蛋白水平

Fig.4 The BCR-ABL pathway-related proteins levels and autophagy-related proteins levels in K562 cells treated with different concentrations of TSA for 24 h were detected by Western blot

结果显示,随着TSA浓度增加,P62蛋白含量逐渐减少,LC3-II/LC3-I逐渐增加(图4C和图4D),表明TSA可以促进CML细胞自噬的发生。为进一步证明TSA通过增强CML细胞自噬促进细胞凋亡,引入自噬抑制剂氯喹(CQ)阻断自噬流,发现CQ的使用可部分回复TSA引起的细胞凋亡(图4F),且伴随着P62回复,LC3-II阻滞(图4E)。以上结果说明,TSA通过增强CML细胞自噬促进其凋亡。

3 讨论

CML是血液系统的恶性克隆性肿瘤,IM的使用有效延长了患者生存期,但由于BCR-ABL激酶区点突变、白血病干细胞的存在常常使病人对TKIs产生耐药,导致疾病复发或急变,临床上目前尚无有效的应对方式,亟需寻找新的治疗靶点^[1-5]。基于HDAC抑制剂TSA在多种肿瘤细胞中可以通过增强细胞自噬影响肿瘤细胞的增殖和凋亡^[12-15],本研究着眼于TSA对CML急变期细胞系K562及耐药细胞株K562/G01增殖、凋亡的影响,并深入探究其作用机制。

本研究发现,TSA具有显著抑制CML细胞恶性增殖的作用;流式细胞术、DAPI染色及Western blot等实验结果显示,TSA的使用明显促进了CML细胞的凋亡,这与陈曙平等^[17]研究相符,在此基础上我们进一步探寻TSA对CML细胞抑增殖促凋亡作用的相关机制。CML细胞中BCR-ABL融合蛋白持续激活的酪氨酸激酶活性使得下游相关信号通路异常活化,诱导血液细胞恶性增殖,导致CML的发生发展。我们的结果显示,随着TSA浓度的增加,p-BCR-ABL和p-STAT5蛋白水平显著降低,BCR-ABL、STAT5、c-Myc蛋白水平降低。说明TSA通过降低p-BCR-ABL、BCR-ABL蛋白水平,有效抑制BCR-ABL/STAT5/c-Myc信号轴,下调c-Myc蛋白,最终抑制CML细胞系K562、K562/G01的恶性增殖。与IM相比,TSA对CML细胞的杀伤能力更强;与单独使用IM、TSA相比,TSA与IM联用组中的CML凋亡率显著增加,晚期凋亡明显增多,说明TSA与IM联用可以显著增强对CML细胞的杀伤力。

已有研究证实,部分HDAC抑制剂可诱导细胞自噬而引起细胞凋亡^[18],且近年相关研究表明,TSA可以通过促进多种肿瘤细胞的自噬来诱发其凋亡,但TSA能否通过诱导自噬来促进CML细胞凋亡尚未有报道。本研究使用不同浓度TSA处理CML

细胞,细胞出现不同程度凋亡,且自噬底物P62蛋白明显减少,LC3-II/LC3-I增加,证明使用TSA促进了K562细胞的自噬,自噬抑制剂CQ的引入可部分回复TSA引起的凋亡,进一步说明TSA可以通过诱导CML细胞发生自噬促进细胞凋亡。

综上所述,本研究揭示了TSA在CML细胞中的作用机制,一方面可以下调p-BCR-ABL蛋白水平,减少p-STAT5活化,导致c-Myc蛋白水平降低从而抑制CML细胞的恶性增殖;另一方面,可以通过增强CML细胞自噬促使细胞发生凋亡,达到杀死CML细胞的效果;且TSA与IM联用可以增强对CML细胞的杀伤作用。TSA的使用可以满足临床上IM耐药患者的治疗需求,有望成为CML治疗急变期或耐药患者的潜在药物。

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