

人参皂苷Rg1通过MAPK通路对小鼠再生障碍性贫血治疗的影响

李 焱¹, 段爽爽^{2,3}, 韩净净³, 韩锦煊^{3,4}, 辛春雷^{3,5*}

¹山东理工职业学院, 中医康养康育学院, 山东 济宁

²济宁医学院, 临床医学院, 山东 济宁

³济宁市第一人民医院, 血液内科, 山东 济宁

⁴山东第二医科大学, 临床医学院, 山东 潍坊

⁵新疆维吾尔自治区喀什地区英吉沙县人民医院, 新疆 喀什

收稿日期: 2025年3月8日; 录用日期: 2025年3月31日; 发布日期: 2025年4月9日

摘 要

目的: 本研究旨在评价人参皂苷Rg1对AA的保护作用, 并进一步探讨其机制。方法: 本研究通过注射环磷酰胺(CTX)建立骨髓抑制小鼠模型。CTX + Rg1组小鼠Rg1灌胃13 d。HE检测骨髓、胸腺和脾脏的病理变化。取小鼠眼眶血进行血常规检查。然后用流式细胞仪检测骨髓细胞的比例。通过WB检测MAPK通路中p-p38、p38、p-JNK、JNK、p-ERK、ERK的表达。结果: 病理检查显示, CTX严重破坏小鼠骨髓、胸腺和脾脏的结构特征, 降低骨髓造血细胞的比例。Rg1可通过抑制MAPK信号通路显著减轻小鼠骨髓抑制。结论: 本研究提示人参皂苷Rg1通过MAPK信号通路缓解骨髓抑制作用, 对AA有一定的治疗作用。

关键词

再生障碍性贫血, 人参皂苷Rg1, 骨髓抑制, MAPK信号通路, 骨髓

Effect of Ginsenoside Rg1 in Treating Aplastic Anemia in Mice via MAPK Pathway

Yan Li¹, Shuangshuang Duan^{2,3}, Jingjing Han³, Jinxuan Han^{3,4}, Chunlei Xin^{3,5*}

¹Chinese Medicine Kangyang Kangyu College, Shandong Polytechnic College, Jining Shandong

²Clinical College, Jining Medical University, Jining Shandong

³Department of Hematology, Jining No. 1 People' Hospital, Jining Shandong

⁴School of Clinical Medicine, Shandong Second Medical University, Weifang Shandong

⁵People's Hospital of Yingjisha County, Kashgar Prefecture, Xinjiang Uygur Autonomous Region, Kashgar Xinjiang

Received: Mar. 8th, 2025; accepted: Mar. 31st, 2025; published: Apr. 9th, 2025

*通讯作者。

文章引用: 李焱, 段爽爽, 韩净净, 韩锦煊, 辛春雷. 人参皂苷 Rg1 通过 MAPK 通路对小鼠再生障碍性贫血治疗的影响[J]. 临床个性化医学, 2025, 4(2): 860-869. DOI: 10.12677/jcpm.2025.42254

Abstract

Objective: This study was designed to evaluate the protective effects of ginsenoside Rg1 on AA and further investigate the underlying mechanism. **Methods:** In this study, Cyclophosphamide (CTX) was injected to establish the myelosuppression mouse model. The mice in the CTX + Rg1 group were treated with Rg1 for 13 days. The pathological changes of bone marrow, thymus, and spleen were detected through HE (Hematoxylin-Eosin St). Orbital blood of mice was collected for blood routine examination. Afterwards, the proportions of bone marrow cells were evaluated by flow cytometry assay. MAPK pathway was detected via WB for the expressions of p-p38, p38, p-JNK, JNK, p-ERK, and ERK. **Results:** Pathological examination revealed that CTX severely damaged the structural features of the bone marrow, thymus, and spleens, and decreased the proportion of hematopoietic cells in the bone marrow of mice. Treatment of Rg1 significantly alleviated myelosuppression in mice by inhibiting MAPK signaling pathway. **Conclusion:** This study suggested that ginsenoside Rg1 treated AA by alleviating myelosuppression through MAPK signaling pathway.

Keywords

Aplastic Anemia, Ginsenoside Rg1, Myelosuppression, MAPK Signaling Pathway, Bone Marrow

Copyright © 2025 by author(s) and Hans Publishers Inc.

This work is licensed under the Creative Commons Attribution International License (CC BY 4.0).

<http://creativecommons.org/licenses/by/4.0/>



Open Access

1. 前言

再生障碍性贫血(AA)是一种由物理、化学和生物因素所导致的原发性或继发性骨髓造血干细胞(HSCs)和/或造血微环境异常性疾病[1]。AA 各年龄组均有发生,主要表现为全血细胞减少,可导致严重感染、贫血和出血[2]。AA 是一种由 T 淋巴细胞异常激活和功能亢进所致的骨髓损伤,其中调节性 T 细胞(Treg)/辅助性 T 型 17 (TH17)细胞的免疫失衡是 AA 的主要原因[3] [4]。随着免疫抑制治疗和造血干细胞移植的发展,再生障碍性贫血的预后有了明显的改善。然而,免疫抑制剂在某些患者中仍然无效[5] [6]。

人参(*Panax ginseng* C. A. Meyer)是五加科多年生草本植物,是传统中药材。具有振奋元气、补益津液、固发、健脾益肺、安神的作用[7]。人参皂苷是人参中的主要活性成分。根据皂苷元的结构,人参皂苷分为达玛烷型四环三萜皂苷、奥克梯隆型四环三萜皂苷和齐墩果酸皂苷[8]。近年来研究发现,人参皂苷的药理作用主要包括心肌保护、体内糖脂代谢、抗氧化、抗肿瘤和治疗血液系统疾病等[9]-[12]。人参皂苷能促进红系、粒系和巨核细胞系的增殖和分化,这可能与人参皂苷对造血生长因子(HGF)的影响有关[13]。骨髓基质中的细胞因子作为造血微环境的重要调节因子,可以作用于造血的各个阶段,包括促进造血祖/干细胞的增殖分化,延长造血细胞的存活。体外研究表明人参总皂苷(TSPG)可诱导促红细胞生成素(EPO)、粒细胞-巨噬细胞集落刺激因子(CSF)、白细胞介素 3 (IL-3)、白细胞介素 6 (IL-6)及促红细胞生成素受体和粒细胞-巨噬细胞集落刺激因子受体 α 链的显著升高[14]。人参皂苷还可刺激造血祖细胞 GATA-2 基因的 mRNA 表达和蛋白质合成的增加, GATA-2 与 DNA 结合的增加可调控增殖相关基因的表达,从而促进血细胞增殖[15]。

MAPK 信号通路主要包括 c-jun 氨基末端激酶(JNK)、p38 丝裂原活化蛋白激酶(p38 MAPK)、细胞外信号调节蛋白激酶(ERK)和大丝裂原活化蛋白激酶(ERK5/BMK1) [16], 参与细胞生长、发育、分裂和死亡

过程, 以及细胞间多种生化反应信号的识别、传递和放大[17] [18]。研究发现人参皂苷 Rg1 通过 MAPK 途径抑制炎症因子 IL-1 β 和 IL-6 的表达, 减轻缺血再灌注的神经损伤[19]。张等人发现人参皂苷 Rg1 可通过 MAPK 途径促进小鼠骨髓内皮祖细胞增殖[20]。

本研究用环磷酰胺(CTX)建立小鼠骨髓抑制模型, HE 染色观察骨髓病理变化, 证明该模型是成功的。取小鼠眼眶血用于检查血液中细胞的组成。通过检测小鼠骨髓 MAPK 信号通路的细胞成分和蛋白表达变化, 验证人参皂苷 Rg1 是否能通过 MAPK 信号通路减轻小鼠骨髓抑制, 为临床治疗 AA 提供新的理论依据。

2. 方法

2.1. 动物

选用 SPF 级雄性 BALB/c 小鼠(6~8 周龄) 25 只, 自由饮水和进食。室温保持在 20℃~24℃, 相对湿度为 40%~60%。小鼠购自武汉赛维尔生物科技有限公司。

2.2. 药物

对于 CTX(西格玛, 圣路易斯, 密苏里州, 美国), 将 200 mg 粉末溶解在 20 ml 0.9%的盐水中。人参皂苷 Rg1(中国辽宁大连宏九生物科技有限公司)的化学结构如图 1(A)所示。

2.3. 模型准备

将小鼠随机分为 5 组: 对照组、对照组 + RG1 (15 mg/kg)组、CTX + 生理盐水组、CTX + RG1 (10 mg/kg)组和 CTX + RG1 (15 mg/kg)组, 每组 5 只。动物模型制备流程如图 1(B)所示。

2.4. 血液检查

取眼眶血后处死小鼠。采用血常规检测仪(RJ-0C107223, 迈瑞, 中国)进行全血血常规检查。

2.5. HE 染色

HE 染色按 HE 染色试剂盒(Solarbio, 北京, 中国)的规程进行。简言之, 切片(4 μ m)用苏木精 - 伊红染色 1 min, 并在酸性液体酒精中分化 30 s。染色结束后, 切片用 95%的乙醇脱水 50 s。最后, 切片在二甲苯中清洗并固定。用日本尼康公司的 CI-L 显微镜获取图像, 并用 Image J 软件进行分析。

2.6. 流式细胞术

收集骨髓细胞用于流式细胞分析。将骨髓细胞以每孔 105 个细胞的密度接种于加 10% FBS (胎牛血清)的 2 毫升培养基中。培养不同时间间隔后, 收集细胞, 用 PBS (磷酸盐缓冲液)洗涤 2 次, 用 0.25%胰蛋白酶进行胰蛋白酶化。然后, 将收集的细胞在 1500 转/分下离心 5 分钟。在 5 毫升 PBS 中再悬浮后, 用流式细胞术(Attune 细胞分析仪, BD 生物科学)对细胞进行分析。

2.7. 蛋白质印记

从骨髓中提取总蛋白进行 Western 印迹检测。蛋白样品与 p38 (Abcam, Waltham, MA, USA)、p-p38 (Abcam, Waltham, MA, USA)、JNK (Abcam, Waltham, MA, USA)、p-JNK (Abcam, Waltham, MA, USA)、ERK (Abcam, Waltham, MA, USA)、p-ERK (Abcam, Waltham, MA, USA)共孵育。GADPH (Abcam, 美国马萨诸塞州沃尔瑟姆)作为内部参考。

2.8. 统计分析

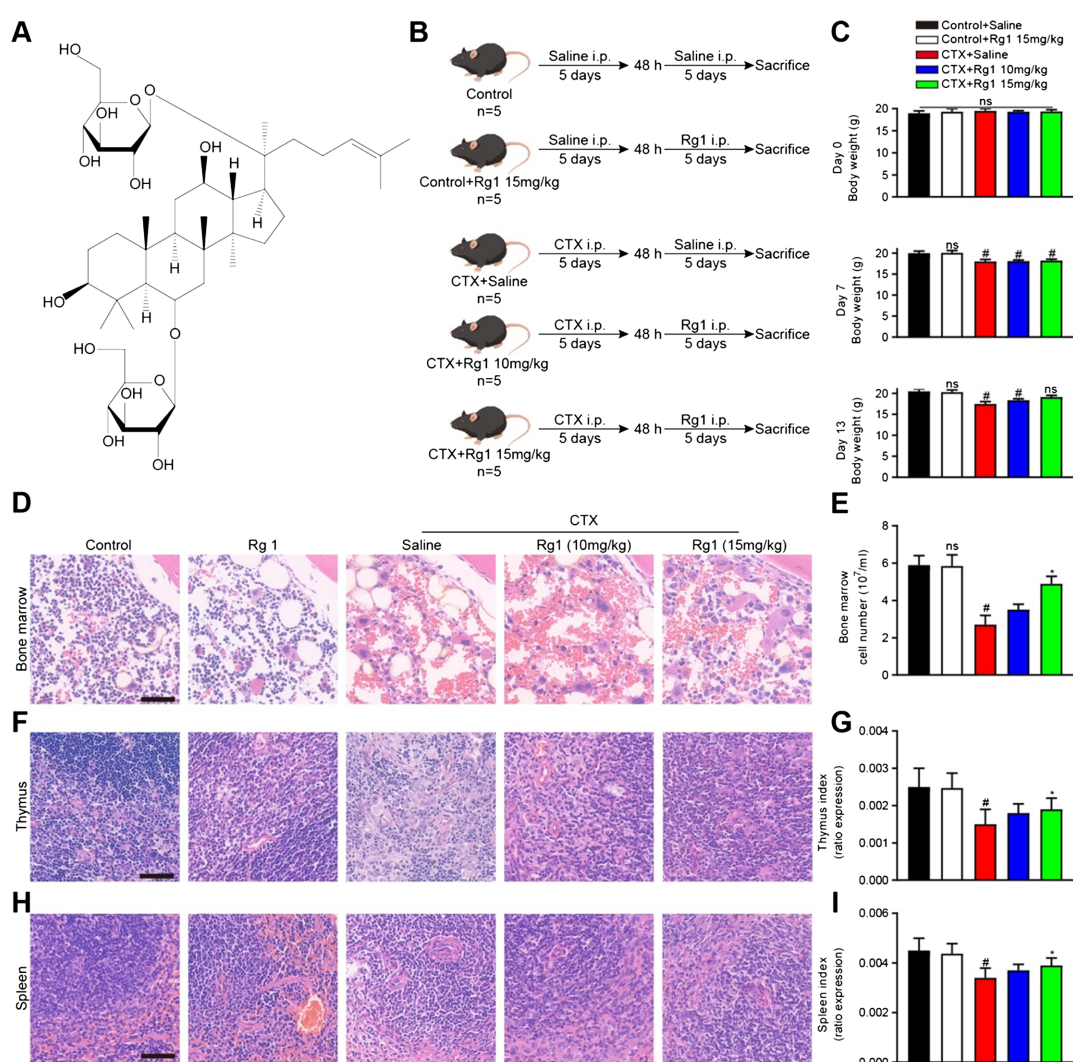
采用 SPSS 24.0 统计软件对实验数据进行统计分析, 计量资料用均数 $\pm$ 标准差($\bar{X} \pm SD$)表示, 满足

正态分布和方差齐性时,采用 t 检验(两组比较)或 LSD 方差分析(多组间比较)。采用 Dunnett's-t3 法进行方差不均匀比较, $P < 0.05$ 为差异有统计学意义。

3. 结果

3.1. 人参皂苷 Rg1 对 CTX 诱导的骨髓抑制小鼠的作用

实验开始前,各组小鼠体重无明显差异。药物干预 7 d 后,CTX 组小鼠体重低于对照组。药物治疗 13 d 后,CTX 组小鼠体重明显低于对照组;而 CTX + Rg1 (15 mg/kg)组与对照组相比,体重无显著差异(图 1(C))。与对照组相比,注射 CTX 后小鼠骨髓细胞数、胸腺和脾脏指数均明显下降。与 CTX 组相比,CTX + Rg1 (15 mg/kg)组小鼠骨髓细胞数、胸腺指数和脾脏指数均显著增加(图 1(D)~(I))。提示 Rg1 可改善 CTX 诱导的小鼠骨髓抑制。



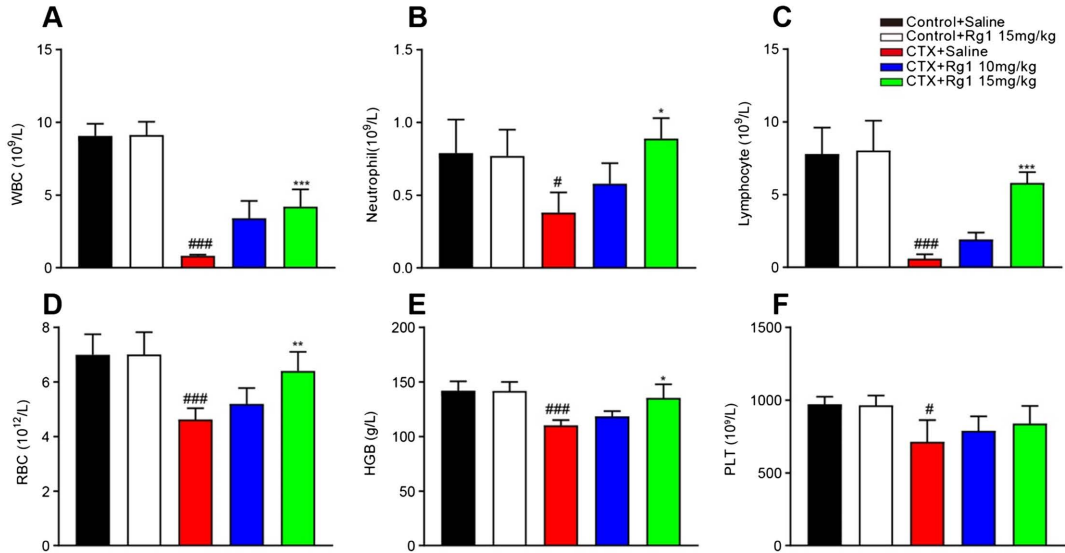
(A) 人参皂苷 Rg1 化学结构, (B) 实验流程图, (C) 小鼠体重图, (D) 骨髓标本 HE 染色, (E) 骨髓细胞统计图, (F) 胸腺 HE 染色, (G) 胸腺指数统计图, (H) 脾脏 HE 染色, (I) 脾脏指数统计图。所有统计图: $n = 5$ 只小鼠; #与对照组比较, $P < 0.05$; *与 CTX 组比较, $P < 0.05$ 。

Figure 1. Ginsenoside Rg1 prevents myelosuppression

图 1. 人参皂苷 Rg1 可预防骨髓抑制

3.2. 人参皂苷 Rg1 对小鼠血细胞的影响

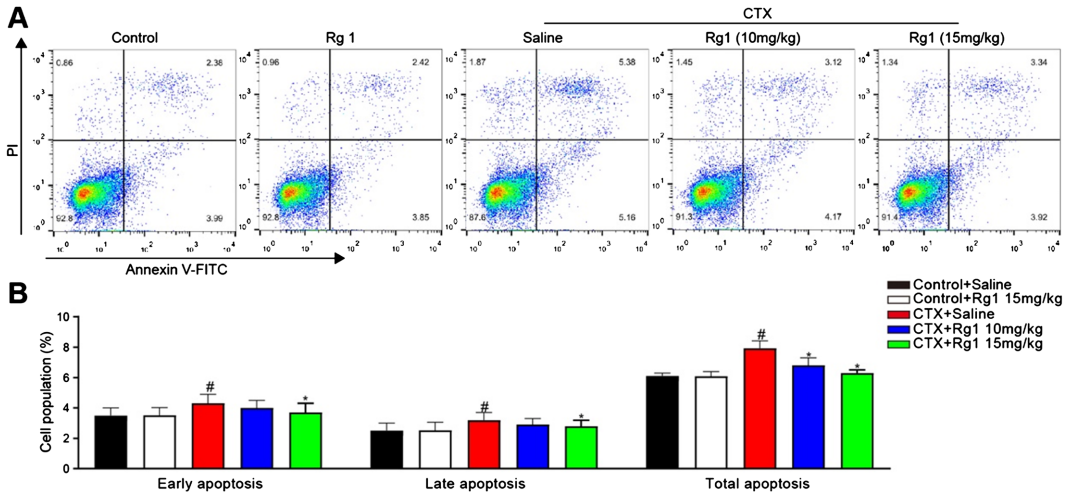
药物治疗后,小鼠眶后采血提取全血,测定全血计数和生化指标。如图 2 所示,CTX 组小鼠白细胞(WBC)、中性粒细胞、淋巴细胞(RBC)、红细胞(RBC)、血红蛋白(HGB)和血小板(PLT)计数较对照组明显下降。与 CTX 组相比,CTX + Rg1 (15 mg/kg)组小鼠 WBC、中性粒细胞、淋巴细胞、RBC、HGB 计数明显增加,但 PLT 计数无明显增加(图 2(A)~(F))。



白细胞数(A), 中性粒细胞(B), 淋巴细胞数(C), 红细胞数(D), 血红蛋白数(E), 血小板数(F)。WBC: 白细胞; RBC: 红细胞; HGB: 血红蛋白; PLT: 血小板; #与对照组比较, $P < 0.05$; ###与对照组比较, $P < 0.001$; **与 CTX 组比较, $P < 0.01$; ***与 CTX 组比较, $P < 0.001$ 。

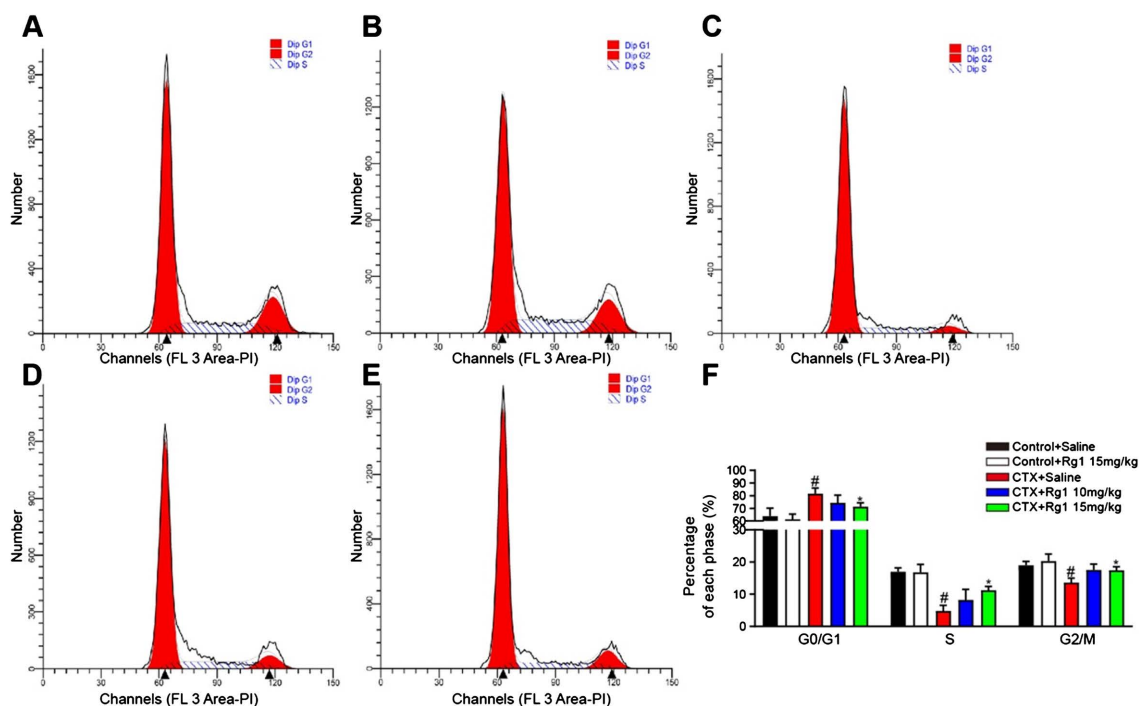
Figure 2. Rg1 increased cell numbers in the peripheral blood of mice with myelosuppression
图 2. Rg1 增加骨髓抑制小鼠外周血中的细胞数量

3.3. 人参皂苷 Rg1 对再生障碍性贫血小鼠 HSCs 自我更新的影响



(A) 具有代表性的流式细胞术结果。(B) 流式细胞术统计图。# $P < 0.05$, 与对照组相比; *与 CTX 组比较, $P < 0.05$ 。

Figure 3. Rg1 inhibits apoptosis of HSCs
图 3. Rg1 抑制造血干细胞凋亡



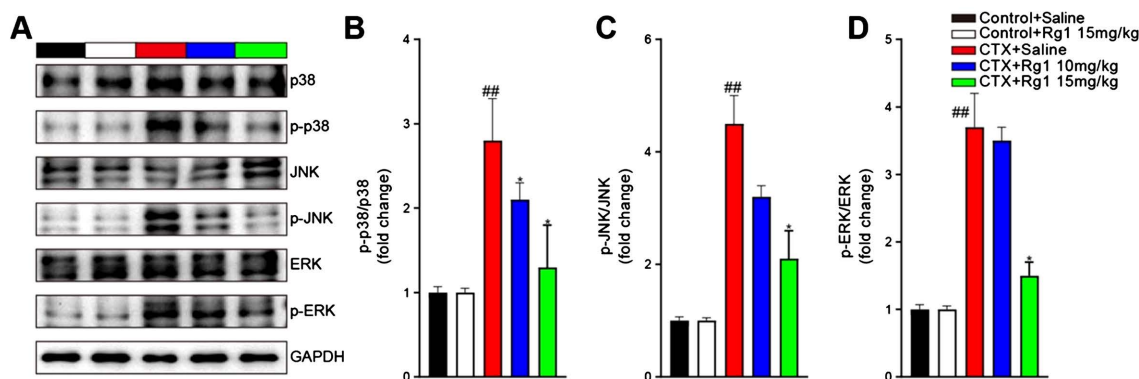
(A)~(E) 具有代表性的流式细胞术结果; (F) 流式细胞术统计图。

Figure 4. Rg1 increased the rate of the cell cycle of LSK

图 4. Rg1 使 LSK 细胞周期加快

流式细胞术显示 CTX 较对照组明显增加 HSCs 凋亡。而 Rg1 (15 mg/kg) 则明显降低 HSCs 的凋亡(图 3(A), 图 3(B))。如图 4 所示, CTX 显著增加 G0/G1 期细胞数量, 降低 S 期和 G2/M 期细胞数量, 说明 CTX 显著抑制细胞生长。而 Rg1 (15 mg/kg) 处理可显著逆转上述变化。

3.4. 人参皂苷 Rg1 对 MAPK 通路的影响



(A) western blot 图像。(B)~(D) 定量 western blot 图像。##与对照组相比, $P < 0.05$; *与 CTX 组比较, $P < 0.05$ 。

Figure 5. Rg1 alleviated myelosuppression in mice by inhibiting MAPK signaling pathway

图 5. Rg1 通过抑制 MAPK 信号通路减轻小鼠骨髓抑制

Western blot 蛋白质印迹法分别测定 p-p38, p38, p-JNK, JNK, p-ERK 和 ERK 蛋白水平。与对照组相比, p-p38/p38、p-JNK/JNK、p-ERK/ERK 蛋白表达明显增加。与 CTX 组相比, Rg1 (15 mg/kg) 可降低

p-P38/p38、p-JNK/JNK 和 p-ERK/ERK 的表达水平(图 5(A)~(D))。因此,我们认为 Rg1 通过激活 MAPK 信号通路减轻 CTX 诱导的骨髓抑制。

4. 讨论

再生障碍性贫血(AA)是儿童期常见的难治性血液疾病之一。AA 患者因机体骨髓造血干细胞和(或)骨髓造血微环境功能障碍导致贫血;造血红髓被脂肪取代,导致血细胞计数降低[21]。在中医学中,AA 被认为是“急性消耗病”和“骨髓缺乏症”[22]。越来越多的研究揭示了传统中草药治疗 AA 的有效性[23]-[25]。

多年来,人参皂苷 Rg1 一直用于治疗 AA 和骨髓损害。通过 SIRT6/NF- κ B 信号转导轴抑制造血缺损,延缓造血干/祖细胞衰老[26] [27];通过调节 SIRT1-FOXO3 和 SIRT3-SOD2 信号转导途径,维持 HSC 并调节 HSC 在骨髓中的增殖,防止 HSC 衰老,恢复造血[28] [29]。本研究通过注射 CTX 成功地建立了小鼠骨髓抑制模型。CTX 是一种常用的化疗药物,抑制骨髓造血诱导 AA [30]。我们观察到注射 CTX 后 7 天和 13 天小鼠体重下降。此外,CTX 还能降低小鼠骨髓细胞数、胸腺和脾脏指数。血常规结果显示 CTX 组小鼠 WBC、淋巴细胞、RBC、HGB、血小板 PLT 均明显降低。Rg1 尤其是 15 mg/kg 注射液的 Rg1 能明显减轻 CTX 所致的小鼠骨髓抑制。因此,这些结果提示 Rg1 对 AA 有一定的改善作用。

造血是一个产生各种类型成熟血细胞的动态过程[31] [32]。骨髓是人出生后最重要的造血器官。在小鼠中,初级血液系统在血岛中产生血细胞,并从胚胎第 7.5 天开始在卵黄囊中产生一批原始红系细胞,主要包括红细胞、巨噬细胞(MFS)和巨核细胞(MKS) [33]。最终,在胚胎第 10.5 天左右,造血部位迁移到主动脉-性腺-中肾(AGM)区域,这是永久造血[34]。与成人骨骼研究一样,小鼠胎儿肝脏血液系统也由多个谱系组成[35]。淋巴细胞主要包括 T 淋巴细胞、B 淋巴细胞和自然杀伤(NK)细胞,而红细胞、粒细胞、巨核细胞和单核巨噬细胞属于髓系细胞[36] [37]。不成熟的祖细胞,包括粒细胞-巨噬细胞祖细胞(GMP)、普通髓系祖细胞(CMP)、巨核细胞红系祖细胞(MEP)和普通淋巴样祖细胞(CLP),并不完全依赖于特定的谱系,可以通过适当的刺激重新定向[38]-[40]。

造血干细胞(HSCs)在造血中起着重要的作用。HSCs 的稳态决定了各种造血/血细胞的命运。在小鼠中,HSC 由 Lin-Sca-1 + c-Kit + (LSK)免疫表型广义定义,并分为两种类型:长期 HSC (LT-HSC)和短期 HSC (ST-HSC) [41]。原始 HSCs 产生定向祖细胞,进一步分化为成熟血细胞[42]。本研究通过流式细胞术观察到 CTX 对小鼠骨髓细胞有明显的影响,使 CMP、GMP、MEP 和 CLP 减少。此外,CTX 还增加了 HSCs 的凋亡,这与前人的研究一致。Rg1 通过逆转 CTX 诱导的骨髓细胞损伤而改善小鼠造血功能障碍。

当 GTP 与 RAS 结合时,RAS 被激活,将胞浆中的 RAF 募集到细胞膜上,最终激活 MAPK。MAPK 被激活后,可转导入细胞核,激活转录因子。研究表明,G-CSF 结合 GCSFR 可通过 Ras/MEK/ERK 信号通路促进中性粒细胞生成和骨髓前体细胞向粒细胞分化[43] [44]。动物实验结果表明,MEK 激酶抑制剂 UO126 能抑制 G-CSF 介导的骨髓细胞增殖[45]。相反,激活 MAPK 可增强 G-CSF 刺激状态阴性的骨髓细胞的增殖。p38 MAPK 是 MAPK 的亚类之一,可直接参与细胞凋亡、细胞因子产生、细胞骨架识别和转录调控[46]。既往研究表明,细胞骨架蛋白可直接参与 p38 通路的调控,在细胞分化、迁移、增殖和凋亡中发挥重要作用,增加酪氨酸酶基因的表达水平,在骨髓抑制中发挥重要作用[47] [48]。CTX 组 p-p38/p38、p-JNK/JNK、p-ERK/ERK 表达明显增高。同时,Rg1 显著逆转了这些蛋白的表达。

5. 结论

人参皂苷 Rg1 通过抑制 MAPK 信号通路改善小鼠骨髓抑制,为临床治疗 AA 提供了理论依据。

基金项目

新疆维吾尔自治区自然科学基金 2020D01A129。

伦理说明

本项目已通过济宁医学院临床医学院伦理委员会审核(JNRM-2021025)。

参考文献

- [1] DeZern, A.E. and Churpek, J.E. (2021) Approach to the Diagnosis of Aplastic Anemia. *Blood Advances*, **5**, 2660-2671. <https://doi.org/10.1182/bloodadvances.2021004345>
- [2] Furlong, E. and Carter, T. (2020) Aplastic Anaemia: Current Concepts in Diagnosis and Management. *Journal of Paediatrics and Child Health*, **56**, 1023-1028. <https://doi.org/10.1111/jpc.14996>
- [3] Kordasti, S., Costantini, B., Seidl, T., Perez Abellan, P., Martinez Llordella, M., McLornan, D., et al. (2016) Deep Phenotyping of Tregs Identifies an Immune Signature for Idiopathic Aplastic Anemia and Predicts Response to Treatment. *Blood*, **128**, 1193-1205. <https://doi.org/10.1182/blood-2016-03-703702>
- [4] Liu, C., Sun, Y. and Shao, Z. (2019) Current Concepts of the Pathogenesis of Aplastic Anemia. *Current Pharmaceutical Design*, **25**, 236-241. <https://doi.org/10.2174/1381612825666190313113601>
- [5] Peslak, S.A., Olson, T. and Babushok, D.V. (2017) Diagnosis and Treatment of Aplastic Anemia. *Current Treatment Options in Oncology*, **18**, 70-92. <https://doi.org/10.1007/s11864-017-0511-z>
- [6] Bacigalupo, A. (2017) How I Treat Acquired Aplastic Anemia. *Blood*, **129**, 1428-1436. <https://doi.org/10.1182/blood-2016-08-693481>
- [7] Mancuso, C. and Santangelo, R. (2017) *Panax ginseng* and *Panax quinquefolius*: From Pharmacology to Toxicology. *Food and Chemical Toxicology*, **107**, 362-372. <https://doi.org/10.1016/j.fct.2017.07.019>
- [8] Luo, M., Yan, D., Sun, Q., Tao, J., Xu, L., Sun, H., et al. (2019) Ginsenoside Rg1 Attenuates Cardiomyocyte Apoptosis and Inflammation via the TLR4/NF- κ B/NLRP3 Pathway. *Journal of Cellular Biochemistry*, **121**, 2994-3004. <https://doi.org/10.1002/jcb.29556>
- [9] Chen, J., Zhang, X., Liu, X., Zhang, C., Shang, W., Xue, J., et al. (2019) Ginsenoside Rg1 Promotes Cerebral Angiogenesis via the PI3K/Akt/mTOR Signaling Pathway in Ischemic Mice. *European Journal of Pharmacology*, **856**, Article ID: 172418. <https://doi.org/10.1016/j.ejphar.2019.172418>
- [10] Jiang, L., Yin, X., Chen, Y., Chen, Y., Jiang, W., Zheng, H., et al. (2021) Proteomic Analysis Reveals Ginsenoside Rb1 Attenuates Myocardial Ischemia/Reperfusion Injury through Inhibiting ROS Production from Mitochondrial Complex I. *Theranostics*, **11**, 1703-1720. <https://doi.org/10.7150/thno.43895>
- [11] Li, L., Wang, Y., Guo, R., Li, S., Ni, J., Gao, S., et al. (2020) Ginsenoside Rg3-Loaded, Reactive Oxygen Species-Responsive Polymeric Nanoparticles for Alleviating Myocardial Ischemia-Reperfusion Injury. *Journal of Controlled Release*, **317**, 259-272. <https://doi.org/10.1016/j.jconrel.2019.11.032>
- [12] Zhen, N., Jin, L., Ma, J., Zhu, J., Gu, S., Wang, J., et al. (2018) Ginsenoside Rg1 Impairs Homologous Recombination Repair by Targeting CTBP-Interacting Protein and Sensitizes Hepatoblastoma Cells to DNA Damage. *Anti-Cancer Drugs*, **29**, 756-766. <https://doi.org/10.1097/cad.0000000000000646>
- [13] Yang, H., Liu, M., Luo, P., Yao, X. and Zhou, H. (2022) Network Pharmacology Provides a Systematic Approach to Understanding the Treatment of Ischemic Heart Diseases with Traditional Chinese Medicine. *Phytomedicine*, **104**, Article ID: 154268. <https://doi.org/10.1016/j.phymed.2022.154268>
- [14] Raghavendran, H.R.B., Sathyanath, R., Shin, J., Kim, H.K., Han, J.M., Cho, J., et al. (2012) *Panax ginseng* Modulates Cytokines in Bone Marrow Toxicity and Myelopoiesis: Ginsenoside Rg1 Partially Supports Myelopoiesis. *PLOS ONE*, **7**, e33733. <https://doi.org/10.1371/journal.pone.0033733>
- [15] Suzuki, M., Shimizu, R. and Yamamoto, M. (2011) Transcriptional Regulation by GATA1 and GATA2 during Erythropoiesis. *International Journal of Hematology*, **93**, 150-155. <https://doi.org/10.1007/s12185-011-0770-6>
- [16] Yue, J. and López, J.M. (2020) Understanding MAPK Signaling Pathways in Apoptosis. *International Journal of Molecular Sciences*, **21**, Article 2346. <https://doi.org/10.3390/ijms21072346>
- [17] Falcicchia, C., Tozzi, F., Arancio, O., Watterson, D.M. and Origlia, N. (2020) Involvement of P38 MAPK in Synaptic Function and Dysfunction. *International Journal of Molecular Sciences*, **21**, Article 5624. <https://doi.org/10.3390/ijms21165624>
- [18] Zheng, Y., Han, Z., Zhao, H. and Luo, Y. (2020) MAPK: A Key Player in the Development and Progression of Stroke.

- CNS & Neurological Disorders-Drug Targets, **19**, 248-256. <https://doi.org/10.2174/1871527319666200613223018>
- [19] Xie, W., Zhou, P., Sun, Y., Meng, X., Dai, Z., Sun, G., *et al.* (2018) Protective Effects and Target Network Analysis of Ginsenoside Rg1 in Cerebral Ischemia and Reperfusion Injury: A Comprehensive Overview of Experimental Studies. *Cells*, **7**, Article 270. <https://doi.org/10.3390/cells7120270>
 - [20] Zhang, J., Xiong, L., Tang, W., Tang, L. and Wang, B. (2018) Hypoxic Culture Enhances the Expansion of Rat Bone Marrow-Derived Mesenchymal Stem Cells via the Regulatory Pathways of Cell Division and Apoptosis. *In Vitro Cellular & Developmental Biology—Animal*, **54**, 666-676. <https://doi.org/10.1007/s11626-018-0281-3>
 - [21] Young, N.S. (2018) Aplastic Anemia. *New England Journal of Medicine*, **379**, 1643-1656. <https://doi.org/10.1056/nejmra1413485>
 - [22] Zhu, N., Wu, D. and Ye, B. (2018) The Progress of Traditional Chinese Medicine in the Treatment of Aplastic Anemia. *Journal of Translational Internal Medicine*, **6**, 159-164. <https://doi.org/10.2478/jtim-2018-0031>
 - [23] Yang, H., Xu, X., Jiang, X. and Yao, Z. (2019) Treatment of Menorrhagia Due to Aplastic Anemia by Hysteroscopic Resection of Endometrial Functional Layer and Levonorgestrel-Releasing Intra-Uterine System. *Medicine*, **98**, e15156. <https://doi.org/10.1097/md.00000000000015156>
 - [24] Dijiong, W., Yiping, S., Baodong, Y., Bingmu, F., Shengyun, L., Zhilu, C., *et al.* (2016) Efficacy and Advantages of Modified Traditional Chinese Medicine Treatments Based on “Kidney Reinforcing” for Chronic Aplastic Anemia: A Randomized Controlled Clinical Trial. *Journal of Traditional Chinese Medicine*, **36**, 434-443. [https://doi.org/10.1016/s0254-6272\(16\)30059-0](https://doi.org/10.1016/s0254-6272(16)30059-0)
 - [25] Lu, Y., Du, Z., Li, Y., Wang, J., Zhao, M., Jiang, Y., *et al.* (2018) Effects of Baoyuan Decoction, a Traditional Chinese Medicine Formula, on the Activities and mRNA Expression of Seven CYP Isozymes in Rats. *Journal of Ethnopharmacology*, **225**, 327-335. <https://doi.org/10.1016/j.jep.2018.07.023>
 - [26] Cai, S., Zhou, Y., Liu, J., Li, C., Jia, D., Zhang, M., *et al.* (2018) Alleviation of Ginsenoside Rg1 on Hematopoietic Homeostasis Defects Caused by Lead-Acetate. *Biomedicine & Pharmacotherapy*, **97**, 1204-1211. <https://doi.org/10.1016/j.biopha.2017.10.148>
 - [27] Tang, Y.L., Zhou, Y., Wang, Y.P., Wang, J.W., Ding, J.C. (2015) SIRT6/NF- κ B Signaling Axis in Ginsenoside Rg1-Delayed Hematopoietic Stem/Progenitor Cell Senescence. *International Journal of Clinical and Experimental Pathology*, **8**, 5591-5596.
 - [28] Tang, Y., Zhou, Y., Wang, Y., He, Y., Ding, J., Li, Y., *et al.* (2020) Ginsenoside Rg1 Protects against Sca-1+ HSC/HPC Cell Aging by Regulating the SIRT1-FOXO3 and SIRT3-SOD2 Signaling Pathways in a γ -Ray Irradiation-Induced Aging Mice Model. *Experimental and Therapeutic Medicine*, **20**, 1245-1252. <https://doi.org/10.3892/etm.2020.8810>
 - [29] Zeng, Y., Hu, W., Jing, P., Chen, X., Wang, Z., Wang, L., *et al.* (2018) The Regulation of Ginsenoside Rg1 Upon Aging of Bone Marrow Stromal Cell Contribute to Delaying Senescence of Bone Marrow Mononuclear Cells (BMNCs). *Life Sciences*, **209**, 63-68. <https://doi.org/10.1016/j.lfs.2018.07.025>
 - [30] Yang, L., Duan, F., Su, D., Li, Y., Ma, L., Shi, B., *et al.* (2020) The Effects of CTX Damage or Inhibition of Bone Marrow Hematopoiesis and GM-CSF Stimulation of Bone Marrow Hematopoiesis on the Peripheral Blood TCR β CDR3 Repertoire of BALB/C Mice. *Immunopharmacology and Immunotoxicology*, **42**, 110-118. <https://doi.org/10.1080/08923973.2020.1728309>
 - [31] Laurenti, E. and Göttgens, B. (2018) From Haematopoietic Stem Cells to Complex Differentiation Landscapes. *Nature*, **553**, 418-426. <https://doi.org/10.1038/nature25022>
 - [32] Seita, J. and Weissman, I.L. (2010) Hematopoietic Stem Cell: Self-Renewal versus Differentiation. *WIREs Systems Biology and Medicine*, **2**, 640-653. <https://doi.org/10.1002/wsbm.86>
 - [33] Baron, M.H., Isern, J. and Fraser, S.T. (2012) The Embryonic Origins of Erythropoiesis in Mammals. *Blood*, **119**, 4828-4837. <https://doi.org/10.1182/blood-2012-01-153486>
 - [34] Sugimura, R., Jha, D.K., Han, A., Soria-Valles, C., da Rocha, E.L., Lu, Y., *et al.* (2017) Haematopoietic Stem and Progenitor Cells from Human Pluripotent Stem Cells. *Nature*, **545**, 432-438. <https://doi.org/10.1038/nature22370>
 - [35] Hung, C., Wang, K., Liou, Y., Wang, J., Huang, A.Y., Lee, T., *et al.* (2020) Negative Regulation of the Differentiation of Flk2⁺ CD34⁺ LSK Hematopoietic Stem Cells by EKLF/KLF1. *International Journal of Molecular Sciences*, **21**, Article 8448. <https://doi.org/10.3390/ijms21228448>
 - [36] Kondo, M. (2010) Lymphoid and Myeloid Lineage Commitment in Multipotent Hematopoietic Progenitors. *Immunological Reviews*, **238**, 37-46. <https://doi.org/10.1111/j.1600-065x.2010.00963.x>
 - [37] Kondo, M., Wagers, A.J., Manz, M.G., Prohaska, S.S., Scherer, D.C., Beilhack, G.F., *et al.* (2003) Biology of Hematopoietic Stem Cells and Progenitors: Implications for Clinical Application. *Annual Review of Immunology*, **21**, 759-806. <https://doi.org/10.1146/annurev.immunol.21.120601.141007>
 - [38] Mold, J.E., Venkatasubrahmanyam, S., Burt, T.D., Michaëlsson, J., Rivera, J.M., Galkina, S.A., *et al.* (2010) Fetal and

- Adult Hematopoietic Stem Cells Give Rise to Distinct T Cell Lineages in Humans. *Science*, **330**, 1695-1699. <https://doi.org/10.1126/science.1196509>
- [39] Nishizawa, M., Chonabayashi, K., Nomura, M., Tanaka, A., Nakamura, M., Inagaki, A., *et al.* (2016) Epigenetic Variation between Human Induced Pluripotent Stem Cell Lines Is an Indicator of Differentiation Capacity. *Cell Stem Cell*, **19**, 341-354. <https://doi.org/10.1016/j.stem.2016.06.019>
- [40] Will, B. and Steidl, U. (2010) Multi-Parameter Fluorescence-Activated Cell Sorting and Analysis of Stem and Progenitor Cells in Myeloid Malignancies. *Best Practice & Research Clinical Haematology*, **23**, 391-401. <https://doi.org/10.1016/j.beha.2010.06.006>
- [41] Agger, K., Nishimura, K., Miyagi, S., Messling, J., Rasmussen, K.D. and Helin, K. (2019) The KDM4/JMJD2 Histone Demethylases Are Required for Hematopoietic Stem Cell Maintenance. *Blood*, **134**, 1154-1158. <https://doi.org/10.1182/blood.2019000855>
- [42] Ueda, T., Yokota, T., Okuzaki, D., Uno, Y., Mashimo, T., Kubota, Y., *et al.* (2019) Endothelial Cell-Selective Adhesion Molecule Contributes to the Development of Definitive Hematopoiesis in the Fetal Liver. *Stem Cell Reports*, **13**, 992-1005. <https://doi.org/10.1016/j.stemcr.2019.11.002>
- [43] Peng, H., Yu, Y., Gu, H., Qi, B. and Yu, A. (2022) MicroRNA-483-5p Inhibits Osteogenic Differentiation of Human Bone Marrow Mesenchymal Stem Cells by Targeting the RPL31-Mediated RAS/MEK/ERK Signaling Pathway. *Cellular Signalling*, **93**, Article ID: 110298. <https://doi.org/10.1016/j.cellsig.2022.110298>
- [44] Tsubaki, M., Satou, T., Itoh, T., Imano, M., Yanae, M., Kato, C., *et al.* (2012) Bisphosphonate- and Statin-Induced Enhancement of OPG Expression and Inhibition of CD9, M-CSF, and RANKL Expressions via Inhibition of the Ras/MEK/ERK Pathway and Activation of P38mapk in Mouse Bone Marrow Stromal Cell Line ST2. *Molecular and Cellular Endocrinology*, **361**, 219-231. <https://doi.org/10.1016/j.mce.2012.05.002>
- [45] Yip, R.K.H., Rimes, J.S., Capaldo, B.D., Vaillant, F., Mouchemore, K.A., Pal, B., *et al.* (2021) Mammary Tumour Cells Remodel the Bone Marrow Vascular Microenvironment to Support Metastasis. *Nature Communications*, **12**, Article No. 6920. <https://doi.org/10.1038/s41467-021-26556-6>
- [46] Chang, S., Li, H., Huang, Y., Tasi, W., Chou, Y. and Lu, S. (2016) SB203580 Increases G-CSF Production via a Stem-Loop Destabilizing Element in the 3' Untranslated Region in Macrophages Independently of Its Effect on P38 MAPK Activity. *Journal of Biomedical Science*, **23**, Article No. 3. <https://doi.org/10.1186/s12929-016-0221-z>
- [47] Decean, H.P., Brie, I.C., Tatmir, C.B., Perde-Schrepler, M., Fischer-Fodor, E. and Virag, P. (2018) Targeting MAPK (p38, ERK, JNK) and Inflammatory CK (GDF-15, GM-CSF) in UVB-Activated Human Skin Cells with Vitis Vinifera Seed Extract. *Journal of Environmental Pathology, Toxicology and Oncology*, **37**, 261-272. <https://doi.org/10.1615/jenvironpatholtoxicoloncol.2018027009>
- [48] Koga, Y., Hisada, T., Ishizuka, T., Utsugi, M., Ono, A., Yatomi, M., *et al.* (2016) CREB Regulates TNF- α -Induced GM-CSF Secretion via P38 MAPK in Human Lung Fibroblasts. *Allergy International*, **65**, 406-413. <https://doi.org/10.1016/j.alit.2016.03.006>