

汉防己甲素对放射性肺损伤的保护作用及机制

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摘要 探讨汉防己甲素(Tetrandrine, Tet)对放射性肺损伤(Radiation-induced lung injury, RILI)的保护作用及机制。18只小鼠随机分为对照组、辐射组以及辐射+汉防己甲素组。单次20 Gy剂量照射构建小鼠RILI模型。12周后检测肺系数并行苏木精-伊红染色评估肺损伤。网络药理学方法筛选潜在分子机制。Western blot检测髓过氧化物酶(MPO)、F4/80、白细胞介素1 β (IL1 β)、白细胞介素18(IL18)、白细胞介素6(IL6)、CD86、CD163、NOD样受体热蛋白结构域相关蛋白3(NLRP3)、凋亡相关斑点样蛋白(ASC)和半胱氨酸天冬氨酸蛋白水解酶1(Caspase1)蛋白的表达。结果表明,与对照组相比,辐射组小鼠肺系数(1.27 $\pm$ 0.05 vs. 1.55 $\pm$ 0.20)、肺组织损伤评分(2.00 $\pm$ 1.27 vs. 6.00 $\pm$ 1.27)、MPO(1.00 $\pm$ 0.21 vs. 1.34 $\pm$ 0.20)、F4/80(1.00 $\pm$ 0.13 vs. 1.28 $\pm$ 0.11)、IL1 β (1.00 $\pm$ 0.18 vs. 1.71 $\pm$ 0.14)、IL6(1.00 $\pm$ 0.17 vs. 1.62 $\pm$ 0.31)、CD86(1.00 $\pm$ 0.29 vs. 1.62 $\pm$ 0.36)蛋白表达均上调,CD163(1.00 $\pm$ 0.21 vs. 0.59 $\pm$ 0.07)表达下调;与辐射组小鼠相比,辐射+汉防己甲素组小鼠肺系数(1.36 $\pm$ 0.07)、肺组织损伤评分(3.17 $\pm$ 1.33)、MPO(1.02 $\pm$ 0.10)、F4/80(0.94 $\pm$ 0.23)、IL1 β (0.97 $\pm$ 0.56)、IL6(1.01 $\pm$ 0.10)、CD86(1.07 $\pm$ 0.34)蛋白表达均下调,CD163(0.99 $\pm$ 0.25)表达上调。网络药理学分析筛选出93个交集基因,KEGG通路分析表明交集基因主要富集于NOD样受体信号通路、PI3K-Akt信号通路和NF- κ B信号通路等。Western blot进一步验证表明,与对照组相比,辐射组小鼠NLRP3(1.00 $\pm$ 0.24 vs. 1.54 $\pm$ 0.46)以及Caspase1(1.00 $\pm$ 0.20 vs. 1.66 $\pm$ 0.30)蛋白表达均上调;与辐射组小鼠相比,辐射+汉防己甲素组小鼠NLRP3(1.02 $\pm$ 0.25)以及Caspase1(0.74 $\pm$ 0.37)蛋白表达均下调。汉防己甲素可能通过调控NLRP3/Caspase1通路抑制巨噬细胞M1极化介导的炎症反应,从而改善RILI。

关键词 汉防己甲素,放射性肺损伤,NLRP3/Caspase1通路,巨噬细胞极化,炎症因子

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The protective effect and mechanisms of tetrandrine on radiation-induced lung injury

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ABSTRACT This study aims to investigate the protective effects of tetrandrine on radiation-induced lung injury (RILI) and elucidate its potential mechanisms. Eighteen mice were randomly assigned to one of three groups: the control group, the irradiation group, and the irradiation plus tetrandrine group. Mice were exposed to a single full thoracic dose of 20 Gy radiation to establish a model of RILI. The lung coefficient was evaluated 12 weeks after radiation. Hematoxylin-eosin staining was used to assess the lung tissue damage. The network pharmacology method was used to screen for potential molecular mechanisms. The protein expression of myeloperoxidase (MPO), F4/80, interleukin 1 β (IL1 β), interleukin 18 (IL18), interleukin 6 (IL6), CD86, CD163, NOD-like receptor family pyrin domain containing 3 (NLRP3), apoptosis-associated speck-like protein (ASC), and cysteinyl aspartate specific proteinase 1 (Caspase1) was assessed using Western blot. The results showed that compared with the control group, the coefficient (1.27 $\pm$ 0.05 vs. 1.55 $\pm$ 0.20), histology score (2.00 $\pm$ 1.27 vs. 6.00 $\pm$ 1.27), and protein expression levels of MPO (1.00 $\pm$ 0.21 vs. 1.34 $\pm$ 0.20), F4/80 (1.00 $\pm$ 0.13 vs. 1.28 $\pm$ 0.11), IL1 β (1.00 $\pm$ 0.18 vs. 1.71 $\pm$ 0.14), IL6 (1.00 $\pm$ 0.17 vs. 1.62 $\pm$ 0.31), and CD86 (1.00 $\pm$ 0.29 vs. 1.62 $\pm$ 0.36) increased in the irradiation group, whereas the protein expression of CD163 (1.00 $\pm$ 0.21 vs. 0.59 $\pm$ 0.07) was decreased. Compared with the IR group, the coefficient (1.36 $\pm$ 0.07), histology score (3.17 $\pm$ 1.33), and the protein expression levels of MPO (1.02 $\pm$ 0.10), F4/80 (0.94 $\pm$ 0.23), IL1 β (0.97 $\pm$ 0.56), IL6 (1.01 $\pm$ 0.10), and CD86 (1.07 $\pm$ 0.34) decreased in the IR+Tet group, whereas the protein expression of CD163 (0.99 $\pm$ 0.25) increased. Network pharmacology analysis identified 93 intersecting genes. KEGG pathway analysis indicated that the intersecting genes were mainly enriched in the NOD-like receptor signaling pathway, PI3K-Akt signaling pathway, and NF- κ B signaling pathway. Western blot further confirmed that compared with the control group, the protein expression of NLRP3 (1.00 $\pm$ 0.24 vs. 1.54 $\pm$ 0.46) and Caspase1 (1.00 $\pm$ 0.20 vs. 1.66 $\pm$ 0.30) was upregulated in the irradiation group; compared with the IR group, the protein expression of NLRP3 (1.02 $\pm$ 0.25) and Caspase1 (0.74 $\pm$ 0.37) was downregulated in the IR+Tet group. Tetrandrine can alleviate RILI, possibly by regulating the NLRP3/Caspase1 pathway to suppress M1 macrophage polarization and inhibit inflammatory responses.

KEYWORDS Tetrandrine, Radiation-induced lung injury, NLRP3/Caspase1 pathway, Macrophage polarization, Inflammatory factor

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放射治疗是胸部恶性肿瘤的关键治疗手段之一^[1],但其不可避免地会对周围健康肺组织产生副作用^[2]。放射性肺损伤便是胸部恶性肿瘤患者接受放疗后最常见的并发症之一^[3]。约14.6%~37.2%的胸部放疗患者会发生放射性肺损伤,这严重影响了患者的治疗效果和生活质量^[4]。临床上通过调整肺的受照模式(如闪光放疗和适形调强放疗等)以及限制双肺受照剂量和体积,对健康人体肺组织的保护作用已得到证实^[5-6]。然而,放射性肺损伤发病机理尚未完全阐明,且目前尚无有效治疗方法^[7]。因此,临床上亟须探索新型、低毒和安全有效的辐射防护药物用于防治放射性

肺损伤。研究表明,传统中医制剂、草药疗法及植物提取物在疾病防治中具有显著优势^[8]。多种植物提取物如羽扇烯酮^[9]、柚皮素^[10]和双氢青蒿素^[11]等可通过减轻炎症、氧化应激和细胞凋亡展现出肺部保护作用。汉防己甲素是传统中药材汉防己根部提取的生物碱,凭借其独特的药理特性已成为极具潜力的候选药物^[12]。汉防己甲素分子式为C₃₈H₄₂N₂O₆^[13],作为中国唯一获批的植物源性抗矽肺药物,其自20世纪80年代起便广泛用于临床治疗多种疾病^[14],如炎症性疾病、高血压、哮喘、痢疾、高血糖、结核、疟疾和发热等^[15]。研究发现汉防己甲素在新型冠状病毒所致肺损伤^[16]

和肺纤维化^[17]等肺部疾病中同样具有改善作用。此外,汉防己甲素也可抑制肺癌和乳腺癌等胸部恶性肿瘤细胞生长^[18]。然而,汉防己甲素能否改善放射性肺损伤目前尚不清楚。因此,本研究旨在阐明汉防己甲素对放射性肺损伤的保护作用及可能机制。

1 材料与方法

1.1 仪器与试剂

汉防己甲素(MCE公司)。二甲基亚砜(DMSO)(Sigma公司)。聚乙二醇400(PEG400)(MCE公司)。直线加速器(德国SIEMENS公司,型号:ONCOR)。一抗: β -actin(Abclonal公司,1:10 000);髓过氧化物酶(MPO)(Proteintech公司,1:1 000);F4/80(Proteintech公司,1:1 000);NOD样受体热蛋白结构域相关蛋白3(NLRP3)(Cell Signaling Technology公司,1:1 000);凋亡相关斑点样蛋白(ASC)(Proteintech公司,1:1 000);半胱氨酸蛋白酶1(Caspase1)(Santa Cruz公司,1:1 000);白细胞介素1 β (IL1 β)(Boster公司,1:1 000);白细胞介素18(IL18)(Proteintech公司,1:1 000);CD163(Proteintech公司,1:500);CD86(Proteintech公司,1:500);白细胞介素6(IL6)(Proteintech公司,1:500)。二抗:辣根过氧化物酶标记羊抗鼠IgG(Proteintech公司,1:1 000);辣根过氧化物酶标记羊抗兔IgG(Proteintech公司,1:1 000)。

1.2 动物建模与药物干预

SPF级C57BL/6J小鼠随机分为三组:对照组(Control)、辐射组(IR)和辐射+汉防己甲素组(IR+Tet),每组6只。辐射方法参照文献[19]:单次20 Gy剂量照射构建小鼠放射性肺损伤模型。IR+Tet组给予汉防己甲素干预(30 mg/kg,腹腔注射,前4周给药1次/天,后8周给药3次/周)。Control组和IR组注射等体积溶媒(1% DMSO/PEG400)^[20]。

1.3 取材与肺系数评估

12周后称量各组小鼠体重,右下肺用于评估肺系数(右下肺湿重/小鼠体重),左上肺进行HE

染色评估肺组织损伤情况,右中肺用于Western blot分析。

1.4 苏木精-伊红染色(HE)及评分

参照文献行常规石蜡包埋、切片、脱蜡、水化及染色^[21-22]。评分指标包含肺间质壁和肺泡增厚程度和炎性细胞浸润程度。0分:<10%肺视野改变;1分:10%~30%肺视野改变;2分:30%~50%肺视野改变;3分:50%~70%肺视野改变;4分:70%以上肺视野改变。损伤评分为两种指标评分之和。

1.5 网络药理学分析

采用PubChem在线数据库(<https://pubchem.ncbi.nlm.nih.gov/>)通过检索关键词“Tetrandrine”获取汉防己甲素的分子结构图和Smiles序列,将Smiles序列导入SwissTargetPrediction在线数据库(<https://www.swisstargetprediction.ch/>)获取汉防己甲素的药物靶点。采用GeneCards在线数据库(<https://www.genecards.org/>)通过检索关键词“Radiation induced lung injury”获取放射性肺损伤的靶点。通过Venn平台(<https://bioinformatics.psb.ugent.be/webtools/Venn/>)获取交集基因。将交集基因导入String平台(<https://cn.string-db.org/>)获得蛋白蛋白互作(PPI)网络,并将交集基因通过R软件(版本4.2.2)进行GO和KEGG富集分析^[23]。

1.6 Western blot

参照文献[24]提取蛋白后BCA法(CWBIO公司)测定蛋白浓度。采用十二烷基硫酸钠-聚丙烯酰胺凝胶电泳分离。经转膜及5%脱脂奶粉封闭2 h后分别加入一抗(β -actin, MPO, F4/80, NLRP3, ASC, Caspase1, IL1 β , IL18, CD163, CD86和IL6)孵育2 h后再4℃低温冰箱孵育12 h,次日洗膜后分别加入二抗(辣根过氧化物酶标记的羊抗鼠IgG或羊抗兔IgG)孵育2 h后洗膜,ECL化学发光液(CWBIO公司)显色后成像并分析。

1.7 统计学方法

数据分析通过GraphPad Prism 10.6.1进行,采用 $\bar{x} \pm s$ 表示。比较组间差异采用单因素方差分析。 $p < 0.05$ 为差异具有统计学意义。

2 结果

2.1 汉防己甲素对各组小鼠体重和肺系数的影响

为明确辐射或汉防己甲素干预对小鼠一般状况的影响，本研究首先探讨了汉防己甲素对各组小鼠体重的影响。如图1(a)所示，与Control小鼠相比，IR小鼠在4周、8周和12周时的体重减轻或增加无统计学差异 ($p>0.05$)；与IR组小鼠相比，IR+Tet小鼠在4周、8周和12周时的体重减轻或增加无统计学差异 ($p>0.05$)；结果表明辐射或

汉防己甲素干预对小鼠体重等一般状况无明显影响。

放射性肺损伤小鼠可表现出肺组织炎性水肿^[25]，故本研究探讨了汉防己甲素对各组小鼠肺系数（肺湿重/体重）的影响。如图1(b)所示，与Control组小鼠 (1.27 ± 0.05) 相比，IR组小鼠肺系数 (1.55 ± 0.20) 显著增加 ($p<0.01$)；而与IR组小鼠相比，IR+Tet组小鼠肺系数 (1.36 ± 0.07) 显著降低 ($p<0.05$)，结果表明辐射可诱导小鼠出现肺组织炎性水肿，而汉防己甲素干预可改善放射性肺损伤小鼠肺组织炎性水肿。

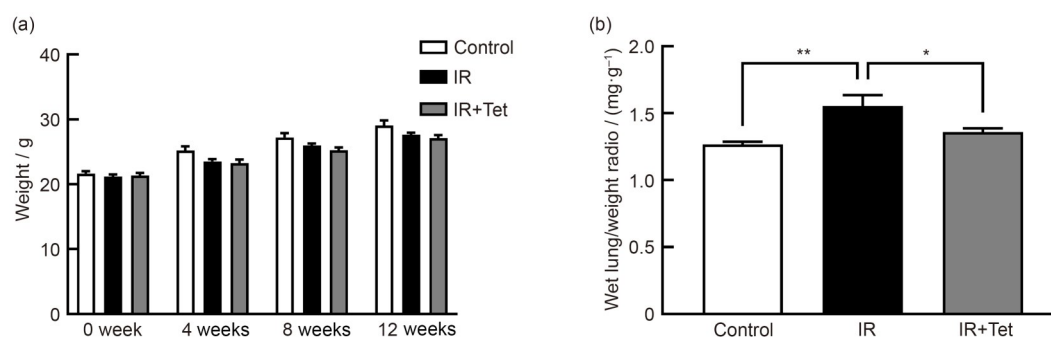


图1 汉防己甲素对各组小鼠体重和肺系数的影响：(a)小鼠0周、4周、8周和12周体重统计分析结果；(b)肺系数统计分析结果；* $p<0.05$ ，** $p<0.01$

Fig.1 Effects of tetrandrine on body weight and lung coefficient of mice in each group: (a) statistical analysis of the body weights of mice at 0 weeks, 4 weeks, 8 weeks, and 12 weeks old; (b) statistical analysis of lung coefficient of mice; * $p<0.05$, ** $p<0.01$

2.2 汉防己甲素对各组小鼠肺组织炎性损伤的影响

放射性肺损伤小鼠在组织病理学上可表现出炎性细胞浸润增加，肺泡和肺间质壁增厚^[22]，故本研究基于上述两种指标评分探讨了汉防己甲素对各组小鼠肺组织炎性损伤的影响。如图2所示，

与Control组小鼠肺组织炎性损伤评分 (2.00 ± 1.27) 相比，IR组小鼠肺组织炎性损伤评分 (6.00 ± 1.27) 显著增加 ($p<0.001$)；而与IR组小鼠相比，IR+Tet组小鼠肺组织炎性损伤评分 (3.17 ± 1.33) 显著降低 ($p<0.01$)，结果表明辐射可诱导小鼠肺组织炎性损伤，而汉防己甲素干预可显著改善放射性肺损伤小鼠肺组织炎性损伤。

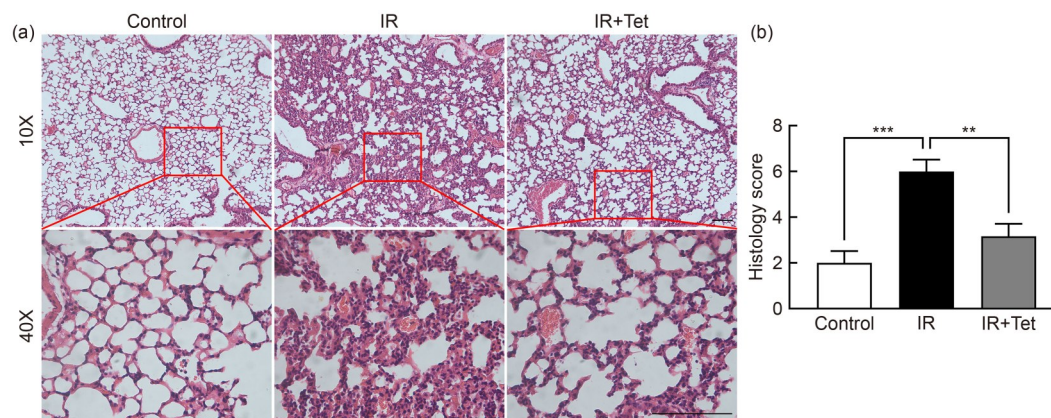


图2 汉防己甲素对各组小鼠肺组织炎性损伤的影响：

(a)HE 染色典型图片,Bar=100 μm ; (b)组织损伤评分统计分析；** $p<0.01$ ，*** $p<0.001$

Fig.2 Effects of tetrandrine on inflammatory injury of lung tissue in each group of mice:

(a) typical image of HE staining, Bar = 100 μm ; (b) statistical analysis of tissue damage score; ** $p<0.01$, *** $p<0.001$

2.3 汉防己甲素对各组小鼠中性粒细胞以及巨噬细胞表达的影响

当肺组织受到射线照射后,射线可诱导肺上皮或内皮细胞受损进而释放损伤相关分子模式分子,这些分子可诱导中性粒细胞和巨噬细胞等向受损部位浸润聚集^[26],故本研究采用 Western blot 方法探讨了汉防己甲素对各组小鼠中性粒细胞以及巨噬细胞表达的影响。图3(a)~3(c)所示,与 Control 组小鼠中性粒细胞标志物(MPO, $1.00 \pm$

0.21)和巨噬细胞标志物(F4/80, 1.00 ± 0.13)蛋白表达相比,IR 组小鼠 MPO (1.34 ± 0.20)和 F4/80 (1.28 ± 0.11)蛋白表达均显著增加 ($p < 0.05$);而与 IR 组小鼠相比,IR+Tet 组小鼠 MPO (1.02 ± 0.10)和 F4/80 (0.94 ± 0.23)蛋白表达均显著降低 ($p < 0.05$),结果表明辐射可诱导小鼠肺组织中性粒细胞和巨噬细胞浸润增加,而汉防己甲素干预对模型小鼠中性粒细胞和巨噬细胞浸润具有显著抑制作用。

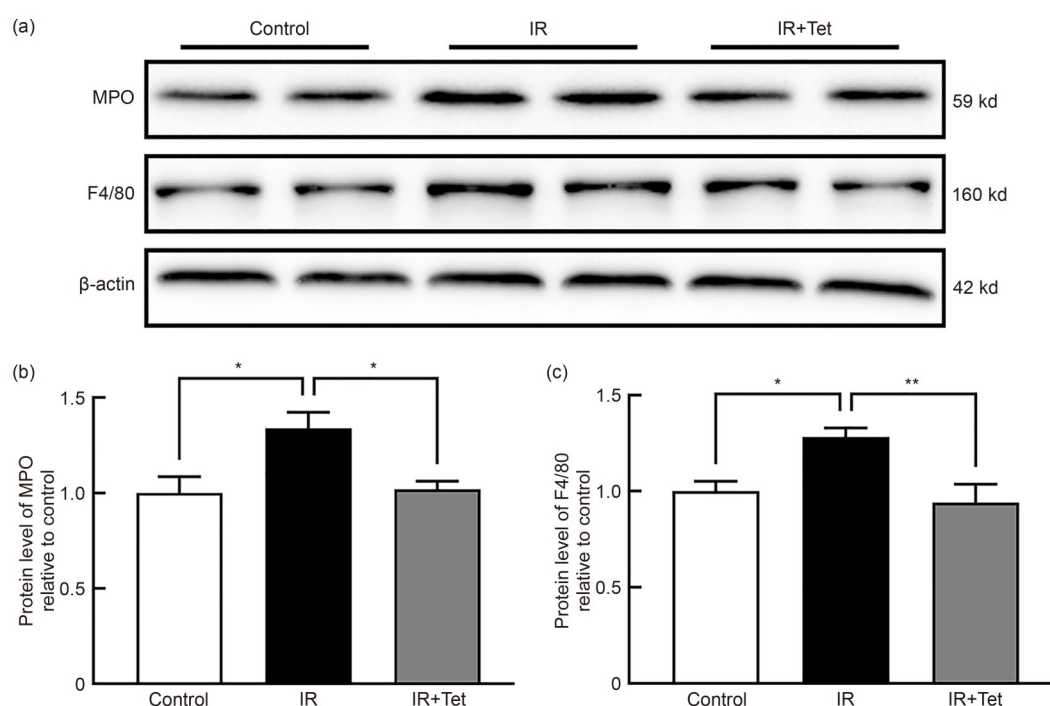


图3 汉防己甲素对各组小鼠中性粒细胞以及巨噬细胞表达的影响:(a)MPO和F4/80的蛋白表达;(b~c)MPO和F4/80的蛋白相对表达量;* $p < 0.05$,** $p < 0.01$

Fig.3 The effect of tetrandrine on neutrophils and macrophages infiltration in each group of mice: (a) the protein expression of MPO and F4/80; (b~c) relative protein expression levels of MPO and F4/80; * $p < 0.05$, ** $p < 0.01$

2.4 汉防己甲素对各组小鼠炎症因子表达和肺巨噬细胞极化的影响

浸润的炎症细胞可产生和分泌多种促炎细胞因子促进组织炎症^[27],故本研究探讨了汉防己甲素对各组小鼠炎症细胞因子表达的影响。图4(a)~4(e)所示,与 Control 组小鼠炎症因子 Pro-IL1β (1.00 ± 0.45)、IL1β (1.00 ± 0.18)、IL18 (1.00 ± 0.25)和 IL6 (1.00 ± 0.17)的蛋白表达相比,IR 组小鼠 IL1β (1.71 ± 0.14)和 IL6 (1.62 ± 0.31)蛋白表达均显著增加 ($p < 0.05$),Pro-IL1β (1.26 ± 0.11)和 IL18 (1.25 ± 0.32)蛋白表达无统计学差异 ($p > 0.05$);与 IR 组小鼠相比,IR+Tet 组小鼠 IL1β

(0.97 ± 0.56)、IL18 (0.77 ± 0.17)和 IL6 (1.01 ± 0.10)蛋白表达均显著降低 ($p < 0.05$),Pro-IL1β (0.92 ± 0.20)蛋白表达无统计学差异 ($p > 0.05$),结果表明辐射可诱导小鼠肺组织炎症细胞因子释放增加,而汉防己甲素干预具有抑制放射性肺损伤小鼠炎症细胞因子合成释放作用。

研究发现不同的巨噬细胞表型可表现出截然不同的生物学效应,从促炎表型(M1型)向抗炎表型(M2型)转换对于调控炎症因子分泌以及恢复组织稳态至关重要^[28],故本研究探讨了汉防己甲素对各组小鼠肺巨噬细胞 M1/M2 型极化的影响。图4(f)~4(h)所示,与 Control 组小鼠 CD86 (M1 型巨噬细胞标志物, 1.00 ± 0.29)和 CD163

(M2型巨噬细胞标志物, 1.00 ± 0.21) 的蛋白表达相比, IR组小鼠CD86 (1.62 ± 0.36) 蛋白表达显著增加, CD163 (0.59 ± 0.07) 蛋白表达显著降低; 与IR组小鼠相比, IR+Tet组小鼠CD86 (1.07 ± 0.34)

蛋白表达显著降低, CD163 (0.99 ± 0.25) 蛋白表达显著增加, 结果表明辐射可诱导小鼠肺组织巨噬细胞向M1型促炎型极化, 而汉防己甲素干预可促进肺巨噬细胞向M2型抗炎型极化。

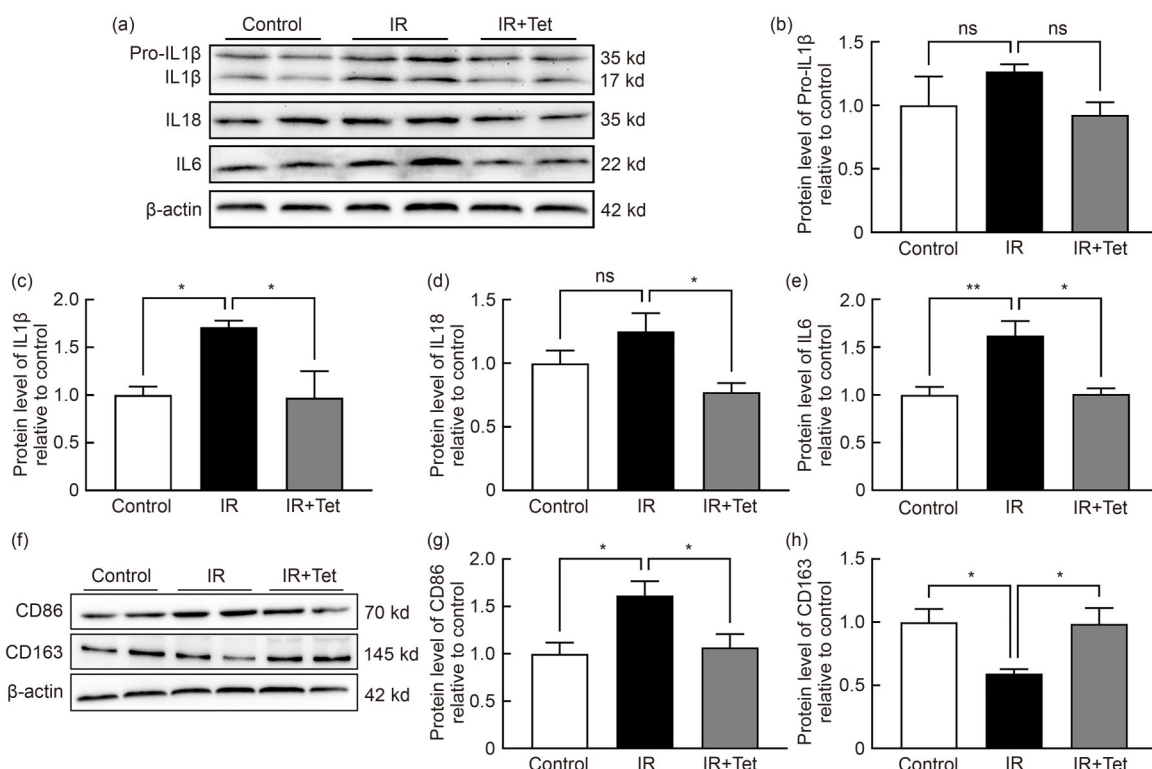


图4 汉防己甲素对各组小鼠炎症因子表达和肺巨噬细胞极化的影响:(a)Pro-IL1β、IL1β、IL18和IL6的蛋白表达;(b~e)Pro-IL1β、IL1β、IL18和IL6的蛋白相对表达量;(f)CD86和CD163的Western blot条带;(g~h)CD86和CD163的蛋白相对表达量;^{ns} $p \geq 0.05$, * $p < 0.05$, ** $p < 0.01$

Fig.4 The effect of tetrandrine on the expression of inflammatory factors and the polarization of lung macrophages in each group of mice: (a) the protein expression of Pro-IL1β, IL1β, IL18 and IL6; (b-e) relative protein expression levels of Pro-IL1β, IL1β, IL18 and IL6; (f) the representative bands of CD86 and CD163; (g-h) relative protein expression levels of CD86 and CD163; ^{ns} $p \geq 0.05$, * $p < 0.05$, ** $p < 0.01$

2.5 汉防己甲素对放射性肺损伤的网络药理学分析

为探讨汉防己甲素改善放射性肺损伤的潜在分子机制, 本研究进行了网络药理学分析。图5(a)展示了PubChem数据库中汉防己甲素的分子结构图。通过SwissTargetPrediction数据库获得汉防己甲素潜在药物靶点共102个, 随后通过GeneCards数据库鉴定出放射性肺损伤潜在靶点共7973个, 采用Venn平台进一步分析共发现93个重叠靶点, 占汉防己甲素靶点总数的91.2%(图5(b))。图5(c)展示了交集基因的蛋白质-蛋白质相互作用(PPI)网络分析结果。

GO富集分析包含三个类别: 生物过程(BP)、细胞组分(CC)和分子功能(MF), 其中共富集

到1778个BP条目、80个CC条目和214个MF条目。图5(d)分别展示了三个类别中的前6个条目, BP的条目分别为肽基丝氨酸磷酸化、肽基丝氨酸修饰、MAPK级联反应的正向调控、肽基酪氨酸磷酸化、肽基酪氨酸修饰和蛋白质自磷酸化; CC的条目分别为膜筏、膜微结构域、转移含磷基团的转移酶复合物、蛋白激酶复合物、突触前膜的组成成分和突触前膜的内在成分; MF的条目分别为蛋白质丝氨酸/苏氨酸激酶活性、蛋白质丝氨酸激酶活性、蛋白质酪氨酸激酶活性、神经递质受体活性、G蛋白偶联受体活性和非跨膜蛋白酪氨酸激酶活性。

KEGG通路富集分析共鉴定出151条可能参与汉防己甲素改善放射性肺损伤的信号通路。图5(e)展示的多个信号通路包括NOD样受体信号通

路、Wnt 信号通路、VEGF 信号通路、Toll 样受体信号通路、TNF 信号通路、Rap1 信号通路、PI3K-Akt 信号通路、p53 信号通路、NF- κ B 信号通路、

mTOR 信号通路、MAPK 信号通路和趋化因子信号传导通路等。

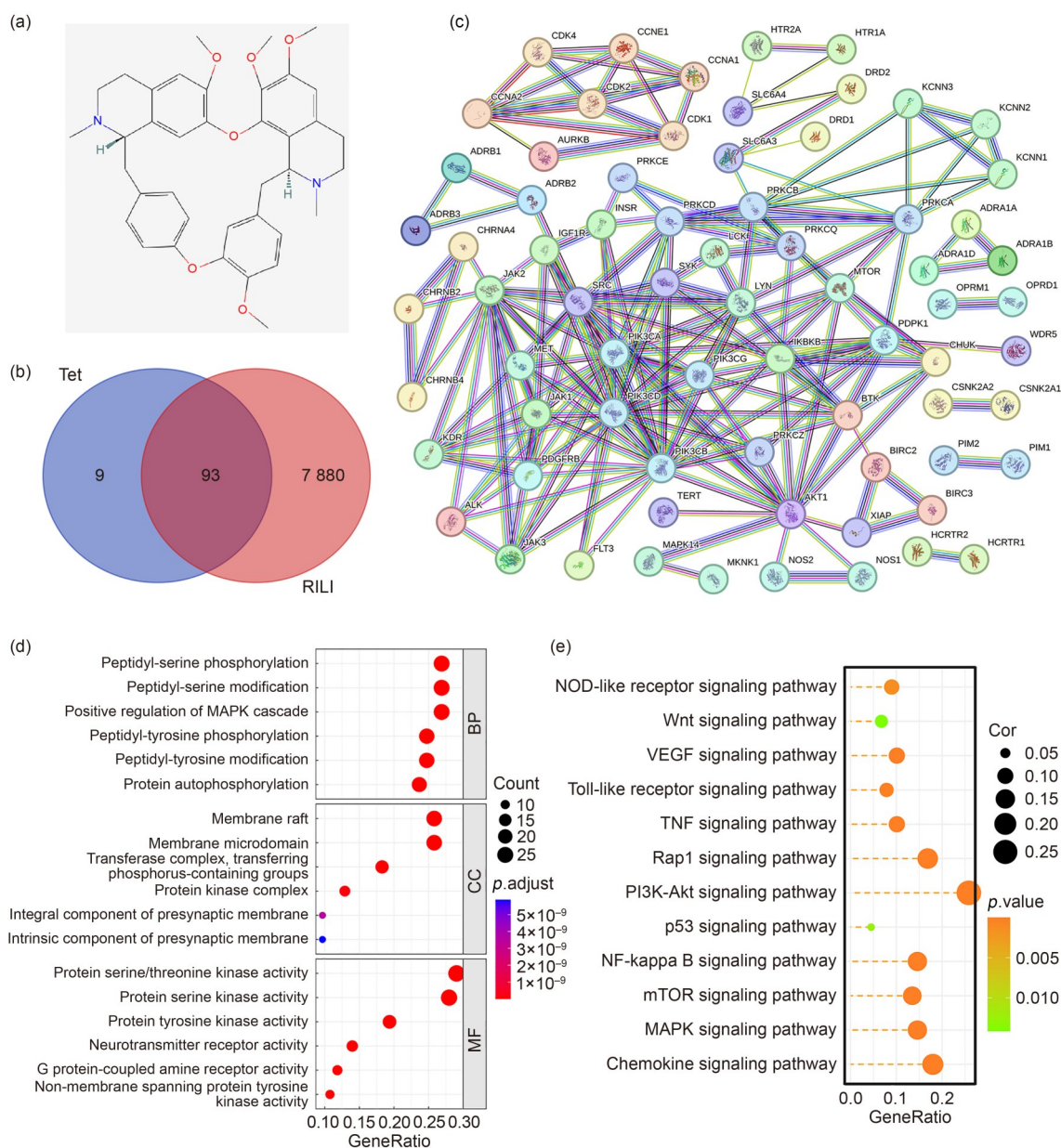


图5 汉防己甲素对放射性肺损伤的网络药理学分析:(a)汉防己甲素的分子结构图;(b)汉防己甲素和放射性肺损伤靶点的Venn图;(c)基于重叠靶点构建的PPI网络;(d)重叠靶点的GO功能分析;(e)重叠靶点的KEGG分析

Fig.5 Network pharmacology analysis for tetrandrine and radiation induced lung injury: (a) the chemical structure depiction of tetrandrine; (b) venn diagram of tetrandrine and radiation induced lung injury; (c) PPI network is constructed based on intersecting targets; (d) the results of GO analysis based on intersecting targets; (e) the results of KEGG analysis based on intersecting targets

2.6 汉防己甲素对各组小鼠 NLRP3/Caspase1 通路的影响

基于网络药理学分析结果提示, NOD 样受体信号通路可能是汉防己甲素改善放射性肺损伤的潜在信号通路之一, 研究表明 NLRP3 信号通路在调控巨噬细胞极化过程中扮演重要作用^[29], 故本

研究进一步通过分子生物学实验验证了汉防己甲素对各组小鼠肺 NLRP3/Caspase1 信号通路表达的影响。图 6 (a) ~6 (d) 所示, 与 Control 组小鼠 NLRP3 (1.00±0.24)、ASC (1.00±0.27) 和 Caspase1 (1.00±0.20) 的蛋白表达相比, IR 组小鼠 NLRP3 (1.54±0.46) 和 Caspase1 (1.66±0.30)

蛋白表达显著增加，ASC (1.16 ± 0.20) 蛋白表达差异无统计学意义；与 IR 组小鼠相比，IR+Tet 组小鼠 NLRP3 (1.02 ± 0.25)、ASC (0.84 ± 0.09) 和 Caspase1 (0.74 ± 0.37) 蛋白表达显著降低，结果表

明辐射可激活小鼠肺组织 NLRP3/Caspase1 信号通路，而汉防己甲素干预可抑制辐射小鼠肺组织 NLRP3/Caspase1 信号通路活化。

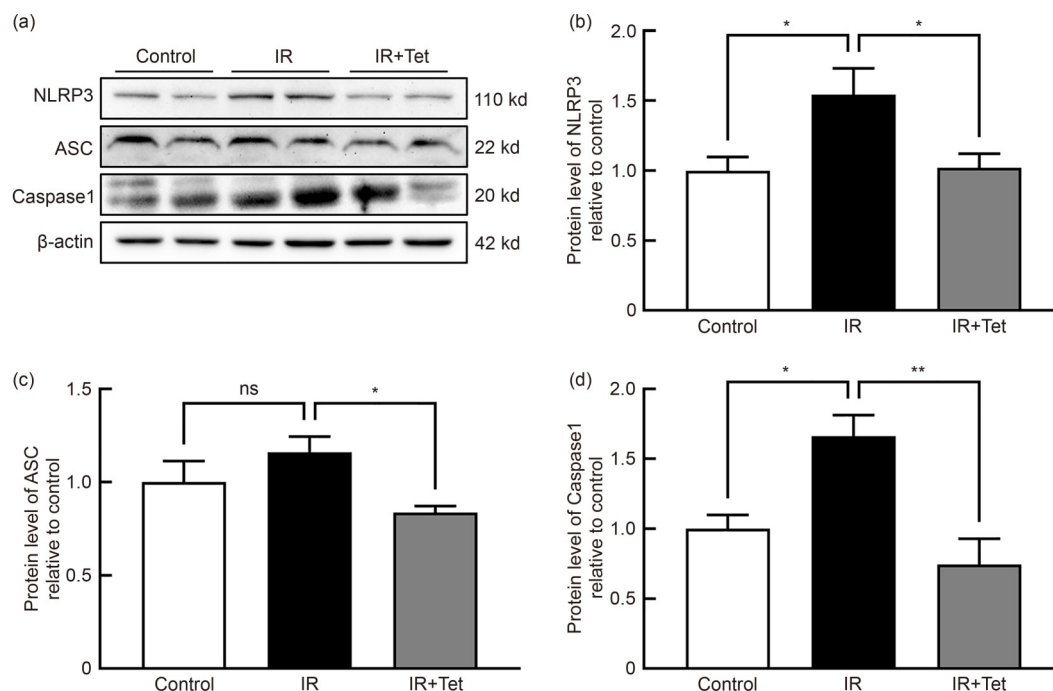


图6 汉防己甲素对各组小鼠 NLRP3/Caspase1 通路的影响：(a) NLRP3、ASC 和 Caspase1 的 Western blot 条带；(b-d) NLRP3、ASC 和 Caspase1 的蛋白相对表达量；^{ns} $p \geq 0.05$, * $p < 0.05$, ** $p < 0.01$

Fig.6 The effect of tetrandrine on the expression of NLRP3/Caspase1 pathway in each group of mice: (a) the representative bands of NLRP3, ASC and Caspase1; (b-d) relative protein expression levels of NLRP3, ASC and Caspase1; ^{ns} $p \geq 0.05$, * $p < 0.05$, ** $p < 0.01$

3 讨论

目前国内外学者已开发多种辐射防护药物。美国食品药品监督管理局 (FDA) 已经批准阿米福汀 (Amifostine) 用于接受高剂量放疗的肿瘤患者^[4]。国内学者也发现吡非尼酮与糖皮质激素联合使用可减轻 2 级或 3 级放射性肺损伤^[30]。然而，由于给药途径有限、保护窗口狭窄及主要不良反应，这些辐射防护剂的广泛应用受到限制^[31-32]。既往研究证实汉防己甲素可抑制成纤维细胞活化及胶原沉积进而拮抗矽肺患者肺纤维化^[33]，同时汉防己甲素也可抑制肺癌和乳腺癌等多种癌症进展。本研究基于肺系数和 HE 染色等方法证实汉防己甲素对放射性肺损伤同样具有保护作用。基于这些理论，后续如能进一步开展相关临床研究验证汉防己甲素对胸部肿瘤和放射性肺损伤的双重保护作用，将有望大大提高胸部肿瘤放疗患者的生存率和生活质量。

既往观点认为放射性肺损伤是电离辐射对 II 型肺泡上皮细胞和毛细血管的直接损伤所致^[27]，但近期研究表明放射性肺损伤是氧化应激损伤、靶细胞损伤及促炎细胞因子释放的级联反应所致^[34]。电离辐射通过直接作用或者间接作用损伤细胞内的 DNA，致使受辐照细胞出现损伤进而诱导炎性细胞向损伤部位大量浸润^[6]。这些免疫细胞的聚集通常伴随着大量炎症因子（如白细胞介素 3 (IL3)、白细胞介素 6 (IL6)， γ -干扰素 (IFN- γ)，转化生长因子- β (TGF- β)、 α 肿瘤坏死因子 (TNF- α) 等) 的合成和释放^[11]。这些炎症因子可诱导组织进一步炎性损伤，受损伤的细胞再募集大量免疫细胞聚集，从而形成靶细胞损伤及促炎细胞因子释放的级联反应^[27]。本研究中辐射损伤模型小鼠肺组织中巨噬细胞标志物 F4/80 和中性粒细胞标志物 MPO 表达均明显上调，且伴随着炎症因子合成和释放增加，而汉防己甲素干预可显著逆转这一现象，表明汉防己甲素可抑制辐射模型小鼠免

疫细胞聚集和促炎细胞因子释放的级联反应。

究竟如何去打破免疫细胞聚集和促炎细胞因子释放这一正反馈级联反应呢？巨噬细胞的表型转换可能在其中扮演重要角色。炎症是机体抵御外源性病原体和内源性组织损伤的主要防御机制，其过程依次经历四个阶段：启动、进展、消退和组织重建，巨噬细胞在炎症的四个阶段均发挥着不可或缺的作用^[35]。当组织发生炎症损伤时，循环单核细胞会被募集至损伤部位并分化为组织巨噬细胞，这些巨噬细胞表现出显著的可塑性。在炎症启动和进展期，IFN- γ 或细菌内毒素（LPS）等信号促进巨噬细胞向M1表型极化，进而产生高水平的炎症细胞因子（如TNF- α ，IL1 β 和IL6等）和活性氧，加剧炎症反应^[36]。而在炎症消退和组织重建期，白细胞介素4（IL4）、白细胞介素13（IL13）或白细胞介素10（IL10）等信号促进巨噬细胞向M2表型极化，进而分泌抗炎细胞因子（如IL10和TGF- β ）以及血管内皮生长因子（VEGF）和血小板源性生长因子（PDGF）等，促进组织修复与重塑，从而发挥抗炎作用^[37]。因此，从促炎状态（M1）向抗炎状态（M2）表型的及时转换对于快速恢复组织稳态至关重要。M1型巨噬细胞极化介导炎症反应促进放射性肺损伤发生发展已得到证实^[38]。汉防己甲素在痛风性关节炎和骨质疏松症中也可调控巨噬细胞M1/M2表型转换^[39-40]。在本研究中Western blotting结果显示辐射模型小鼠M1型巨噬细胞标志物CD86表达增加，M2型巨噬细胞标志物CD163表达降低，而汉防己甲素干预可显著逆转这一现象，表明汉防己甲素可调控辐射模型小鼠肺巨噬细胞M1/M2表型转换从而抑制免疫细胞聚集和促炎细胞因子释放的级联反应。

网络药理学是一种基于系统生物学理论的分析方法，该方法全面评估活性成分、生物靶点、信号通路及生物过程，为后续研究提供指导^[23]。为探讨汉防己甲素改善放射性肺损伤的潜在分子机制，本研究进行了网络药理学分析。筛选出汉防己甲素与放射性肺损伤存在93个交集基因，KEGG通路分析表明交集基因主要富集于NOD样受体信号通路、PI3K-Akt信号通路和NF- κ B信号通路等，表明这些交集基因或富集信号通路可能是汉防己甲素改善放射性肺损伤的潜在靶点或信号通路。

基于网络药理学分析结果以及研究发现，通

过调节NOD样受体信号通路可以实现巨噬细胞从促炎状态向抗炎状态的表型转换^[41]，故研究推测汉防己甲素是否通过调控NLRP3信号通路从而调控巨噬细胞极化呢？NLRP3、ASC和Caspase1前体（Pro-Caspase1）结合寡聚化为NLRP3炎症小体，在该小体内Pro-Caspase1发生自切割进而能够将白细胞介素前体Pro-IL1 β 和Pro-IL18加工为成熟形式^[42]。在肺缺血再灌注损伤^[43]和创伤性神经损伤^[44]等多个模型中都已证实抑制NLRP3/Caspase1通路可以实现巨噬细胞从M1促炎表型向M2抗炎表型的转换，进而抑制炎症级联反应。本研究中发现辐射可激活小鼠肺组织NLRP3/Caspase1信号通路，而汉防己甲素干预可抑制辐射小鼠肺组织NLRP3/Caspase1信号通路活化。

4 结论

汉防己甲素抑制NLRP3/Caspase1通路调控模型小鼠巨噬细胞M1/M2表型转换从而抑制免疫细胞聚集和促炎细胞因子释放的级联反应，减轻放射性肺损伤。

作者贡献声明 乃爱桃负责研究方案设计、小鼠辐射和药物干预、网络药理学分析、Western blotting实验、数据分析以及论文撰写；李志敏和曾慧承担组织学评分；何贵成协助小鼠辐射和药物干预；杨巧和廖明初指导整体实验设计以及论文修改。全体作者均已阅读并认可该论文的最终版本。

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