



PPAR α 在UVB诱导皮肤损伤中的作用及潜在机制研究*

江枫菽¹, 刘一帆¹, 王铭渝², 谢晓涛¹, 马合丽亚·阿地力¹, 杜梦洁¹,
王佳佳³, 熊海³, 张舒羽^{1, 3 Δ}

1. 四川大学华西基础医学与法医学院 放射医学研究室(成都 610041); 2. 四川大学华西公共卫生学院/
四川大学华西第四医院(成都 610041); 3. 西藏大学医学院(拉萨 850000)

【摘要】目的 太阳光中的中波紫外线(ultraviolet B, UVB)是WHO 1类致癌物,可以被表皮吸收,过量UVB照射会导致皮肤损伤和光老化。过氧化物酶体增殖物激活受体 α (peroxisome proliferator-activated receptor alpha, PPAR α)是核受体家族的重要成员,在脂质代谢中发挥核心作用。本研究以PPAR $\alpha^{-/-}$ 与野生型小鼠为对象,旨在观察并探讨PPAR α 缺失对UVB照射后损伤进程的影响及皮肤脂质谱的变化。**方法** 采用单次高剂量UVB照射(2 J/cm²)构建小鼠皮肤紫外光损伤模型,将C57BL/6J小鼠分为PPAR $\alpha^{-/-}$ 组和野生型组,通过皮肤光损伤评分、苏木精-伊红(HE)染色、Western blot进行定性与定量分析。另采用连续多次低剂量UVB照射构建小鼠皮肤紫外光老化模型,将C57BL/6小鼠分为PPAR $\alpha^{-/-}$ 组和野生型组,同样以HE染色和Western blot进行检测。此外,分别采集接受或不接受单次高剂量UVB照射(2 J/cm²)的两种基因型小鼠皮肤样本进行脂质组学分析。**结果** 在急性光损伤模型中,与野生型组小鼠相比,PPAR $\alpha^{-/-}$ 组小鼠于照射后第0~32天内皮肤光损伤评分显著升高,伤口愈合速度更慢。在光老化模型中,与野生型组小鼠相比,PPAR $\alpha^{-/-}$ 组小鼠皮肤细胞中衰老相关蛋白质表达水平上调(p16: 0.11 $\pm$ 0.02 vs. 0.82 $\pm$ 0.18, P <0.05; p21: 0.54 $\pm$ 0.03 vs. 1.29 $\pm$ 0.07, P <0.01; p53: 0.54 $\pm$ 0.04 vs. 1.33 $\pm$ 0.06, P <0.01; β -半乳糖苷酶: 0.80 $\pm$ 0.06 vs. 1.20 $\pm$ 0.15, P <0.05),同时皮肤毛囊数量减少、形态皱缩。脂质组学分析结果显示,UVB照射下PPAR α 缺失显著加剧了皮肤脂质代谢的紊乱,涉及神经酰胺(d18:1/30:2)、O-酰基- ω -羟基脂肪酸(44:4)、磷脂酰乙醇胺(50:1)、溶血磷脂酰胆碱(19:1)、溶血磷脂酰丝氨酸(44:11)和磷脂酰胆碱(19:1/20:1)等多种脂质的异常表达。**结论** PPAR α 可以减轻UVB诱导的皮肤损伤和光老化,其缺失会加重皮肤损伤和脂质代谢紊乱。

【关键词】 紫外线 光损伤 光老化 过氧化物酶体增殖物激活受体 α 脂质组学

Role and Potential Mechanisms of Peroxisome Proliferator-Activated Receptor α in Ultraviolet B Radiation-Induced Skin Damage

Jiang Fengdi¹, Liu Yifan¹, Wang Mingyu², Xie Xiaotao¹, Maheliya Adili¹, Du Mengjie¹, Wang Jiajia³, Xiong Hai³, Zhang Shuyu^{1, 3 Δ} . 1. Laboratory of Radiation Medicine, West China School of Basic Medical Sciences & Forensic Medicine, Sichuan University, Chengdu 610041, China; 2. West China School of Public Health and West China Fourth Hospital, Sichuan University, Chengdu 610041, China; 3. Medical College of Xizang University, Lhasa 850000, China
 Δ Corresponding author

This study was supported by the National Natural Science Foundation of China (No. U25A20151) and the Key Research and Development Program of the Xizang Autonomous Region Science and Technology Plan (No. XZ202501ZY0131).

[Abstract] Objective Ultraviolet B radiation (UVB) in sunlight is classified by the WHO as a Group 1 carcinogen. UVB is readily absorbed by the epidermis, and excessive exposure causes skin injury and photoaging. Peroxisome proliferator-activated receptor α (PPAR α), a key member of the nuclear receptor family, plays a central role in lipid metabolism. This study aims to observe and investigate the effects of PPAR α deletion on the progression of UVB-induced damage and changes in the skin lipid profile using PPAR α -knockout (PPAR $\alpha^{-/-}$) and wild-type mice. **Methods** A mouse model of ultraviolet-induced skin damage was established using excessive UVB exposure (2 J/cm²) administered for a single time. C57BL/6J mice were divided into PPAR $\alpha^{-/-}$ and wild-type groups. Qualitative and quantitative analyses were performed using skin photodamage scoring, hematoxylin-eosin (HE) staining, and Western blotting. A photoaging model was established using repeated low-dose UVB exposure, and the C57BL/6 mice were again divided into PPAR $\alpha^{-/-}$ and wild-type groups for qualitative and quantitative analyses through HE staining and Western blotting. Skin samples collected from PPAR $\alpha^{-/-}$ and wild-type mice either sham-irradiated or exposed to a single dose 2 J/cm² UVB irradiation

* 国家自然科学基金(No. U25A20151)和西藏自治区科技计划项目重点研发计划(No. XZ202501ZY0131)资助

Δ 通信作者

出版日期: 2026-07-20

were subjected to lipidomic analysis. **Results** In the photodamage model, PPAR $\alpha^{-/-}$ mice exhibited significantly higher skin photodamage scores and delayed wound healing than wild-type controls on days 0-32 after a single excessive UVB exposure. In the photoaging model, the expression levels of senescence-associated proteins were markedly up-regulated in the skin of PPAR $\alpha^{-/-}$ mice compared with wide-type mice (wild-type vs. PPAR $\alpha^{-/-}$) (p16: 0.11 ± 0.02 vs. 0.82 ± 0.18 , $P < 0.05$; p21: 0.54 ± 0.03 vs. 1.29 ± 0.07 , $P < 0.01$; p53: 0.54 ± 0.04 vs. 1.33 ± 0.06 , $P < 0.01$; β -galactosidase: 0.80 ± 0.06 vs. 1.20 ± 0.15 , $P < 0.05$). In addition, PPAR $\alpha^{-/-}$ mice exhibited reduced numbers of hair follicles and follicular atrophy. Lipidomic analysis revealed that PPAR α deletion aggravated UVB-induced skin lipid metabolic disturbances, involving aberrant expression of multiple lipids, including Cer(d18:1/30:2), OAHFA(44:4), PE(50:1), LPC(19:1), LPS(44:11), and PC(19:1/20:1). **Conclusion** PPAR α plays a protective role in UVB-induced skin damage and photoaging. Its deficiency aggravates skin damage and lipid metabolic disturbances.

[Key words] Ultraviolet radiation Photodamage Photoaging Peroxisome proliferator-activated receptor α Lipidomics

皮肤不仅是人体最大的器官,更是应对外界环境压力的第一道物理屏障。中波紫外线(ultraviolet B, UVB)是诱发皮肤光损伤和光老化的主要环境因子^[1-2]。急性暴露于过量UVB可诱发皮肤红斑、水肿及急性炎症反应^[3-4];而慢性累积性暴露则驱动皮肤结构和功能的显著退化性改变,典型特征包括粗糙皱纹、皮肤松弛、色素沉着异常以及胶原蛋白等细胞外基质的降解,并显著增加皮肤癌和光线性皮肤病的易感性^[5-6]。UVB致损的核心分子机制主要涉及直接DNA损伤和触发活性氧(reactive oxygen species, ROS)爆发性生成,进而激活氧化应激和炎症级联反应,从而加速皮肤衰老和病理损伤的进程^[7-8]。

UVB不仅会导致皮肤DNA损伤和炎症反应,还会改变皮肤脂质的组成。研究表明,UVB照射会导致大鼠角质形成细胞中磷脂酰胆碱、溶血磷脂酰胆碱、磷脂酰乙醇胺和神经酰胺水平上调,鞘磷脂和磷脂酰丝氨酸含量下调^[9];长期亚红斑剂量UVB照射则会显著减少无毛小鼠角质层中的神经酰胺、游离脂肪酸和胆固醇^[10]。因此,脂质代谢紊乱可能是UVB诱导皮肤病理改变的重要环节。过氧化物酶体增殖物激活受体 α (perxisome proliferator-activated receptor alpha, PPAR α)属于核受体超家族成员,也是一种转录因子,它是脂质代谢的关键调控因子,能够通过促进脂肪酸氧化、调控脂质合成与分解来维持细胞和组织的脂质稳态^[11-12]。已有研究表明,PPAR α 缺失会加重电离辐射所致的皮肤损伤^[13-14]。由此推测,PPAR α 可能通过影响脂质代谢途径,从而在一定程度上决定UVB诱导的皮肤损伤和光老化的严重程度。然而,目前关于PPAR α 在UVB诱导的皮肤损伤和光老化中的作用以及PPAR α 缺失对UVB照射后皮肤脂质的影响尚未见报道。

基于此,本研究采用C57BL/6背景的PPAR α 基因敲除小鼠和野生型小鼠,构建单次大剂量UVB诱导的皮肤损伤模型以及多次小剂量UVB诱导的光老化模型,比较两

者在皮肤外观改变、组织学结构、衰老相关蛋白质表达以及损伤修复能力等方面的差异。同时,结合液相色谱-串联质谱脂质组学技术,对不同处理条件下的皮肤脂质组成进行全面分析,揭示PPAR α 在维持皮肤脂质稳态、减轻UVB诱导皮肤损伤及光老化中的关键作用。本研究不仅有助于阐明紫外线导致皮肤损伤的代谢机制,也为开发以脂质代谢和PPAR α 为靶点的防护及干预策略提供理论依据。

1 材料与方法

1.1 实验动物和试剂

野生型(wild-type, WT)C57BL/6雄性小鼠(6~8周龄,体质量18~20 g)购于成都达硕实验动物公司,PPAR α 基因敲除(PPAR $\alpha^{-/-}$)C57BL/6雄性小鼠(6~8周龄,体质量18~20 g)购于苏州大学动物研究所。磷酸盐缓冲溶液(phosphate buffer saline, PBS)、SDS-PAGE蛋白质上样缓冲液购于上海碧云天生物;GAPDH、p16、p21、p53、 β -galactosidase一抗购于美国Cell Signaling Technology;HRP标记二抗购于英国Abcam;ECL化学发光超敏显色试剂盒购于上海翌圣生物;法国Bio-Sun紫外线辐照仪(UVB波长312 nm)。

1.2 PPAR $\alpha^{-/-}$ 繁育与基因型鉴定

将C57BL/6J背景的PPAR α 基因敲除种鼠(PPAR $\alpha^{-/-}$)与野生型种鼠(WT;基因型为PPAR $\alpha^{+/+}$)交配,获得F1代PPAR α 杂合子小鼠(PAPR $\alpha^{+/-}$);随后将F1代PAPR $\alpha^{+/-}$ 雌雄小鼠进行交配繁育,获得PPAR $\alpha^{+/+}$ 、PAPR $\alpha^{+/-}$ 和PPAR $\alpha^{-/-}$ 后代。取后代小鼠尾尖组织进行基因型鉴定。根据鉴定结果,选取6~8周龄雄性PPAR $\alpha^{-/-}$ 小鼠作为基因敲除组,选取相同繁育批次的雄性PPAR $\alpha^{+/+}$ 小鼠作为WT对照组。PAPR $\alpha^{+/-}$ 小鼠仅用于繁育和基因型鉴定,不纳入后续UVB照射实验。采用一步法小鼠基因型鉴定试

剂盒提取基因组DNA。*PPAR α* 基因型鉴定采用两组PCR反应,分别检测突变型等位基因和野生型等位基因。共同引物17026序列为5'-CACACCAAGCAGCA GACACT-3';突变型等位基因特异性引物oIMR1100序列为5'-GCTATCAGGACATAGCGTTGG-3',扩增产物长度为400 bp;野生型等位基因特异性引物oIMR8076序列为5'-CCCATTTCGGTAGCAGGTAGTCTT-3',扩增产物长度为533 bp。突变型等位基因的PCR扩增程序为:95℃预变性5 min;95℃变性30 s、58℃退火30 s、72℃延伸30 s,循环扩增40次;随后于72℃终延伸3 min,25℃保温。野生型等位基因采用降落PCR程序:95℃预变性5 min;95℃变性30 s、65℃退火30 s、72℃延伸30 s,退火温度每个循环降低0.5℃,共20个循环;随后进行95℃变性30 s、60℃退火30 s、72℃延伸30 s,共20个循环;最后于72℃终延伸3 min,25℃保温。PCR扩增产物经1.5%琼脂糖凝胶电泳检测。仅出现533 bp野生型条带者判定为*PPAR $\alpha^{+/+}$* ;同时出现533 bp野生型条带和400 bp突变型条带者判定为*PPAR $\alpha^{+/-}$* ;仅出现400 bp突变型条带者判定为*PPAR $\alpha^{-/-}$* 。

1.3 动物模型构建

将C57BL/6小鼠分为*PPAR $\alpha^{-/-}$* 组($n=6$)和WT组($n=9$),小鼠背部脱毛后分别接受不同方式的UVB照射以建立模型。根据相关研究,2 J/cm² UVB照射6~8周龄C57BL/6J野生型雄性小鼠时,小鼠背部皮肤会逐渐出现损伤然后修复^[15-16]。因此,紫外光损伤模型选择2 J/cm²的UVB照射剂量。紫外光老化模型建立则选择前7 d每日接受150 mJ/cm² UVB照射,随后14 d内隔日接受300 mJ/cm² UVB照射的照射方案^[17-18]。为了观察*PPAR α* 对UVB连续低剂量照射后小鼠皮肤组织的影响,在两组小鼠接受第一次低剂量UVB照射后开始对其背部皮肤进行拍照记录,并在照射后的不同时间点采集小鼠背部皮肤组织进行分析。本研究经四川大学实验动物中心伦理委员会批准(批准号SCU43-2601-03)。

1.4 HE染色

小鼠皮肤组织样本在4%组织固定液中固定24 h后,经脱水和石蜡包埋处理,切成3 μ m厚的切片,采用HE染色,显微镜下观察组织形态结构。HE染色由赛维尔生物公司完成。

1.5 蛋白质免疫印迹(Western blot)

提取小鼠皮肤组织总蛋白质,经SDS-聚丙烯酰胺凝胶电泳(SDS-PAGE)分离后,电转移至聚偏二氟乙烯(PVDF)膜。用含5%脱脂奶粉的封闭液于室温封闭1 h,随后于4℃条件下与一抗孵育过夜。洗涤后,用加入辣根过氧化物酶标记的二抗于室温孵育1 h,再次充分洗涤。

采用化学发光法显色,曝光并采集图像。利用Image J软件对蛋白质条带进行灰度值分析,以内参为参照,计算目的蛋白与内参蛋白灰度值的比值,作为目的蛋白的相对表达水平。

1.6 脂质组学分析

为研究单次高剂量UVB照射后对皮肤脂质组成的影响,本研究设未照射野生型对照组(WT-CON)、UVB照射野生型组(WT-UVB)及UVB照射*PPAR $\alpha^{-/-}$* 组(*PPAR $\alpha^{-/-}$* -UVB)。C57BL/6J小鼠背部脱毛后接受单次UVB照射(2 J/cm²),照射后第4天采集背部皮肤组织,采用超声辅助萃取法提取皮肤组织样本中的总脂质。色谱分离使用Waters ACQUITY UPLC I-Class Plus超高效液相色谱系统,配备HSS T3色谱柱,以乙腈-水和乙腈-异丙醇为流动相进行梯度洗脱。质谱检测在Q-Exactive高分辨质谱仪上完成,采用加热电喷雾离子源,分别在正、负离子模式下采集数据,质量扫描范围为 m/z 120~1800。原始数据处理使用LipidSearch 4.2进行检索,R软件完成峰对齐、归一化及缺失值填补,采用主成分分析(principal component analysis, PCA)、偏最小二乘判别分析(partial least squares-discriminant analysis, PLS-DA)和正交偏最小二乘判别分析(orthogonal partial least squares discriminant analysis, OPLS-DA)进行分析。差异脂质的筛选标准为VIP>1且FDR-adjusted P (Q-value)<0.05。脂质组学检测由上海欧易生物医学科技有限公司完成。

1.7 统计学方法

应用SPSS 24.0软件进行统计学分析,所有实验重复3次,经正态性检验实验数据符合正态分布采用 $\bar{x}\pm s$ 表示。相对体重和皮肤光损伤评分采用重复测量双因素方差分析(用Bonferroni's multiple comparisons test进行 P 值校正),其余数据组间比较采用 t 检验分析。 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 *PPAR α* 缺失加剧高剂量UVB所致皮肤损伤

本研究建立了单次高剂量UVB照射小鼠模型,并持续监测其体质量和皮肤光损伤评分。在第32天观察皮肤组织学改变(图1A)。基因型鉴定证实*PPAR $\alpha^{-/-}$* 小鼠基因型鉴定结果见图1B;Western blot分析结果显示,*PPAR $\alpha^{-/-}$* 小鼠皮肤组织*PPAR α* 蛋白质表达量是*PPAR $\alpha^{+/+}$* 小鼠的2.60倍($P<0.01$)(图1C)。

照射后32 d内,两组小鼠体质量均呈波动性变化趋势。与野生型小鼠相比,*PPAR $\alpha^{-/-}$* 小鼠在UVB照射后表现出更为显著的体质量下降(图2A),提示*PPAR α* 缺失可

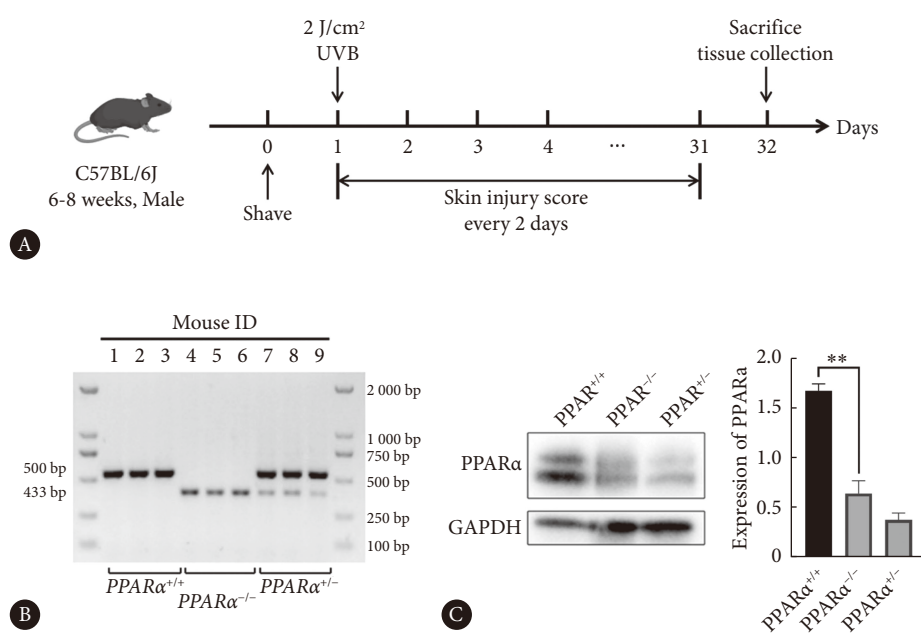


图1 小鼠单次高剂量UVB照射实验的实验设计及小鼠基因型鉴定

Fig 1 Experimental design of single high-dose UVB irradiation in mice and genotyping of mice

A, Experimental design: Male C57BL/6J mice aged 6-8 weeks were divided into PPAR α ^{-/-} and wild-type groups. After dorsal hair removal, the mice received a single dose of 2 J/cm² UVB irradiation. Skin photodamage scoring and body mass recording were performed every 2 days, and the experiment was terminated on day 32. B, Genotyping results of PPAR α ^{+/+}, PPAR α ^{-/-}, and PPAR α ^{+/-} mice. C, Western blot analysis of PPAR α protein expression in skin tissues of PPAR α ^{+/+}, PPAR α ^{-/-}, and PPAR α ^{+/-} mice, with quantitative analysis of band gray values. ** $P < 0.01$.

能削弱了小鼠应对急性光损伤的全身稳态维持能力。皮肤光损伤评分的监测结果显示, 两组小鼠的皮肤损伤程度均呈先加重后减轻的变化趋势。然而, 与野生型小鼠相比, PPAR α ^{-/-}组小鼠皮肤损伤更严重, 且恢复迟缓。照射后第10天, 两组小鼠光损伤评分均达峰值, 但

PPAR α ^{-/-}组的评分显著高于野生型组; 在随后的恢复期内, PPAR α ^{-/-}组评分仍显著高于野生型组(图2B)。大体形态学观察显示, PPAR α ^{-/-}小鼠背部皮肤呈现更为明显的红斑反应及广泛的溃疡形成。照射后第24天, 野生型小鼠背部损伤已基本愈合, 而PPAR α ^{-/-}小鼠背部仍可见

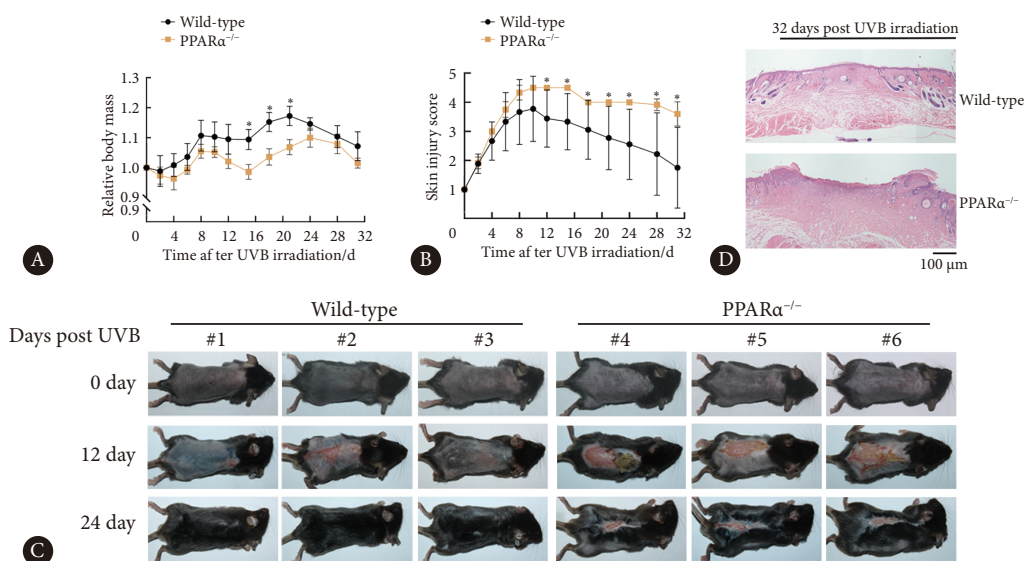


图2 PPAR α 可以减轻小鼠单次高剂量UVB照射后的皮肤光损伤

Fig 2 PPAR α alleviates skin photodamage in mice after single high-dose UVB irradiation

A, Relative body mass changes of mice in the Wild-type group ($n = 9$) and PPAR α ^{-/-} group ($n = 6$) from day 0 to day 32 (relative to each mouse's pre-irradiation body mass). B, Skin photodamage scores of mice in the Wild-type group ($n = 9$) and PPAR α ^{-/-} group ($n = 6$) from day 0 to day 32. C, Representative dorsal skin photographs of mice in the two groups from day 0 to day 32. D, HE staining of dorsal skin tissues of mice in the two groups on day 32. * $P < 0.05$.

大面积未愈合的溃疡区域(图2C)。照射后第32天,皮肤组织HE染色结果表明,野生型小鼠皮肤结构已基本恢复完整,而 $PPAR\alpha^{-/-}$ 小鼠表皮与真皮连接连续性中断,真皮层组织结构明显破坏(图2D)。上述结果提示, $PPAR\alpha$ 缺失可加重单次高剂量UVB诱导的皮肤损伤,并延缓伤口愈合进程。

2.2 $PPAR\alpha$ 缺失加重慢性UVB诱导的皮肤色素沉着与毛囊退变

光老化小鼠模型建立方法见图3A。结果显示,照射后第9天, $PPAR\alpha^{-/-}$ 小鼠背部即出现明显色素沉着,且着色范围进行性扩大、色泽加深;至第18天,其色素沉着面积显著大于野生型对照组(图3B)。为进一步观察 $PPAR\alpha$ 对UVB连续低剂量照射后小鼠皮肤结构的影响,于照射后第22天对小鼠皮肤进行HE染色。结果显示, $PPAR\alpha^{-/-}$ 组小鼠皮肤毛囊数量明显减少、形态皱缩,而野生型组小鼠毛囊结构完整、分布均匀(图3C)。

细胞衰老的过程中会伴随p53、p21和p16等蛋白的表达上调^[19]。为验证 $PPAR\alpha$ 缺失是否会影响皮肤组织衰老相关蛋白质的表达,于照射后第22天采集两组小鼠的背部皮肤组织,利用Western blot进行检测。结果如图4,与野生型小鼠相比, $PPAR\alpha^{-/-}$ 小鼠皮肤组织中p16($0.11 \pm$

0.02 vs. 0.82 ± 0.18 , $P < 0.05$), p21(0.54 ± 0.03 vs. 1.29 ± 0.07 , $P < 0.01$), p53(0.54 ± 0.04 vs. 1.33 ± 0.06 , $P < 0.01$), β -半乳糖苷酶(0.80 ± 0.06 vs. 1.20 ± 0.15 , $P < 0.05$)蛋白的表达水平均显著升高。此外, $PPAR\alpha^{-/-}$ 小鼠皮肤组织中BAX的表达水平降低(0.97 ± 0.20 vs. 0.75 ± 0.08 , $P < 0.01$),而BCL2的表达水平升高(0.68 ± 0.22 vs. 1.29 ± 0.12 , $P < 0.05$)。上述结果提示, $PPAR\alpha$ 缺失不仅促进慢性UVB暴露条件下衰老相关蛋白的表达,还可能使BAX/BCL2介导的凋亡调控平衡向抗凋亡方向偏移。综上, $PPAR\alpha$ 缺失会加重慢性UVB暴露下的皮肤衰老表型,表现为色素沉着加重、衰老相关标志物上调及毛囊萎缩,并伴随凋亡调控蛋白表达改变。上述结果表明, $PPAR\alpha$ 可能是维持皮肤稳态和延缓UVB诱导光老化进程的重要调控因子。

2.3 脂质组学揭示 $PPAR\alpha$ 缺失加剧UVB诱导的皮肤脂质代谢紊乱

PUVB照射后第4天采集三组小鼠的背部皮肤组织进行脂质组学分析(图5A)。与WT-CON组相比,WT-UVB组共鉴定出456种上调脂质与406种下调脂质;而与WT-UVB组相比, $PPAR\alpha^{-/-}$ -UVB组则呈现395种上调与624种下调脂质(图5B)。PCA与PLS-DA均显示三组样本间存在明显分离,表明皮肤脂质组成受基因型及UVB暴

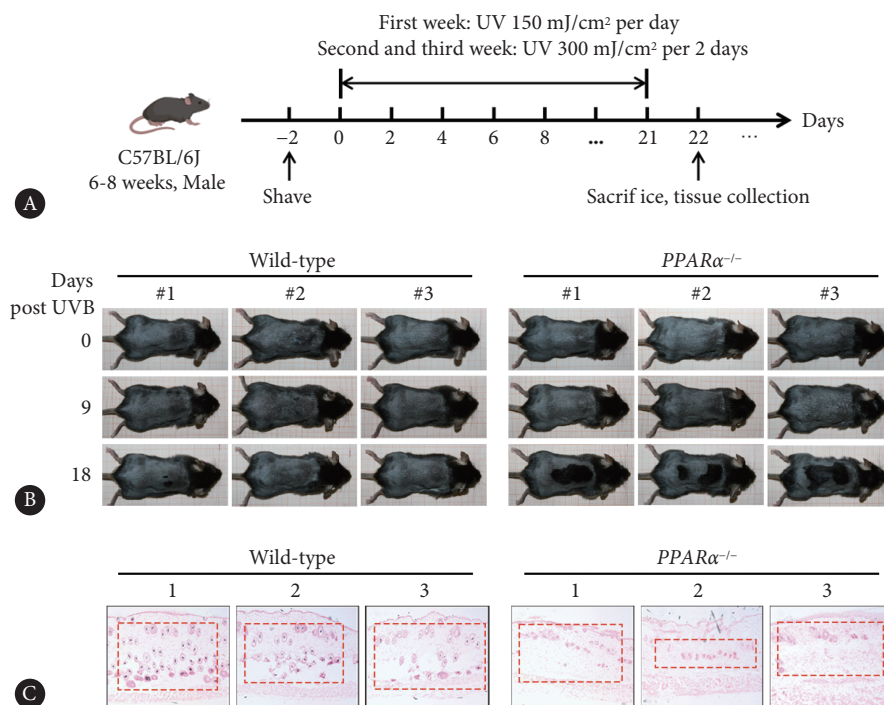


图 3 $PPAR\alpha$ 可以减轻小鼠多次低剂量UVB照射后的皮肤光损伤

Fig 3 $PPAR\alpha$ alleviates skin photodamage in mice after repeated low-dose UVB irradiation

A, Experimental design: Male C57BL/6J mice aged 6-8 weeks were divided into $PPAR\alpha^{-/-}$ and wild-type groups. After dorsal hair removal, the mice received daily UVB irradiation at 150 mJ/cm^2 during the first week, followed by 300 mJ/cm^2 every other day in the second week. The experiment was terminated on day 22. B, Representative dorsal skin photographs of mice in the two groups from day 0 to day 18. C, HE staining of dorsal skin tissues of mice in the two groups on day 22, with the red dashed boxes marking the areas with dense hair follicle distribution (original magnification $\times 100$).

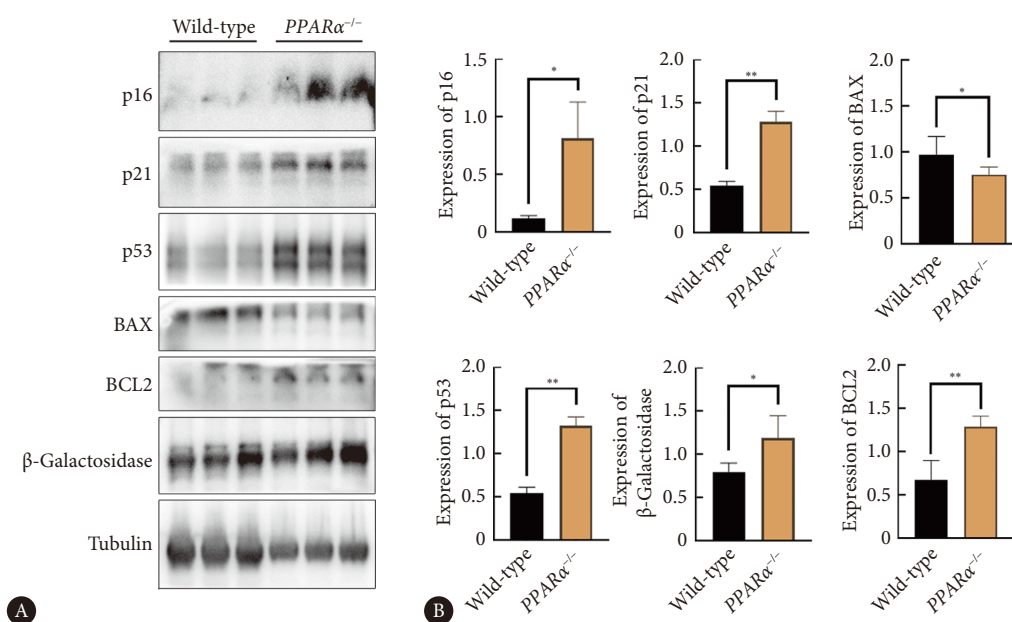


图4 PPAR α 可以减轻小鼠多次低剂量UVB照射后皮肤组织的衰老和凋亡相关蛋白质表达

Fig 4 PPAR α reduces the expression of senescence- and apoptosis-related proteins in mouse skin tissues after repeated low-dose UVB irradiation

A, Western blot results of senescence- and apoptosis-related proteins in dorsal skin tissues of PPAR α ^{-/-} and Wild-type mice on day 22. B, Quantitative analysis of the gray values of Western blot bands for senescence- and apoptosis-related proteins in dorsal skin tissues of PPAR α ^{-/-} and Wild-type mice on day 22 ($n = 3$). * $P < 0.05$, ** $P < 0.01$.

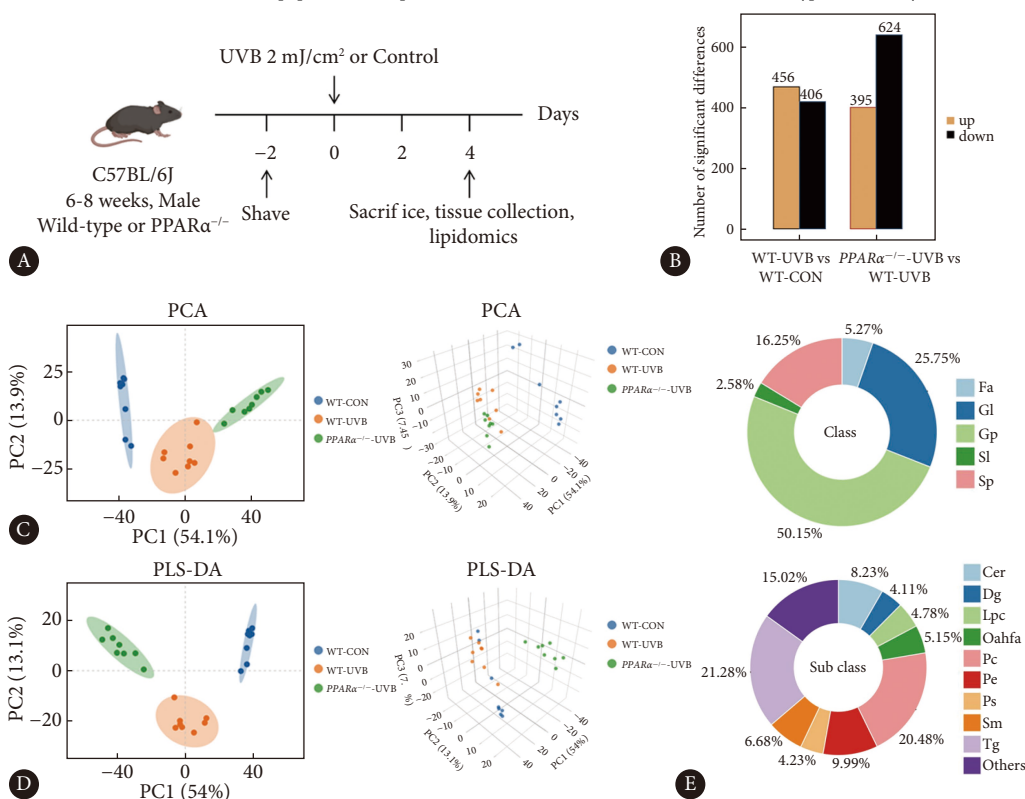


图5 脂质组学分析PPAR α 缺失对UVB照射后小鼠皮肤脂质的影响

Fig 5 Lipidomics analysis of the effect of PPAR α knockout on skin lipids in mice after UVB irradiation

A, Schematic diagram of the experimental protocol: A mouse skin UV damage model was established using 2 J/cm² UVB irradiation. C57BL/6 mice were divided into three groups, including wild-type non-irradiated control group (WT-CON), wild-type irradiated group (WT-UVB), and PPAR α ^{-/-} irradiated group (PPAR α ^{-/-}-UVB). Mouse skin tissues were collected on day 4 post-irradiation for lipidomics sequencing analysis. B, The number of differentially expressed lipids in the skin tissues of the three groups. C, Principal component analysis (PCA) results of the lipidomics data. D, Partial least squares-discriminant analysis (PLS-DA) results of the lipidomics data. E, Statistical chart of the composition of lipid species classified by class and sub-class.

露状态显著影响(图5C、5D)。脂质类别构成分析表明,甘油磷脂(glycerophospholipids, GP)为主要脂质类别,三酰甘油(triacylglycerol, TG)为其最主要亚类(图5E)。

基于脂质组学数据制作韦恩图(图6A)以分析差异脂质亚类的重叠情况。结果显示,在“WT-UVB vs. WT-CON”上调组中特异性检测到8种脂质亚类,分别为溶血磷脂酰丝氨酸(lysophosphatidylserine, LPS)、溶血磷脂酰甘油(lysophosphatidylglycerol, LPG)、磷脂酰乙醇胺(phosphatidylethanolamine, PE)衍生物、溶血二甲氨基磷脂酰乙醇胺(lysodimethylphosphatidylethanolamine, LdMePE)、溶血磷脂酰胆碱(lysophosphatidylcholine, LPC)、溶血磷脂酰乙醇胺(lysophosphatidylethanolamine,

LPE)、TG、溶血磷脂酰甲酯(lysophosphatidylmethyl ester, LPMe);在“PPAR $\alpha^{-/-}$ -UVB vs. WT-UVB上调组中,仅检测到1种特异性脂质亚类,即二酰甘油(diacylglycerol, DG);两组间共有的脂质亚类共8种,包括含N-乙酰葡萄糖胺基三糖基神经酰胺(glucosylceramide with N-acetylglucosamine trisaccharide moiety, CerG3GNAc1)、磷脂酰肌醇磷酸(phosphatidylinositol phosphate, PIP)、单酰甘油(monoacylglycerol, MG)、游离脂肪酸(free fatty acid, FFA)、鞘磷脂(sphingomyelin, SM)、磷脂酸(phosphatidic acid, PA)、二糖基神经酰胺(disaccharide ceramide, CerG2)及O-酰基- ω -羟基脂肪酸[(O-acyl)- ω -hydroxy fatty acid, OAHFA]。图6B展示了WT-UVB组与

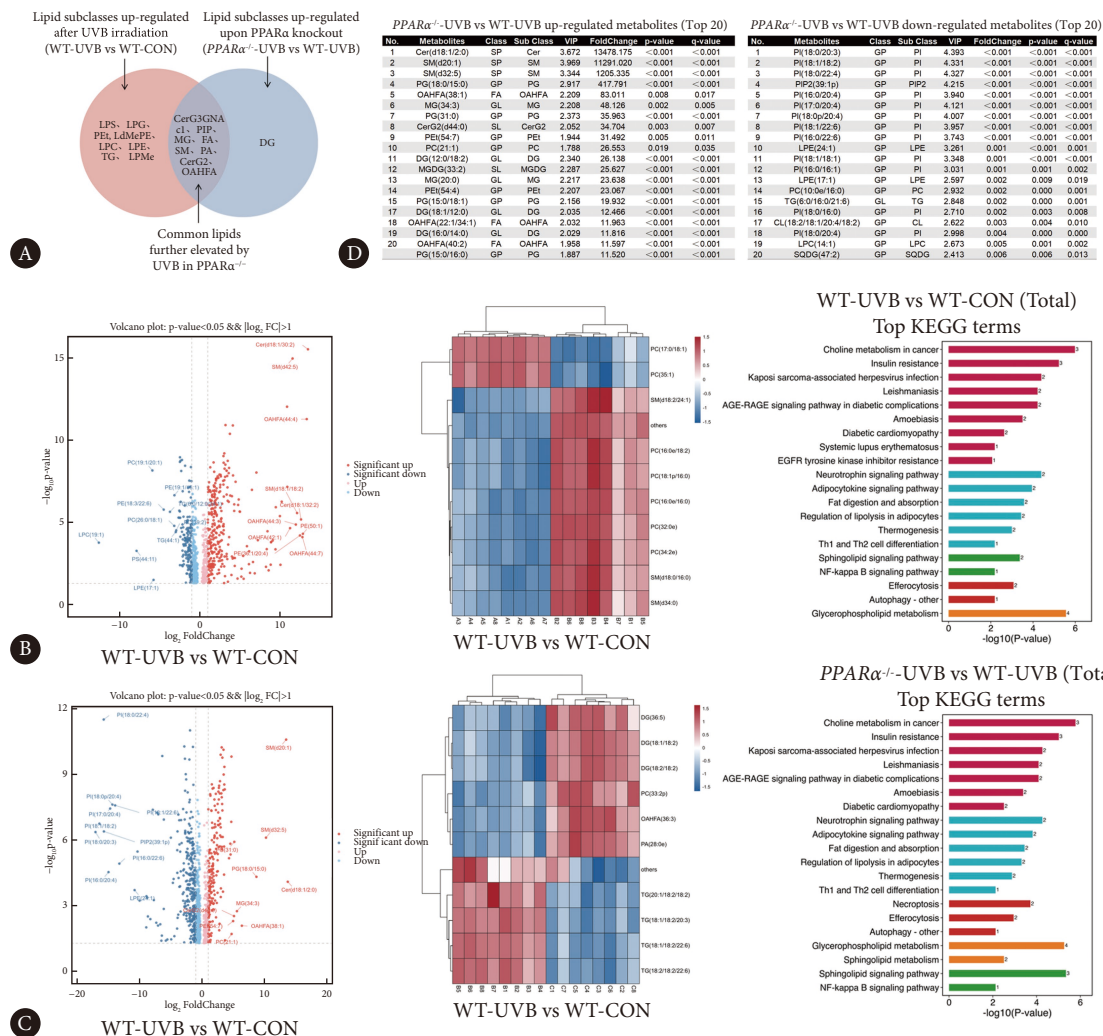


图 6 脂质组学分析PPAR α 缺失影响的小鼠皮肤脂质及相关通路

Fig 6 Lipidomics analysis of mouse skin lipids and related pathways affected by PPAR α deficiency

A, Venn diagram showing the upregulated lipid subclasses in UVB-irradiated wild-type mice vs. non-irradiated wild-type mice, upregulated lipid subclasses in UVB-irradiated PPAR $\alpha^{-/-}$ mice vs. UVB-irradiated wild-type mice, and their intersection. B, Volcano plot, heatmap, and KEGG pathway enrichment analysis of differentially expressed lipids between UVB-irradiated wild-type mice and non-irradiated wild-type mice. C, Volcano plot, heatmap, and KEGG pathway enrichment analysis of differentially expressed lipids between UVB-irradiated PPAR $\alpha^{-/-}$ mice and UVB-irradiated wild-type mice. D, List of differentially expressed lipids between UVB-irradiated PPAR $\alpha^{-/-}$ mice and UVB-irradiated wild-type mice.

WT-CON组差异脂质的火山图、热图及KEGG通路富集分析结果。火山图与热图显示,UVB照射后,野生型小鼠皮肤中 Cer(d18:1/30:2)、SM(d42:5)、OAHFA(44:4)等脂质表达上调,而LPC(19:1)、PC(19:1/20:1)、PE(18:3/22:6)等脂质表达下调。KEGG通路富集分析表明,UVB照射所致差异脂质主要富集于“NF- κ B信号通路”“自噬”“胞葬作用”“脂肪的消化与吸收”“脂肪细胞中脂肪分解的调控”“甘油磷脂代谢”等通路。

脂质组学分析进一步揭示了UVB照射下PPAR α 缺失对皮肤脂质谱的显著调控作用。图6C展示了WT-UVB与PPAR $\alpha^{-/-}$ -UVB小鼠的差异脂质的火山图、热图以及KEGG通路富集分析结果。图6D则列出了PPAR $\alpha^{-/-}$ -UVB小鼠与WT-UVB相比,表达量最为显著的前20种上调和下调脂质代谢物。结果表明,与WT-UVB组相比,PPAR $\alpha^{-/-}$ -UVB小鼠皮肤中SM(d20:1)、SM(d32:5)、Cer(d18:1/2:0)等脂质上调;而PI(18:0/22:4)、PI(18:0p/20:4)、PI(17:0/20:4)等脂质下调。其中,Cer(d18:1/2:0)在PPAR $\alpha^{-/-}$ -UVB小鼠中上调较显著,差异倍数(fold change)达13 478.175($P<0.001$)。其他显著上调的脂质还包括SM(d20:1)、SM(d32:5)、PG(18:0/15:0)、OAHFA(38:1)及MG(34:3);显著下调的脂质包括PI(18:0/20:3)、PI(18:1/18:2)、PI(18:0/22:4)、PI(16:0/20:4)及PI(17:0/20:4)等。KEGG通路富集分析显示,WT-UVB组与PPAR $\alpha^{-/-}$ -UVB组间的差异脂质主要富集于“NF- κ B信号通路”“自噬”“胞葬作用”“程序性坏死”“脂肪的消化与吸收”“脂肪细胞中脂肪分解的调控”“甘油磷脂代谢”“鞘脂代谢”等通路。

脂质组学结果表明,单次2 J/cm² UVB照射可显著改变皮肤脂质谱,而PPAR α 缺失可能进一步放大了这种紊乱,尤其表现为鞘脂类、甘油磷脂类等多种脂质的显著失衡,并涉及NF- κ B信号、自噬、脂肪代谢等多条通路。这提示PPAR α 可能通过维持皮肤脂质稳态,从而减轻UVB诱导的皮肤损伤。

3 讨论

UVB是导致皮肤急性损伤和慢性光老化的主要外源性因素。研究表明,UVB不仅直接损伤细胞结构,还会显著改变皮肤脂质的组成与空间分布^[20],而脂质稳态对于维持角质层屏障和细胞生理状态至关重要^[21]。PPAR α 作为脂质代谢和炎症调控的关键核受体,其在肝脏、心脏等组织中已被广泛研究^[22],但其在UVB诱导的皮肤损伤及光老化中的作用尚不明确。本研究探讨了PPAR α 在UVB诱导的皮肤损伤和光老化中的作用,并且通过脂质组学测序揭示其通过影响脂质稳态调节UVB诱导的皮肤

损伤的潜在机制。

在急性高剂量UVB照射后,PPAR $\alpha^{-/-}$ 小鼠皮肤表现出更明显的损伤和愈合延缓;在连续低剂量UVB照射后,PPAR $\alpha^{-/-}$ 小鼠皮肤组织中p16、p21、p53和 β -半乳糖苷酶表达上调,皮肤结构变化。这提示PPAR α 可以减轻UVB诱导的皮肤损伤,以及在皮肤光老化中具有抗细胞衰老功能。但其作用侧重点可能略有不同:UVB导致的皮肤急性损伤主要机制为DNA损伤、氧化应激、炎症反应和细胞凋亡,而慢性光老化则涉及胶原降解、抗氧化系统受损、内质网应激和自噬功能障碍等机制^[23-26]。研究表明,PPAR α 能够抑制促炎因子的产生,如NF- κ B,从而减轻炎症反应。在特应性皮炎模型中,PPAR α 缺陷小鼠表现出显著增加的皮肤炎症和免疫细胞浸润,而PPAR α 激动剂的应用显著减少了抗原诱导的皮肤炎症^[27]。PPAR α 缺失会显著增加p16、p21和p53等衰老相关基因的表达,这些基因通过抑制细胞周期进程和促进细胞凋亡来加速衰老^[28]。据此推测,在急性损伤中,PPAR α 可能主要通过缓解炎症反应和维持屏障修复来减轻损害;而在慢性光老化中,PPAR α 的缺失加速了细胞衰老和组织退变,提示其在延缓皮肤光老化进程中发挥重要作用。这些发现强调了深入研究PPAR α 下游调控网络的必要性。

脂质组学分析揭示,PPAR $\alpha^{-/-}$ 小鼠在UVB照射后出现显著的脂质谱紊乱。Cer和OAHFA等脂质升高,而PC、LPC和PE等脂质下降。这些变化提示了脂质代谢失衡对皮肤损伤的参与。Cer过度积累可能导致角质层脂质层状结构紊乱,引发经皮水分流失和屏障脆弱化^[29-30];OAHFA的失衡则会影响与角蛋白质结合的 ω -羟基脂质形成,从而削弱角质层的屏障完整性^[31-32]。PE和PC的减少则会破坏细胞膜稳定性,并使其更易受到ROS攻击,促进脂质过氧化和铁死亡的发生^[33-34]。综上,PPAR α 可能通过协同调控Cer、OAHFA、PC及PE等关键脂质的代谢平衡,维持皮肤屏障结构完整和细胞稳态,其缺失会导致上述脂质的表达异常加剧,进而引发皮肤屏障破坏、炎症反应增强及细胞衰老加速。这些发现揭示了PPAR α 在皮肤光损伤中连接脂质代谢与组织功能的关键作用。

本研究仍存在一些不足。首先,脂质组学仅在组织水平上进行,尚未结合单细胞层面的脂质代谢动态,因此不同细胞类型(如角质形成细胞、成纤维细胞、免疫细胞)在脂质调控中的具体贡献仍不清晰。其次,虽然我们推测脂质过氧化和铁死亡可能参与PPAR α 缺失导致的损伤,但缺乏直接的功能实验验证。未来可通过基因编辑或药理学干预进一步明确其机制。此外,本研究主要集中于小鼠模型,临床样本的验证尚待进行。值得注意的

是,本研究中的脂质组学分析涉及大量指标的比较,虽然我们采用了严格的统计筛选标准,但由于多重假设检验的固有特性,仍不能完全排除假阳性结果的可能性。因此,脂质组学的结果应被视为探索性分析,关键的差异脂质及代谢通路在未来的研究中需要通过靶向脂质组学或其他分子生物学实验进一步验证。

综上,本研究揭示了PPAR α 可以减轻UVB诱导的皮肤损伤与光老化,并且尤其强调了其通过调控Cer、OAHFA、PC和PE等脂质维持屏障功能与细胞稳态的机制。这一发现不仅为理解光损伤的代谢基础提供了新思路,也提示PPAR α 可能成为防治皮肤光老化和相关疾病的重要靶点,为开发以PPAR α 激动剂为核心的外用或口服光保护制剂提供了实验依据。未来,结合脂质标志物筛查与个体化皮肤分型,有望实现精准预防与治疗,最终降低UVB相关皮肤疾病及光老化负担。

* * *

作者贡献声明 江枫负责论文构思、数据审编、正式分析、调查研究、研究方法、可视化和初稿写作,刘一帆负责论文构思、正式分析、调查研究和研究方法,王铭渝、谢晓涛、马合丽亚·阿地力、杜梦洁和王佳佳负责正式分析、调查研究和可视化,熊海负责研究项目管理、监督指导和审读与编辑写作,张舒羽负责论文构思、数据审编、经费获取、研究方法、研究项目管理、提供资源、监督指导、可视化、初稿写作和审读与编辑写作。所有作者已同意将文章提交至本刊,并对将要发表版本进行最终定稿,且同意对工作的所有方面负责。

Author Contribution Jiang Fengdi is responsible for conceptualization, data curation, formal analysis, investigation, methodology, visualization, and writing--original draft. Liu Yifan is responsible for conceptualization, formal analysis, investigation, and methodology. Wang Mingyu, Xie Xiaotao, Maheliya Adili, Du Mengjie, and Wang Jiajia are responsible for formal analysis, investigation, and visualization. Xiong Hai is responsible for project administration, supervision, and writing--review and editing. Zhang Shuyu is responsible for conceptualization, data curation, funding acquisition, methodology, project administration, resources, supervision, visualization, writing--original draft, and writing--review and editing. All authors consented to the submission of the article to the Journal. All authors approved the final version to be published and agreed to take responsibility for all aspects of the work.

利益冲突 本文作者张舒羽是本刊编委会编委。该在编辑评审过程中所有流程严格按照期刊政策进行,且未经其本人经手处理。除此之外,所有作者均声明不存在利益冲突

Declaration of Conflicting Interests Zhang Shuyu is a member of the Editorial Board of the journal. All processes involved in the editing and reviewing of this article were carried out in strict compliance with the journal's policies and there was no inappropriate personal involvement by the author. Other than this, all authors declare no competing interests.

参 考 文 献

[1] Rittie L, Fisher G J. UV-light-induced signal cascades and skin aging[J].

- [2] Xu J, Zhang X, Song Y, et al. Heat-killed *Lactocaseibacillus paracasei* ameliorated UVB-induced oxidative damage and photoaging and its underlying mechanisms[J/OL]. *Antioxidants* (Basel), 2022, 11(10): 1875. <https://doi.org/10.3390/antiox11101875>.
- [3] Zou W, González A, Jampallah D, et al. Skin color-specific and spectrally-selective naked-eye dosimetry of UVA, B and C radiations[J/OL]. *Nat Commun*, 2018, 9(1): 3743. <https://pmc.ncbi.nlm.nih.gov/articles/PMC6156228/>. DOI: 10.1038/s41467-018-06273-3.
- [4] Lim H Y, Jeong D, Park S H, et al. Antiwrinkle and antimelanogenesis effects of tyndallized lactobacillus acidophilus KCCM12625P[J/OL]. *Int J Mol Sci*, 2020, 21(5): 1620. <https://doi.org/10.3390/ijms21051620>.
- [5] Nguyen Q T N, Fang M, Do N Q, et al. Anemopsis californica attenuates photoaging by regulating MAPK, NRF2, and NFATc1 signaling pathways[J/OL]. *Antioxidants* (Basel), 2021, 10(12): 1882. <https://doi.org/10.3390/antiox10121882>.
- [6] Kong Y H, Xu S P. Juglanin administration protects skin against UVB-induced injury by reducing Nrf2-dependent ROS generation[J]. *Int J Mol Med*, 2020, 46(1): 67. DOI: 10.3892/ijmm.2020.4593.
- [7] Wu P Y, Lin T Y, Hou C W, et al. 1, 2-Bis[(3-Methoxyphenyl) Methyl]Ethane-1, 2-Dicarboxylic acid reduces UVB-induced photodamage *in vitro* and *in vivo*[J/OL]. *Antioxidants* (Basel), 2019, 8(10): 452. <https://doi.org/10.3390/antiox8100452>.
- [8] Wang J, Qiu H, Xu Y, et al. The biological effect of recombinant humanized collagen on damaged skin induced by UV-photoaging: An *in vivo* study[J]. *Bioact Mater*, 2022, 11: 154. DOI: 10.1016/j.bioactmat.2021.10.004.
- [9] Luczaj W, Domingues M D R, Domingues P, et al. Changes in lipid profile of keratinocytes from rat skin exposed to chronic UVA or UVB radiation and topical application of cannabidiol[J/OL]. *Antioxidants* (Basel), 2020, 9(12): 1178. <https://doi.org/10.3390/antiox9121178>.
- [10] Bak H, Hong S P, Jeong S K, et al. Altered epidermal lipid layers induced by long-term exposure to suberythemal-dose ultraviolet[J]. *Int J Dermatol*, 2011, 50(7): 832. DOI: 10.1111/j.1365-4632.2010.04817.x.
- [11] Probert P M, Leitch A C, Dunn M P, et al. Identification of a xenobiotic as a potential environmental trigger in primary biliary cholangitis[J]. *J Hepatol*, 2018, 69(5): 1123. DOI: 10.1016/j.jhep.2018.06.027.
- [12] Zhao Q, Tang P, Zhang T, et al. Celastrol ameliorates acute liver injury through modulation of PPAR α [J/OL]. *Biochem Pharmacol*, 2020, 178: 114058. <https://doi.org/10.1016/j.bcp.2020.114058>.
- [13] Liu P, Yu D, Sheng W, et al. PPAR α activation by fenofibrate ameliorates radiation-induced skin injury[J]. *J Eur Acad Dermatol Venereol*, 2022, 36(3): 421. DOI: 10.1111/jdv.17745.
- [14] Sun C, Song B, Sheng W, et al. Fenofibrate attenuates radiation-induced oxidative damage to the skin through fatty acid binding protein 4 (FABP4)[J/OL]. *Front Biosci* (Landmark Ed), 2022, 27(7): 214. <https://www.imrpress.com/journal/FBL/27/7/10.31083/j.fbl2707214>.
- [15] Zhang X, Feng C, Wang S, et al. A novel amphibian-derived peptide alleviated ultraviolet B-induced photodamage in mice[J/OL]. *Biomed Pharmacother*, 2021, 136: 111258. <https://doi.org/10.1016/j.biopha.2021.111258>.
- [16] Miyauchi-Hashimoto H, Horio T. Suppressive effect of ultraviolet B radiation on contact sensitization in mice. II. Systemic immunosuppression is modulated by ultraviolet irradiation and hapten application[J]. *Photodermatol Photoimmunol Photomed*, 1996, 12(4): 137. DOI: 10.1111/j.1600-0781.1996.tb00190.x.
- [17] Qin D, Lee W H, Gao Z, et al. Protective effects of antioxidant-RL from *Odorrana livida* against ultraviolet B-irradiated skin photoaging[J]. *Peptides*, 2018, 101: 124. DOI: 10.1016/j.peptides.2018.01.013.
- [18] Yin S, Wang Y, Liu N, et al. Potential skin protective effects after UVB irradiation afforded by an antioxidant peptide from *Odorrana andersoni*[J/OL]. *Biomed Pharmacother*, 2019, 120: 109535. <https://doi.org/10.1016/j.biopha.2019.109535>.
- [19] Luo C, Zhou S, Zhou Z, et al. Wnt9a promotes renal fibrosis by accelerating cellular senescence in tubular epithelial cells[J]. *J Am Soc Nephrol*, 2018, 29(4): 1238. DOI: 10.1681/ASN.2017050547.

- [20] Dalmau N, Andrieu-Abadie N, Tauler R, *et al.* Untargeted lipidomic analysis of primary human epidermal melanocytes acutely and chronically exposed to UV radiation[J]. *Mol Omics*, 2018, 14(3): 170. DOI: [10.1039/c8mo00040j](https://doi.org/10.1039/c8mo00040j).
- [21] Jung Y R, Lee J H, Sohn K C, *et al.* Adiponectin signaling regulates lipid production in human sebocytes[J/OL]. *PLoS One*, 2017, 12(1): e0169824. <https://doi.org/10.1371/journal.pone.0169824>.
- [22] Finck B N. The PPAR regulatory system in cardiac physiology and disease[J]. *Cardiovasc Res*, 2007, 73(2): 269. DOI: [10.1016/j.cardiores.2006.08.023](https://doi.org/10.1016/j.cardiores.2006.08.023).
- [23] Chen J, Tai M, Chen J, *et al.* Panax ginseng extract prevents UVB-induced skin photodamage by modulating VMP1-mediated ER stress[J/OL]. *Phytomedicine*, 2024, 134: 156010. [https://linkinghub.elsevier.com/retrieve/pii/S0944-7113\(24\)00667-6](https://linkinghub.elsevier.com/retrieve/pii/S0944-7113(24)00667-6). DOI: [10.1016/j.phymed.2024.156010](https://doi.org/10.1016/j.phymed.2024.156010).
- [24] Umar S A, Shahid N H, Nazir L A, *et al.* Pharmacological activation of autophagy restores cellular homeostasis in ultraviolet-(B)-induced skin photodamage[J/OL]. *Front Oncol*, 2021, 11: 726066. <https://doi.org/10.3389/fonc.2021.726066>.
- [25] Wang S, Yang M, Yin S, *et al.* A new peptide originated from amphibian skin alleviates the ultraviolet B-induced skin photodamage[J/OL]. *Biomed Pharmacother*, 2022, 150: 112987. <https://doi.org/10.1016/j.biopha.2022.112987>.
- [26] Ma T, He J, Long Q, *et al.* Orientin attenuates UVB-induced skin photodamage by inhibiting ROS generation via the AMPK/Nrf2 axis[J/OL]. *Int Immunopharmacol*, 2025, 155: 114655. <https://doi.org/10.1016/j.intimp.2025.114655>.
- [27] Staumont-Salle D, Abboud G, Brenuchon C, *et al.* Peroxisome proliferator-activated receptor alpha regulates skin inflammation and humoral response in atopic dermatitis[J/OL]. *J Allergy Clin Immunol*, 2008, 121(4): 962. [https://www.jacionline.org/article/S0091-6749\(07\)03613-5/fulltext](https://www.jacionline.org/article/S0091-6749(07)03613-5/fulltext). DOI: [10.1016/j.jaci.2007.12.1164](https://doi.org/10.1016/j.jaci.2007.12.1164).
- [28] Wang S, Zhang X, Hou Y, *et al.* SIRT6 activates PPAR α to improve doxorubicin-induced myocardial cell aging and damage[J/OL]. *Chem Biol Interact*, 2024, 392: 110920. <https://doi.org/10.1016/j.cbi.2024.110920>.
- [29] Schild J, Kalvodova A, Zbytovska J, *et al.* The role of ceramides in skin barrier function and the importance of their correct formulation for skincare applications[J]. *Int J Cosmet Sci*, 2024, 46(4): 526. DOI: [10.1111/ics.12972](https://doi.org/10.1111/ics.12972).
- [30] Sakai T, Hatano Y. Stratum corneum pH and ceramides: key regulators and biomarkers of skin barrier function in atopic dermatitis[J]. *J Dermatol Sci*, 2025, 118(2): 51. DOI: [10.1016/j.jdermsci.2025.04.001](https://doi.org/10.1016/j.jdermsci.2025.04.001).
- [31] Paananen R O, Viitaja T, Olzynska A, *et al.* Interactions of polar lipids with cholesterol ester multilayers elucidate tear film lipid layer structure[J]. *Ocul Surf*, 2020, 18(4): 545. DOI: [10.1016/j.jtos.2020.06.001](https://doi.org/10.1016/j.jtos.2020.06.001).
- [32] Acera A, Ibarrondo O, Mateo-Orobia A J, *et al.* Identification of tear lipid biomarkers in women with dry eye disease and the impact of intense pulsed light therapy: a case-control study[J/OL]. *BMC Ophthalmol*, 2025, 25(1): 496. <https://pmc.ncbi.nlm.nih.gov/articles/PMC12400718/>. DOI: [10.1186/s12886-025-04315-1](https://doi.org/10.1186/s12886-025-04315-1).
- [33] Santos M, Melo T, Mauricio T, *et al.* The non-enzymatic oxidation of phosphatidylethanolamine and phosphatidylserine and their intriguing roles in inflammation dynamics and diseases[J]. *FEBS Lett*, 2024, 598(17): 2174. DOI: [10.1002/1873-3468.14921](https://doi.org/10.1002/1873-3468.14921).
- [34] Kobylinska A, Bernat P, Posmyk M M. Melatonin mitigates lead-induced oxidative stress and modifies phospholipid profile in tobacco BY-2 suspension cells[J/OL]. *Int J Mol Sci*, 2024, 25(10): 5064. <https://doi.org/10.3390/ijms25105064>.

(2025-08-12收稿, 2026-05-25修回)

编辑 何学令



开放获取 本文使用遵循知识共享署名—非商业性使用4.0国际许可协议(CC BY-NC 4.0), 详细信息请访问

<https://creativecommons.org/licenses/by-nc/4.0/>。

OPEN ACCESS This article is licensed for use under Creative Commons Attribution-NonCommercial 4.0 International license (CC BY-NC 4.0). For more information, visit <https://creativecommons.org/licenses/by-nc/4.0/>.

© 2026 《四川大学学报(医学版)》编辑部

Editorial Office of *Journal of Sichuan University (Medical Sciences)*