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中波紫外线诱导的表皮内质网应激与治疗干预

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摘要 内质网是细胞内最重要的膜性细胞器,对稳定细胞内稳态起关键作用。未折叠或错误折叠蛋白的聚集、细胞内钙离子、氧化还原稳态的改变均能诱发内质网应激(ERS)。ERS参与维持皮肤屏障稳态。中波紫外线(UVB)是导致皮肤损伤的重要因素,UVB诱导表皮发生ERS,进而调控多种生理病理学过程,不仅能够参与表皮屏障稳态维持和角质形成细胞分化命运调控的生理过程;同时还参与UVB诱导的皮肤炎症、角质形成细胞凋亡等病理过程。因此,ERS有望成为UVB介导的皮肤相关疾病的治疗靶点。目前,采用抗氧化剂、核因子 κ B(NF- κ B)抑制剂和内质网 Ca^{2+} 水平调节剂等药物调控UVB诱导的角质形成细胞ERS的策略已显示出潜在的临床应用价值。该文章将围绕UVB诱导的角质形成细胞ERS在皮肤损伤中的作用及靶向ERS的药物在UVB诱导的皮肤损伤中的研究进展进行综述,为ERS在UVB诱导的皮肤损伤中所扮演的角色的研究和以ERS作为靶点、对UVB诱导的皮肤损伤的临床治疗提供新的思路。

关键词 内质网应激;表皮;角质形成细胞;紫外线B;未折叠蛋白反应;活性氧

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皮肤是人体最大的器官,可分为表皮、真皮和皮下组织。表皮主要由角质形成细胞构成,其通过紧密连接(epidermal tight junction, TJ)和有序的逐级分化构成皮肤物理屏障^[1]。紫外线可按照波长被分为长波紫外线(ultraviolet A, UVA)(320~400

nm),中波紫外线(ultraviolet B, UVB)(280~320 nm)和短波紫外线(ultraviolet C, UVC)(100~280 nm)。其中,UVC能够完全被臭氧层吸收,无法对皮肤产生损伤;UVA可深入真皮诱导皮肤衰老和色素沉积^[2]。而UVB被称为“灼烧射线”,相比UVA,它具有更高能量和更大危害。角质形成细胞通过激活一系列响应维持细胞内环境稳态,防止其凋亡、坏死,进而减弱皮肤局部炎症反应。针对UVB诱导的皮肤损伤的防治策略仍较局限;防晒霜的应用是最主要的预防措施;利用抗氧化剂(如维生素E、姜黄素等)中和活性氧(reactive oxygen species, ROS),

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solve the problem of diabetic inflammatory wound healing. **Methods** The membrane was prepared by coaxial electrospinning technology, and its physicochemical and biological properties were evaluated by tensile test, *in vitro* simulation and cell co-culture. **Results** Baicalin combined with gelatin/chitosan membrane was prepared, the fiber diameter was about 100 nm, the tensile strength after crosslinking was 13.38 MPa, the release of baicalin could reach 1 week, and the inflammatory environment was simulated *in vitro*. Baicalin had anti-inflammatory effect within a certain concentration range, and the survival rate of 5-day cells was nearly 100%. **Conclusion** The prepared baicalin combined with gelatin/chitosan membrane has good mechanical strength and excellent biocompatibility, providing a material basis for solving the problem of difficult wound healing.

Key words electrospinning film; wound healing; inflammation; drug release; baicalin

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减少氧化损伤,或利用 DNA 修复酶(如 T4N5 脂质体)乳霜减少细胞突变风险,抑或利用局部抗炎药物(如糖皮质激素)治疗严重紫外线过敏为目前常见的损伤后治疗策略。深入研究 UVB 诱导的皮肤损伤发病机制,将为 UVB 诱导皮肤损伤的防治奠定坚实的理论基础。

在 UVB 诱导的皮肤损伤中,内质网应激(endoplasmic reticulum stress, ERS)是重要一环,其与其他生物学过程间的系统性调控共同塑造了该疾病的病理学图景。随着对 UVB 诱导的 ERS 的深入研究,ERS 有望成为 UVB 诱导的皮肤损伤潜在的治疗靶点。围绕 UVB 诱导皮肤损伤的机制、UVB 诱导的 ERS 及针对 ERS 通路治疗 UVB 诱导的皮肤损伤药物的研究进展进行综述,有助于揭示 ERS 在 UVB 诱导的皮肤损伤中的干预价值,为开发 UVB 诱导皮肤损伤的防治药物提供新的研究方向。

1 UVB 诱导皮肤损伤的机制

UVB 诱导的皮肤损伤可分为急性损伤和慢性损伤。在急性损伤中,最常见的病理表型是晒伤,包含皮肤疼痛、红斑、水肿、水疱、对热敏感等急性反应,这些临床表现与 ROS 生成和免疫系统激活密切相关。慢性损伤包括日光性角化(actinic keratosis, AK)和光老化。AK 的临床表现是鳞状或角化性斑疹或丘疹,为鳞状细胞癌的一种常见的癌前期病变;光老化被定义为皮肤持续受到紫外线照射所产生的衰老性改变,其表现为皱纹、色素沉着改变和肤色丧失。

1.1 UVB 对皮肤细胞的病理学影响 在细胞病理学层面,UVB 促进角质形成细胞增殖分化^[3]、促进细胞骨架蛋白表达、破坏微管或改变其组织形式^[4]、诱导其自噬水平上调^[5]和发生包括自噬性细胞死亡、凋亡、焦亡、坏死性凋亡的程序性细胞死亡(programmed cell death, PCD)^[6]。UVB 能够诱导成纤维细胞衰老、进而促进皮肤整体的光老化进展^[7];同时,在 UVB 刺激下,成纤维细胞通过分泌相关细胞因子促进角质形成细胞存活、DNA 修复进程^[8]。UVB 能够激活黑素细胞以促进其黑色素合成^[9],促进曝光区和非曝光区的黑素细胞增殖和迁移^[10]。但如果黑素细胞的正常细胞周期调控机制遭到 UVB 破坏,将导致其异常增殖,进而诱导不典型色素痣发生。

UVB 对皮肤免疫细胞浸润存在复杂的调节。UVB 诱导 T 细胞、中性粒细胞、促炎型即 M1 型巨噬

细胞向曝光部位募集^[11]、降低朗格汉斯细胞浸润及其活力,但单核细胞及单核细胞来源的树突状细胞的募集则受到促进,进而弥补朗格汉斯细胞在皮肤的缺失^[12]。

1.2 UVB 诱导皮肤损伤的分子机制 UVB 通过多种分子机制加剧了表皮细胞的损伤。UVB 下调叶酸水平^[13],进而抑制了 DNA 甲基转移酶对 DNA 的甲基化;同时,组蛋白的翻译后修饰也同样受到 UVB 影响,两者最终加剧了 UVB 诱导的光老化、提高癌症发生概率^[14]。基质金属蛋白酶(matrix metalloproteinases, MMPs)表达的上调是 UVB 诱导皮肤损伤的另一重要方面^[15]。

氧化应激是 UVB 诱导的皮肤损伤中最关键的因素。在 UVB 照射后,电离辐射增加细胞内超氧阴离子自由基(O_2^-)和过氧化氢(H_2O_2)水平,进而产生大量的 ROS。但 UVB 直接产生的 ROS 较少,更多由酶促反应产生。UVB 诱导产生的 ROS 生成可以分为两个阶段^[16]:在 UVB 照射后短时间内,ROS 主要由 NADPH 氧化酶(NADPH oxidase, NOX)和环氧合酶(cyclooxygenase, COX)催化生成^[17],在 30 min 内达到峰值,且在 1 h 后回归基线水平^[16];而在 UVB 照射后 3~6 h,ROS 能够再次上升,相比第 1 次上升峰值更低但持续时间更长,且可能与线粒体功能障碍相关^[18],过表达过氧化氢酶能够逆转此次上升^[16]。另外,也有文章^[19]指出在 UVB 照射较长一段时间后(>24 h)活性氮(reactive nitrogen species, RNS)占据主导作用而非 ROS。环丁烷嘧啶二聚体(cyclobutane pyrimidine dimers, CPD)和嘧啶-(6-4)-嘧啶酮光产物[purimidine-(6-4)-pyrimidone photoproducts, 6-4PP]是 UVB 诱导的 DNA 损伤的典型形式,由 UVB 直接诱导形成;而 8-羟基-2'-脱氧鸟苷(8-hydroxy-2'-deoxyguanosine, 8-OHdG)是自由基诱导的 DNA 损伤的主要形式^[20]。DNA 氧化损伤积累且未能在进入细胞周期前通过修复途径及时修复,将使细胞携带特定基因如 TP53、CDKN2A 等的突变,进而使细胞恶性转化,促进黑色素瘤和非黑色素瘤的发生^[6,9,14]。

1.3 UVB 诱导的炎症反应 ROS 诱导多种促炎细胞因子和趋化因子,如肿瘤坏死因子 α (tumor necrosis factor α , TNF- α)、干扰素- γ (interferon- γ , IFN- γ)、白介素(interleukin, IL)-1、IL-8 以及前列腺素 E2(prostaglandin E2, PGE2)在角质形成细胞的持续表达和分泌,进而导致免疫细胞如中性粒细胞、巨噬细胞等向光暴露部位聚集^[21-22]。中性粒细胞通

过形成中性粒细胞胞外陷阱(neutrophil extracellular traps, NETs)释放更多的ROS、弹性蛋白酶和髓过氧化物酶来加重皮肤损伤^[23];而巨噬细胞通过经典途径激活转变为M1型巨噬细胞后,也能够通过进一步分泌细胞因子和趋化因子诱导持续的炎症反应^[24]。UVB诱导的皮肤炎症微环境最终导致血管扩张和血管通透性增强、液体渗出进入周围组织,最终表现为皮肤红斑和水肿。

2 UVB 诱导的 ERS

当内质网向高尔基体的转运受到抑制,或是蛋白质合成压力增加而新生蛋白因多种因素不能正常折叠或转运,错误折叠、未折叠蛋白在内质网中聚集,将导致ERS^[25]。生理状态下,ERS水平随着角质形成细胞分化水平增加而增加^[26],环境剂量UVB激活的ERS维持TJ完整性^[1]、促进抗菌肽合成的同时巩固皮肤渗透性屏障^[27];病理状态下,高剂量的UVB诱导ERS的过度激活,将诱导细胞凋亡^[6]、同时ERS激活下游的NF- κ B信号通路,将进一步诱导角质形成细胞的促炎因子表达、分泌,加重皮肤炎症反应^[28]。

ERS发生后,细胞通过激活未折叠蛋白反应(unfolded protein response, UPR)来恢复内质网的稳态。UPR通过三大压力响应蛋白:蛋白激酶R样内质网激酶(PRKR-like endoplasmic reticulum kinase, PERK)、肌醇依赖酶1(inositol-requiring protein 1, IRE1)、转录激活因子6(activating transcription factor 6, ATF6)及其下游通路的激活调控转录、翻译、转运与蛋白质降解以缓解ERS水平^[25]。ERS参与多种皮肤疾病,如毛囊角化病、变异性红斑角化病(erythrokeratoderma variabilis, EKV)、银屑病、红斑痤疮等疾病的发生发展^[29]。

2.1 UVB 诱导的 ERS 的分子机制 在UVB诱导的皮肤损伤中,ERS不仅与氧化应激密切相关,还涉及 Ca^{2+} 的外流。ROS、RNS介导细胞氧化应激,能够破坏内质网的脂质双分子结构,引起内质网结构破坏;同时两者也能与内质网中新生蛋白游离的-SH发生反应,或是耗竭内质网中谷胱甘肽,使新生蛋白不能被正确折叠,进而发生ERS、诱导UPR通路激活;氧化应激还能进一步介导 Ca^{2+} 从内质网的释放,此效应为UVB诱导的ERS的主要推动力量。 Ca^{2+} 对内质网新生蛋白折叠起至关重要的作用,内质网中的 Ca^{2+} 受到 Ca^{2+} 转运体、离子通道、钠钙交换体、 Ca^{2+} 结合/缓冲蛋白和 Ca^{2+} 泵的严密调控以

维持其水平稳定^[30]; Ca^{2+} 稳态对于内质网行使其蛋白合成、折叠、翻译后修饰和转运功能至关重要,同时 Ca^{2+} 不仅通过密切调控多种分子伴侣如钙调蛋白、葡萄糖调节蛋白94(94 ku glucose-regulated protein, GRP94)、免疫球蛋白结合蛋白(binding-immunoglobulin protein, BiP)对ERS起间接调控作用,同时分子伴侣作为稳定的 Ca^{2+} 缓冲蛋白存在于内质网中^[31]。 Ca^{2+} 还能与蛋白质二硫键异构酶(protein disulfide isomerase, PDI)结合支持其与新生肽链结合、促进新生肽链的正确折叠^[30]。 Ca^{2+} 还可作为第二信使调控基因表达、细胞周期进程、代谢,从而以更大的维度对内质网稳态发生调控作用^[32]。UVB诱导的氧化应激能够促进 Ca^{2+} 从内质网释放,诱导ERS,这与内质网内氧化还原状态发生改变,使 Ca^{2+} 泵和离子通道功能受损相关^[33]。这些效应共同诱导PERK-CHOP通路的激活,导致细胞发生ERS依赖的凋亡^[6]。

2.2 ERS 与炎症反应 炎症反应诱导的ERS大多为ROS升高依赖的ERS^[34]。目前尚无文献描述促炎因子是否能够诱导角质形成细胞发生ERS,但促炎因子对ERS存在切实调控的证据已在非皮肤的疾病模型中得到研究。TNF- α 被发现在小鼠纤维肉瘤细胞系L929中以ROS依赖的形式激活ERS、诱导其发生凋亡^[35]。而在人气道平滑肌的研究中,有研究^[36]表明TNF- α 诱导超氧化物生成,进而诱导IRE1 α 磷酸化激活,而超氧化物中和剂Tempol能够抑制此过程。鉴于IFN- γ 被发现能够诱导角质形成细胞的ROS生成^[37]、募集到皮肤的T细胞所分泌的TNF- α 和IFN- γ 能够诱导角质形成细胞表达诱导型一氧化氮合酶(inducible nitric oxide synthase, iNOS),同时促进其活性,进而促进RNS生成^[38],那么UVB所诱导的炎症反应可能能够通过促炎细胞因子如TNF- α 和IFN- γ 及其下游通路激活,使细胞内ROS与RNS进一步生成,进而诱导更大范围或更长时程的ERS,这需要进一步的研究加以证实。

3 针对 ERS 的治疗 UVB 诱导的皮肤损伤的药物研究进展

3.1 抗氧化剂 利用抗氧化剂消耗过度产生的ROS,是治疗UVB诱导的皮肤损伤的普遍策略,抗氧化剂的引入减弱了ROS对内质网稳态的破坏。扇贝多肽是由栉孔扇贝内脏团制备的水溶性小分子抗氧化多肽。其能以剂量依赖的形式耗竭UVB诱导产生的ROS、恢复内质网的氧化还原稳态,进而

抑制 UVB 诱导的 ERS 和 CHOP 介导的凋亡^[39]。与此类似的是,长果锥提取物被发现同样具有抗氧化作用进而耗竭 ROS、抑制 UVB 诱导 ERS 和下游的凋亡^[40]。银杏提取物(Ginkgo biloba L. extract, GBE)同样被发现具有抗氧化作用^[41],同时 NF- κ B 抑制剂吡咯烷二硫代甲酸铵(pyrrolidine dithiocarbamate, PDTC)也能通过抑制 NF- κ B/iNOS 信号通路减弱细胞氧化应激水平^[42]。在 UVB 诱导角质形成细胞 ERS 后联合给药 GBE 与 PDTC,发现联合给药相比单用其中一药具有更好的 ERS 缓解和皮肤光损伤保护效果^[43]。富含花青素的木槿多酚提取物也被发现能够对 UVB 照射导致的表皮损伤起保护作用。除了此提取物的还原效应外,其被发现能够减弱 UVB 照射后角质形成细胞的线粒体膜电位的去极化、降低线粒体的 ROS 生成,进而减弱细胞 ERS 水平^[44]。

3.2 其他药物 人参提取物由多种天然活性组分组成,其中含量最高的是人参皂苷 Rg3^[45]。有研究^[46]表明,Rg3 能够通过调控小泛素相关修饰物 1 (small ubiquitin-related modifier 1, SUMO1) 进而显著增强钙离子转运蛋白心肌肌浆网 Ca^{2+} -ATP 酶(sarcoplasmic/endoplasmic reticulum calcium ATPase 2, SERCA2) SUMO 化水平,进而恢复主动脉弓缩窄(transverse aortic constriction, TAC)下心肌肌浆网 Ca^{2+} 水平。角质形成细胞在受到 UVB 刺激后,内质网 Ca^{2+} 浓度调控蛋白、液泡膜蛋白 1 (vacuole membrane protein 1, VMP1) 显著下调,而人参提取物以剂量依赖的形式逆转此下调,进而抑制 UVB 诱导的内质网 Ca^{2+} 外流、缓解 UVB 诱导的 ERS。

另有研究^[47]发现香芹酚(carvacrol, CRV)能够在体外实验中减弱 UVA 与 UVB 联合诱导的皮肤 ERS 水平,但其发挥作用的具体分子机制并无进一步研究。

4 展望

UVB 诱导的角质形成细胞 ERS 是 UVB 诱导皮肤损伤中的重要环节,此过程受到多种因素、多种细胞内过程如氧化应激、 Ca^{2+} 作为第二信使的信号传导等的系统性调控,同时也影响表皮的多种生理病理学过程如皮肤屏障、表皮分化、炎症反应等。随着对 UVB 诱导的角质形成细胞 ERS 的系统性研究不断深入,ERS 与其他细胞生物学过程或生理病理学过程的相互作用将被更好地揭示;以 UVB 诱导的 ERS 作为干预方向,也为治疗 UVB 诱导的皮肤损伤

指出了值得进一步研究的研究方向。因此,在未来的研究中仍需依托分子机制的进一步研究,探索新型的、干预 UVB 诱导 ERS 的药物。

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Epidermal endoplasmic reticulum stress induced by UVB radiation and therapeutic interventions

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Abstract The endoplasmic reticulum is one of the most prominent membranous organelles that plays a significant role in maintaining intracellular homeostasis. Specific internal or external stimulus leading to the accumulation of unfolded or misfolded proteins, alteration in intracellular calcium levels, or disruptions in redox homeostasis will trigger ER dysfunction and, ultimately, endoplasmic reticulum stress (ERS). Physiologically, ERS is involved in maintaining the homeostasis of the epidermal skin barrier. Ultraviolet B (UVB) induces epidermal ERS, following the activation of a variety of physiological and pathological processes. It participates in the physiological processes of epidermal barrier homeostasis and keratinocyte differentiation, and also contributes to pathological processes such as UVB-induced skin inflammation and keratinocyte apoptosis leading to skin damage. Therefore, ERS is expected to become a therapeutic target for UVB-mediated skin-related diseases. Currently, the clinical potential of modulating UVB-induced keratinocyte ERS through the use of antioxidants, NF-κB inhibitors, and ER Ca²⁺ regulators has been increasingly recognized. This review focuses on the mechanisms underlying UVB-induced skin damage, the molecular mechanisms of UVB-induced keratinocyte ERS, and the current progress of ERS-targeting drugs in UVB-induced skin damage, providing new insights into ERS's roles in UVB-induced skin damage and novel therapeutic strategies targeting ERS for the clinical treatment of UVB-induced skin damage.

Key words endoplasmic reticulum stress; epidermis; keratinocyte; ultraviolet B; unfolded protein response; reactive oxygen species

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