综述

MMP-13在皮肤相关疾病中的研究进展

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摘要　　基质金属蛋白酶(MMPs)是依赖锌的蛋白水解金属酶。MMP-13隶属于胶原酶亚群, 在细胞外基质循环、癌细胞迁移、细胞生长、炎症、血管生成等方面发挥重要作用, 它能降解胶原、明胶和聚集蛋白聚糖。在光老化中MMP-13的表达可受MAPK、NF-κB及TGF-β等多条信号通路影响。在癌症细胞中MMP-13能通过细胞外基质降解, 导致肿瘤细胞的侵袭和转移, 也可能直接调节多条控制组织稳态的信号通路。该文就MMP-13在皮肤相关疾病中的研究进行综述。

关键词　　基质金属蛋白酶; 胶原酶; 皮肤肿瘤; 创伤; 光老化

Research Progress of MMP-13 in Skin-Related Diseases

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Abstract　　MMPs (matrix metalloproteinases) are zinc dependent proteolytic metalloenzymes. MMP-13 belongs to the collagenase subgroup and plays important roles in extracellular matrix circulation, cancer cell migration, cell growth, inflammation, angiogenesis, etc. It can degrade collagen, gelatin and aggregated proteoglycan. The expression of MMP-13 in photoaging can be affected by multiple signaling pathways such as MAPK, NF-κB and TGF-β. In cancer cells, MMP-13 can be degraded through extracellular matrix, leading to invasion and metastasis of tumor cells. It may directly regulate several signaling pathways that control tissue homeostasis. In this paper, the research of MMP-13 in skin-related diseases is reviewed.

Keywords　　matrix metalloproteinases; collagenase; skin tumor; wound; photoaging

基质金属蛋白酶(matrix metalloproteinase, MMPs)是一大类具有广泛的底物特异性的含有锌结合催化结构域的蛋白水解酶。MMP-13作为其家族成员之一, 被认为是正常和病理条件下功能最强的胶原酶[1]。其在细胞外基质循环、胶原降解、癌细胞迁移、细胞生长、血管生成等方面发挥重要作用。本文就MMP-13在光老化、皮肤创伤和皮肤肿瘤研究中的相关进展进行综述。

1　MMP-13的结构与功能

MMP-13的结构(图1)由氨基端信号肽结构域、前肽结构域和催化结构域这3个主要结构域以及1个富含脯氨酸的铰链区域和1个羧基端类血凝素结构域组成。信号肽结构域由17—29氨基酸组成, 此跨膜结构域负责将MMP-13运出细胞。前肽结构域(由77—87氨基酸组成)的氨基酸序列为PRCGXPD, 被称为"半胱氨酸开关", 该结构域通过阻止水分子与锌离子的结合形成催化的必要条件。催化结构域大约包含170个氨基酸, 负责酶的蛋白水解活性。2个锌离子(1个催化锌离子和1个结构锌离子)都结
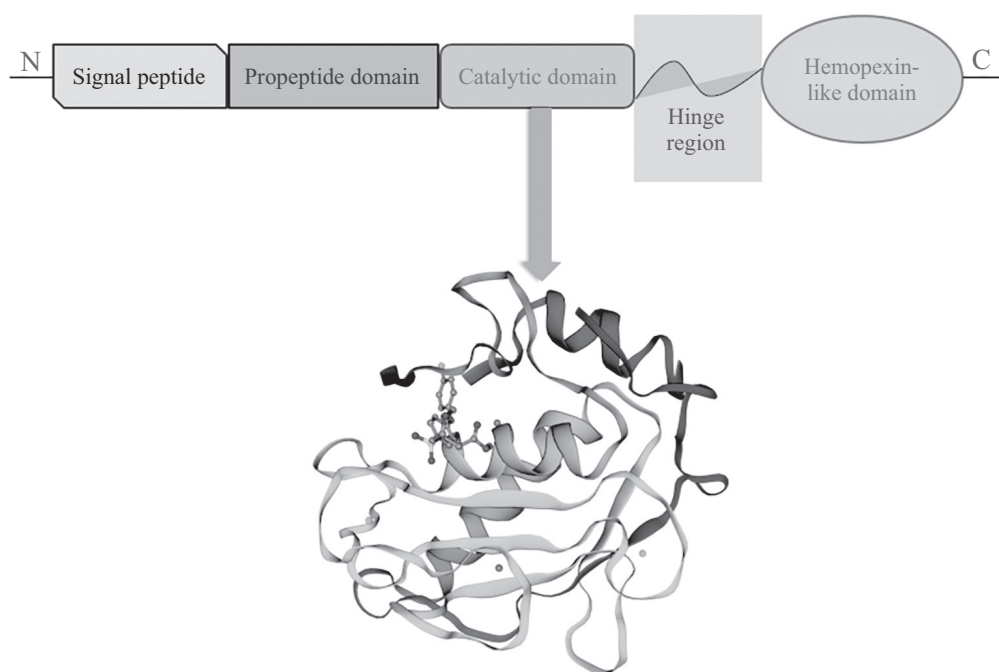
MMP-13通常由1个高度保守的信号肽结构域、1个前肽结构域、1个催化结构域、1个富含脯氨酸的铰链区域和1个羧基端类血凝素结构域组成。球形催化结构域由3个α-螺旋、5个β折叠及8个环区连接组成。绿色配体为钙离子, 紫色配体为锌离子。
MMP-13 typically consists of a highly conserved signal peptide domain, a propeptide domain, a catalytic domain, a proline-rich hinge region, and a C-terminal hemopexin-like domain. The structural organization of spherical catalytic domains: three α-helixes, five β-sheets, connected by eight loops. The calcium ion is in green, the zinc ion is in purple.

图1　MMP-13结构示意图(催化结构域的晶体结构图来自Swiss Institute of Bioinformatics官网)
Fig.1　Structure of MMP-13 (the crystal structure diagram of MMP-13 catalytic domain is available at
**Swiss Institute of Bioinformatics official website)**

合于该区域。MMP-13结构中位于催化锌离子右侧的疏水S1'结合袋具有高度灵活的"S1'特异性环(Ω-loop)", 由残基245—253组成, 这被认为是MMP-13抑制剂选择性结合的决定因素。因此, 口袋的深度对MMP-13抑制剂的设计起到重要作用。羧基端的素样结构域约包含210个氨基酸残基, MMP-13通过该结构域决定了其与底物纤维胶原(I、II型和III型)和明胶相互作用的特性[2-3]。

MMP-13的结构导致其在基膜和细胞外成分的降解过程起着重要作用, MMP-13能破坏肿瘤侵袭的组织学屏障促进肿瘤的侵袭和转移, 其表达与恶性肿瘤的TNM分级相关[4]。伤口愈合和肿瘤发生涉及相似的组织重塑过程, 并由重叠的分子机制驱动[5]。成纤维细胞中的MMP-13是分解真皮成分的关键酶。MMP-13激活后引发I型和III型胶原纤维的降解, 此为紫外线照射诱导皱纹形成的机制[6]。因此, 理解MMP-13在多种皮肤疾病中的作用机制, 并找到这些疾病潜在的治疗靶点具有重要意义。

2　MMP-13与光老化

光老化隶属于外在老化, 是内在老化和慢性紫外线(ultraviolet light, UV)照射对曝光部位皮肤的累积效应[7], 光老化可使皱纹产生并引起各种皮肤疾病, 如不规则色素沉着、晒伤和皮肤癌[8]。MMP-13主要表达于红外线和UV照射后的各种癌症细胞、炎症细胞和早衰细胞, 具有使各种胶原基质变性的独特能力[9]。

UV通过MMP-13引起光老化的机制(图2)为经UVB刺激后产生的活性氧(reactive oxidative species, ROS), 使细胞外基质(extracellular matrix, ECM)塌陷[8]。过量的ROS以及细胞表面多种生长因子受体或细胞因子的活化会激活核因子-κB(nuclear nactor-kappa B, NF-κB)和丝裂原活化蛋白激酶(mitogenactivated protein kinases, MAPKs)调控*MMP-13*的转录。细胞外信号调节激酶(extracellular signal-regulated kinase, ERK)刺激c-Fos的表达, p38激酶和c-Jun氨基末端激酶(c-Jun N-terminal kinase,
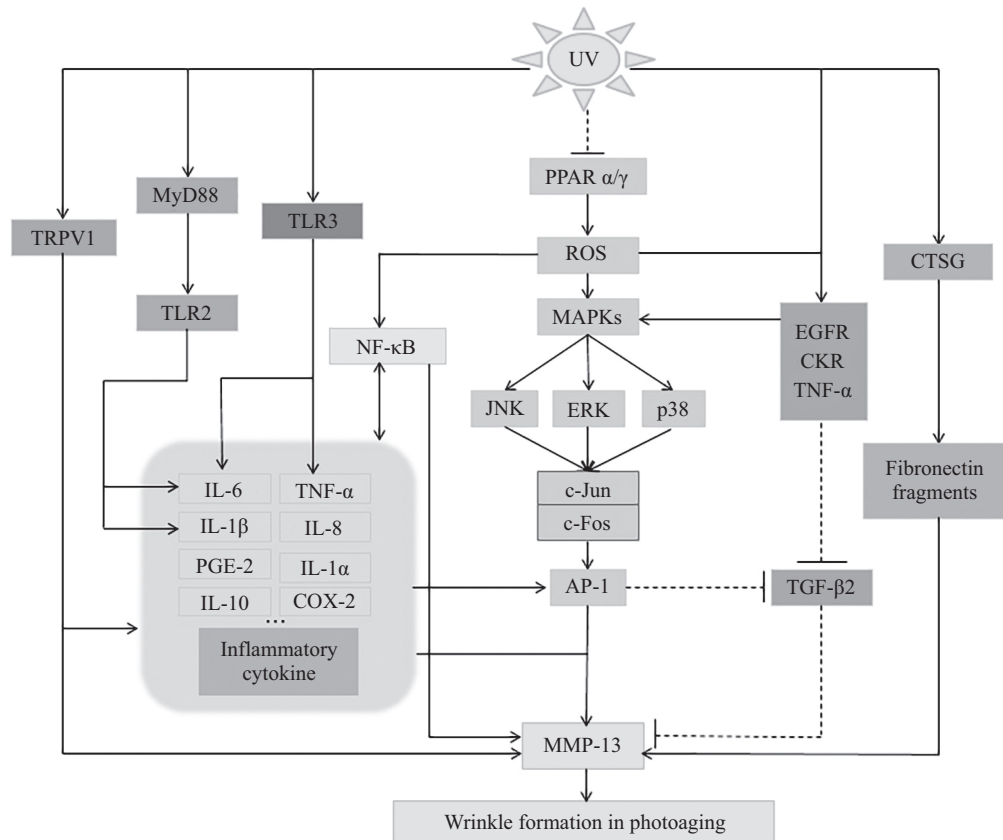
UV照射能通过抑制过氧化物酶体增殖物激活受体α/γ(peroxisome proliferator-activated receptors α/γ, PPAR α/γ), 造成活性氧(ROS)过量积累和细胞表面多种生长因子受体或细胞因子受体激活, 随后激活包括细胞外信号调节激酶(ERK)、c-Jun氨基末端激酶(JNK)和p38激酶在内的丝裂原活化蛋白激酶(MAPKs), 使转录因子激动蛋白-1(AP-1)复合物的表达上调, 促进MMP-13的表达。AP-1、表皮生长因子受体(EGFR)、细胞因子受体(CKR)和TNF-α能抑制TGF-β的表达使MMP-13表达量增加。瞬时受体电位1型(TRPV1)、Toll样受体(TLRs)中的TLR2、TLR3以及通过ROS的过量积累激活的核因子-κB(NF-κB)通过增加炎症因子表达量来激活MMP-13。组织蛋白酶G(CTSG)能使纤连蛋白片段增多诱导MMP-13表达量增加, 促进皱纹形成。

UV irradiation can inhibit peroxisome proliferator-activated receptors α/γ (PPAR α/γ), leading to excessive accumulation of reactive oxidative species (ROS) and activation of multiple growth factor receptors or cytokine receptors on the cell surface. Subsequently, the mitogen-activated protein kinases (MAPKs) including extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK) and p38 kinases are activated to up-regulate the expression of the transcription factor activator protein-1 (AP-1) complex and promote the expression of MMP-13. AP-1, epidermal growth factor receptor (EGFR), cytokine receptor (CKR) and TNF-α can inhibit TGF-β expression and increase MMP-13. Transient receptor potential type 1 (TRPV1), TLR2 and TLR3 in Toll-like receptors (TLRs), and nuclear factor kappa B (NF-κB) activated by excessive accumulation of ROS activate MMP-13 by increasing the expression of inflammatory factors. Cathepsin G (CTSG) can increase fibronectin fragments and increase MMP-13 expression, promoting the formation of wrinkles.

图2　UV通过MMP-13引起光老化的机制
Fig.2　Effects of MMP-13 pathway in photoaging

JNK)的激活增加c-Jun的表达量, 激活c-Jun/AP-1通路, 促进MMP-13的表达。AP-1还能通过抑制转化生长因子-β(transforming growth factor-β, TGF-β)的表达来间接上调MMP-13的表达[10]。瞬时受体电位1型也被UV照射激活并介导MMP-13和促炎细胞因子的表达[11]。此外, 组织蛋白酶G也可能在慢性UV照射的皮肤MMP-13表达量增加中起关键作用[12]。同时有研究表明, 在光老化的发生过程中, UVB诱导的皮肤中MMP-13的表达存在Toll样受体(Toll-like receptors, TLRs)依赖性, TLR2、TLR3均参与了UVB诱导小鼠

MMP-13表达的过程[13-14]。

　　基于MMP-13在光老化过程的重要作用, 表1简要概括一些通过直接抑制和通路调节抑制MMP-13表达发挥抗光老化作用的物质。

3　MMP-13与创面愈合、溃疡及瘢痕

　　皮肤创面愈合中的再上皮化依赖于角质形成细胞的增殖和迁移, MMP-13直接参与小鼠角质形成细胞在伤口愈合过程中的迁移。碱性成纤维生长因子(basic fibroblast growth factor, bFGF)能刺激表皮

表1　通过抑制MMP-13发挥抗光老化作用的物质及其作用机制

Table 1　Substances that exert anti-photoaging effect by inhibiting MMP-13 and their mechanisms

机制 Mechanisms	物质 Substances	作用 Function	参考文献(PMID) Reference (PMID)
Anti-inflammatory effect	Aloe vera gel extract (AVGE)	Inhibit the increase of IL-1β and TNF-α	MISAWA E et al, 2017 (27995657)[15]
	Anacardic acid (AA)	Suppress UV-induced COX-2 and TNF-α	KIM M K et al, 2012 (23228850)[16]
	Peach flower extract	Inhibit UV-induced IL-1β and TNF-α release	KWAK C S et al, 2018 (29399294)[17]
Antioxidant effect	Rosa multiflora flower (RMF) extract	Inactivate NF-κB/p65, JNK and/or ERK	KWAK C S et al, 2020 (32721259)[18]
	Cinnamaldehyde (CIN)	Reduce the ROS production	TANAKA Y et al, 2019 (31735467)[19]
	Perilla frutescens leaves extract (PLE)	Inhibit ROS generation and AP-1 activation	BAE J S et al, 2016 (27888134)[20]
	Fucoxanthin	Reduce UV-induced ROS	URIKURA I et al, 2011 (21512228)[21]
	Ethanol extract of terminalia chebula fruit	Inhibit UVB-induced ROS formation and then attenuate a provocation of the MAPK pathway	YAKAEW S et al, 2016 (27222341)[22]
	Curcuma mangga Val. extract (CME)	Relate to the antioxidant properties	PUJIMULYANI D et al, 2020 (32995615)[23]
	alpha-pinene (AP)	Inhibit NF-κB nuclear translocation	KARTHIKEYAN R et al, 2019 (30521868)[24]
MAPK signaling pathways	Cultivated ginseng (CG)	Suppress UVB-induced activation of NF-κB, c-Jun, and c-Fos and the phosphorylation of MAPK	HWANG Y P et al, 2012 (22749179)[25]
	Chitooligosaccharides (COS)	Decrease the expression of phosphorylated JNK, p38 MAPK, and ERK1/2 proteins, attenuate the regulation/activation of c-Jun and c-Fos	AHN B N et al, 2012 (21947228)[26]
	Penta-1,2,3,4,6-*O*-galloyl-β-*D*-glucose (PGG)	Reduce UVB-induced phosphorylation of ERK	KIM J A et al, 2019 (31731779)[27]
	Lactobacillus plantarum HY7714	Prevent JNK/AP-1 activation	KIM H M et al, 2014 (25112318)[28]
	Naringenin	Block ERK2 kinase activity	JUNG S K et al, 2016 (26861188)[29]
	Kaempferia parviflora extract (KPE)	Reduce the expression of c-Jun and c-Fos	PARK J E et al, 2014 (24313661)[30]
	Bouea macrophylla ethanol extract (BME)	Inactivate the MAPKs/AP-1 signaling pathway	CHEONG Y et al, 2018 (30263735)[8]
	Retinoic acid (RA)	Reduce c-Jun protein expression through RAR-mediated pathway	LI Z et al, 2017 (28849147)[31]
	7,8-dihydro-8-oxo-20 deoxyguanosine (8-oxo-dG)	Attenuate MAPK activation, lead to inhibition of the activation of ATF-2 and c-Jun	LEE J K et al, 2013 (23466236)[32]
TGF-β/Smad signaling pathways	Skin-derived precursors	Inhibit the downregulation of TbRII mRNA and protein through triggering the TGF-β pathway	WANG S et al, 2019 (29943461)[33]
	A mixture of extracts of Kochia scoparia and Rosa multiflora (KR)	Increase TGF-β expression	JEON H et al, 2016 (27854351)[7]
	Adipose-derived stem cells (ADSCs)	Activate TGF-β2 and inhibition of NF-κB signaling	GONG M et al, 2020 (31468588)[34]
Transient receptor potential type 1 (TRPV1)	TIP	Block calcium-mediated TRPV1 downstream signaling	KANG S M et al, 2017 (28551094)[11]
	50-iodoresiniferatoxin (I-RTX)	Inhibit TRPV1	LEE Y M et al, 2011 (21656169)[35]
Peroxisome proliferator-activated receptors (PPARs)	Wy14643	Agitate catalase	SHIN M H et al, 2016 (27611371)[36]
Serine protease family	β-keto-phosphonic acid (KPA)	Inhibit CTSG activity	KUSUMANINGRUM N et al, 2019 (30414203)[12]
Mechanism not clarified	Lactobacillus plantarum HY7714	Inhibit the expression of MMP-13	KIM H M et al, 2014 (25112318)[28]
	Fermented agricultural by-products (FRB, FSB and FSc)	Inhibit the expression of MMP-13	CHOI S I et al, 2019 (31198982)[37]
	Luteolin (3,4,5,7-tetrahydroxyflavone)	Inhibit the expression of MMP-13	LIM S H et al, 2013 (23551430)[38]
	Galactomannan	Inhibit the expression of MMP-13	YANTI et al, 2017 (28250652)[9]
	(2E,5E)-2,5-bis (3-hydroxy-4-methoxybenzylidene) cyclopentanone (BHCP)	Inhibit the expression of MMP-13	JUNG H J et al, 2018 (29891820)[39]
	Low molecular weight (LMW)	Inhibit the expression of MMP-13	YEO I et al, 2018 (29438785)[40]
	Pomegranate juice concentrated powder (PCP)	Reduce the expression of MMP-13	KANG S J et al, 2017 (28810554)[41]
	Cassis polysaccharide (CAPS)	Decrease MMP-13 transcription level	ASHIGAI H et al, 2018 (30175796)[6]

角质形成细胞的迁移过程, 而这种作用也可能是通过诱导MMP-13的表达来实现的。MMP-13还能够通过选择性切割结缔组织生长因子(connective tissue growth factor, CTGF)从VEGF(vascular endothelial growth factor)/CTGF复合物中释放VEGF, 从而促进小鼠皮肤创面的血管生成。在创面愈合的成熟阶段, 肉芽组织肌成纤维细胞的增殖导致创面收缩。而*MMP-13* KO(knock out)小鼠的伤口收缩迟缓, 肌成纤维细胞形成减少。MMP-13可能通过激活潜在的TGF-β1使成纤维细胞增殖和肌成纤维细胞分化参与创面收缩[42]。这些作用提示, 或许可通过应用MMP-13或MMP-13的诱导物来治疗愈合延迟的伤口。

在溃疡及瘢痕中, MMP-13在慢性溃疡的真皮中表达, 参与修复和恶变过程。人纤维母细胞表达的MMP-13在正常的人牙龈和胎儿皮肤伤口以无瘢痕愈合为特征[43]。*MMP-10* KO小鼠损伤后的皮肤通过减少MMP-13的表达量使创面胶原沉积、瘢痕增加和皮肤僵硬[44]。MMP-10还能特异性地增强小鼠M2型巨噬细胞产生的MMP-13的胶原溶解活性, 在伤口愈合过程中调节组织重塑和瘢痕形成[45]。

4 MMP-13与皮肤癌

皮肤癌一般分为非黑色素瘤皮肤癌(nonmelanoma skin cancer, NMSC)和黑色素瘤皮肤癌。

4.1 MMP-13与NMSC

皮肤基底细胞癌(cutaneous basal cell carcinoma, cBCC)和皮肤鳞状细胞癌(cutaneous squamous cell carcinoma, cSCC)分别约占NMSC的80%和20%[46], 在恶性转化的角质形成细胞中已经检测到MMP-13的表达[47], 并且MMP-13蛋白特异性表达于cSCC肿瘤细胞, 不表达于正常表皮细胞, 其阳性细胞数与肿瘤侵袭程度相关[43]。在cSCC细胞中敲低*MMP-13*可导致其生长、迁移和侵袭受损[48]。cSCC的侵袭进展中*MMP-13* mRNA表达于肿瘤浸润前沿, 偶尔也表达于间质成纤维细胞[47]。cSCC中过表达的补体因子I(complement factor I, CFI)通过增加MMP-13的表达量使癌周产生有效的蛋白水解网络, 切割周围的ECM, 增强肿瘤侵袭能力[49]。因此靶向抑制MMP-13能抑制cSCC的生长和侵袭。

有研究表明, p53通过抑制信号传导与转录激活因子3下调MMP-13的表达[50]。下调基因*AIM2*也能通过下调MMP-13而减少cSCC细胞的侵袭[51]。而缺乏*Tpl2*基因能通过上调MMP-13使皮肤癌的侵袭性和转移性增加[52]。MEIDES等[53]证实*MMP-13* KO能降低VEGF的释放, 而雌激素(17β-estradiol, E$_2$)通过上调MMP-13, 减轻*MMP-13* KO对肿瘤生长和血管生成的影响。低水平E$_2$使成纤维细胞和cSCC细胞中MMP-13抑制剂治疗更有效。隐性营养不良大疱性表皮松解症(recessive dystrophic epidermolysis bullosa, RDEB)患者在慢性溃疡或瘢痕处易发生cSCC。病灶周围的正常细胞从非典型增生向癌细胞进展的过程中MMP-13表达水平升高, 提示MMP-13是鉴别RDEB的良性角化过度病变和cSCC的有用标记物[54]。人脐带血来源的非限制性体细胞共培养能通过显著抑制RDEB患者来源的角质形成细胞和cSCC细胞中MMP-13的表达调节角质形成细胞的恶性转化和cSCC的侵袭[43]。血清MMP-13水平对侵袭性cSCC和原位cSCC的鉴别、淋巴结转移的预测具有较高的敏感性和特异性, 提示血清MMP-13可能是早期检测cSCC侵袭性和监测cSCC进展的有价值的生物标志物[46]。

miRNA/miR(microRNA)是一种小的内源性非编码RNA, 可以诱导mRNA降解, 抑制基因转录, 或通过结合靶mRNA转录本的3′非编码区(3′ untranslated regions, 3′-UTRs)导致mRNA脱腺苷化。肿瘤生长负调控因子miR-125b的表达与MMP-13的表达成反比。miR-125b的缺乏可能会削弱癌细胞的分化能力[55]。有实验证实, miR-125b在cSCC中抑制的直接靶点是MMP-13, 其可以通过直接结合*MMP-13* mRNA的3′-UTRs和调控TGF-β通路来下调MMP-13的表达。miR-27b-3p也通过与MMP-13和EGFR的3′-UTRs结合下调MMP-13的表达, 抑制cSCC细胞的增殖、迁移和侵袭[48,56]。这表明抑制cSCC中高表达的MMP-13可能是抗肿瘤药物的治疗靶点。

在BCC中, MMP-13的表达在肿瘤细胞以及病灶周围的成纤维细胞、炎症细胞和内皮细胞中上调。由成纤维细胞和肿瘤细胞分泌的MMP-13促进肿瘤血管生成, 参与ECM的降解从而促进肿瘤侵袭。BCC周围的炎症细胞均呈典型的MMP-13阳性, 表明炎症在调节肿瘤进展中具有重要作用。而内皮细胞来源的MMP-13与内皮细胞增殖和血管分化有关[57]。

4.2 MMP-13与黑色素瘤皮肤癌

MMP-13的表达能力和活性的增强与黑色素瘤细胞在体外的侵袭能力和癌细胞体内移植后的转

移潜能有关[58]。MMP-13在原发性结节性黑色素瘤病灶中表达水平升高[59]。有体外研究表明, 黄连素、多不饱和脂肪酸二十二碳六烯酸(docosahexaenoic acid, DHA)能通过下调MMP-13表达抑制黑色素瘤的侵袭性行为[31]。同时抑制MMP-9和MMP-13的表达能刺激淋巴细胞浸润并下调体内黑色素瘤细胞miR-21和miR-let-7b的表达水平从而影响皮肤黑色素瘤的生存和预后[60]。

4.3 MMP-13的肿瘤抑制功能

上述研究大多旨在探讨MMP-13的表达与皮肤癌侵袭的联系, 但也有研究揭示了MMP-13在肿瘤抑制中的作用。*MMP-13*属于*p38*依赖基因, p63是调控上皮发育和维持的主转录因子。皮肤和黏膜肿瘤的p38α的磷酸化使p63不稳定, 通过降低p63的可用率来驱动MMP-13的表达。*p63*基因敲低的人角质形成细胞中MMP-13的表达量增加, 从而限制角质形成细胞的干细胞特性和致瘤潜能。研究表明, p38α缺失的角质形成细胞和定位于皮肤上皮*p38α*基因敲除的(*p38α*ΔK)肿瘤中MMP-13表达水平降低。*MMP-13* KO小鼠比野生型小鼠的皮肤肿瘤发病率更高、发展更快, 并且*MMP-13* KO小鼠的肿瘤发生率和多重性远高于*p38α*ΔK小鼠。这种差异可能是因为即使*p38α*ΔK小鼠中的MMP-13表达量减少, 但其仍然具有重要功能。其他类型细胞(如皮肤成纤维细胞和髓样细胞)来源产生的MMP-13也可以代偿[5]。目前MMP-13的肿瘤抑制功能机制尚未被阐明, 但MMP家族中其他成员也有与之相似的现象。MMP-3最初被描述为一种有效的致瘤蛋白酶, 但有研究发现*MMP-3* KO小鼠的cSCC比对照组分化更少, 增长更快。*MMP-19* KO小鼠对化学诱导皮肤肿瘤的易感性降低, 表明MMP-19可能促进肿瘤发生, 然而它又是肿瘤血管生成和侵袭的负调控因子[61]。因此, MMP-13在肿瘤发生和恶性行为的调控中可能也存在双向功能, 作为来自不同上游信号通路的效应分子, 其作用机制仍值得我们进一步探究。

5 结语

MMP-13作为MMPs中的一员, 具有强大的降解胶原纤维的作用, 在机体病理生理功能中发挥重要作用, 其过表达和失调与多种疾病相关。过去综述大多集中在其与骨关节炎及恶性肿瘤等疾病关系的研究, 本文首次对其在皮肤疾病中的作用进行综述。

日光通过多种途径增加MMP-13的表达量从而破坏皮肤胶原结构, 导致皱纹形成, 选择性抑制MMP-13的表达可减轻光老化对皮肤的损伤。在皮肤创伤修复中, MMP-13既通过参与炎症反应、胶原重塑发挥积极作用, 又参与慢性皮肤创伤的恶变进程。MMP-13对皮肤肿瘤的发生及恶性肿瘤的侵袭也具有重要意义, 调节MMP-13表达, 使它可作为恶性肿瘤的治疗靶点是值得进一步探索的。目前对其研究并不够充分, 期待未来有更多研究能通过探索调节MMP-13的活性及表达对更多疾病所产生的影响, 为临床治疗提供有效信息。

参考文献 (References)

[1] MIRASTSCHIJSKI U, LUPŠE B, MAEDLER K, et al. Matrix metalloproteinase-3 is key effector of TNF-α-induced collagen degradation in skin [J]. Int J Mol Sci, 2019, 20(20): 5234.

[2] HU Q, ECKER M. Overview of MMP-13 as a promising target for the treatment of osteoarthritis [J]. Int J Mol Sci, 2021, 22(4): 1742.

[3] MONDAL S, ADHIKARI N, BANERJEE S, et al. Matrix metalloproteinase-9 (MMP-9) and its inhibitors in cancer: a minireview [J]. Eur J Med Chem, 2020, 194: 112260.

[4] WANG J R, LI X H, GAO X J, et al. Expression of MMP-13 is associated with invasion and metastasis of papillary thyroid carcinoma [J]. Eur Rev Med Pharmaco, 2013, 17(4): 427-35.

[5] CHOO M K, KRAFT S, MISSERO C, et al. The protein kinase p38α destabilizes p63 to limit epidermal stem cell frequency and tumorigenic potential [J]. Sci Signal, 2018, 11(551): eaau0727.

[6] ASHIGAI H, KOMANO Y, WANG G, et al. Orally administered polysaccharide derived from blackcurrants (*Ribes nigrum* L.) improves skin hydration in ultraviolet-irradiated hairless mice [J]. J Nutr Sci Vitaminol, 2018, 64(4): 301-4.

[7] JEON H, KIM D H, NHO Y H, et al. A mixture of extracts of Kochia scoparia and Rosa multiflora with PPAR α/γ dual agonistic effects prevents photoaging in hairless mice [J]. Int J Mol Sci, 2016, 17(11): 1919.

[8] CHEONG Y, KIM C, KIM M B, et al. The anti-photoaging and moisturizing effects of *Bouea macrophylla* extract in UVB-irradiated hairless mice [J]. Food Sci Biotechnol, 2018, 27(1): 147-57.

[9] YANTI, MADRIENA, ALI S. Cosmeceutical effects of galactomannan fraction from arenga pinnata fruits *in vitro* [J]. Pharmacognosy Res, 2017, 9(1): 39-45.

[10] PITTAYAPRUEK P, MEEPHANSAN J, PRAPAPAN O, et al. Role of matrix metalloproteinases in photoaging and photocarcinogenesis [J]. Int J Mol Sci, 2016, 17(6): 868.

[11] KANG S M, HAN S, OH J H, et al. A synthetic peptide blocking TRPV1 activation inhibits UV-induced skin responses [J]. J Dermatol Sci, 2017, 88(1): 126-33.

[12] KUSUMANINGRUM N, OH J H, LEE D H, et al. Topical treatment with a cathepsin G inhibitor, β-keto-phosphonic acid, blocks ultraviolet irradiation-induced basement membrane damage in hairless mouse skin [J]. Photodermatol Photoimmunol

Photomed, 2019, 35(3): 148-56.

[13] PARK H S, JIN S P, LEE Y, et al. Toll-like receptor 2 mediates a cutaneous reaction induced by repetitive ultraviolet B irradiation in C57/BL6 mice *in vivo* [J]. Exp Dermatol, 2014, 23(8): 591-5.

[14] YAO C, HAN S, TIAN Y D, et al. Toll-like receptor 3 mediates UVB-induced MMP-13 and MMP-3 expressions in mice [J]. J Dermatol Sci, 2017, 87(2): 203-5.

[15] MISAWA E, TANAKA M, SAITO M, et al. Protective effects of Aloe sterols against UVB-induced photoaging in hairless mice [J]. Photodermatol Photoimmunol Photomed, 2017, 33(2): 101-11.

[16] KIM M K, LEE S, KIM E J, et al. Topical application of anacardic acid (6-nonadecyl salicylic acid) reduces UV-induced histone modification, MMP-13, MMP-9, COX-2 and TNF-α expressions in hairless mice skin [J]. J Dermatol Sci, 2013, 70(1): 64-7.

[17] KWAK C S, YANG J, SHIN C Y, et al. Topical or oral treatment of peach flower extract attenuates UV-induced epidermal thickening, matrix metalloproteinase-13 expression and pro-inflammatory cytokine production in hairless mice skin [J]. Nutr Res Pract, 2018, 12(1): 29-40.

[18] KWAK C S, YANG J, SHIN C Y, et al. Rosa multiflora Thunb flower extract attenuates ultraviolet-induced photoaging in skin cells and hairless mice [J]. J Med Food, 2020, 23(9): 988-97.

[19] TANAKA Y, UCHI H, FURUE M. Antioxidant cinnamaldehyde attenuates UVB-induced photoaging [J]. J Dermatol Sci, 2019, 96(3): 151-8.

[20] BAE J S, HAN M, SHIN H S, et al. Perilla frutescens leaves extract ameliorates ultraviolet radiation-induced extracellular matrix damage in human dermal fibroblasts and hairless mice skin [J]. J Ethnopharmacol, 2017, 195: 334-42.

[21] URIKURA I, SUGAWARA T, HIRATA T. Protective effect of Fucoxanthin against UVB-induced skin photoaging in hairless mice [J]. Biosci Biotechnol Biochem, 2011, 75(4): 757-60.

[22] YAKAEW S, ITSARASOOK K, NGOENKAM J, et al. Ethanol extract of Terminalia chebula fruit protects against UVB-induced skin damage [J]. Pharm Biol, 2016, 54(11): 2701-7.

[23] PUJIMULYANI D, SURYANI C L, SETYOWATI A, et al. Cosmeceutical potentials of *Curcuma mangga* Val. extract in human BJ fibroblasts against MMP1, MMP3, and MMP13 [J]. Heliyon, 2020, 6(9): e04921.

[24] KARTHIKEYAN R, KANIMOZHI G, MADAHAVAN N R, et al. Alpha-pinene attenuates UVA-induced photoaging through inhibition of matrix metalloproteinases expression in mouse skin [J]. Life Sci, 2019, 217: 110-8.

[25] HWANG Y P, CHOI J H, KIM H G, et al. Cultivated ginseng suppresses ultraviolet B-induced collagenase activation via mitogen-activated protein kinases and nuclear factor κB/activator protein-1-dependent signaling in human dermal fibroblasts [J]. Nutr Res, 2012, 32(6): 428-38.

[26] AHN B N, KIM J A, HIMAYA S W, et al. Chitooligosaccharides attenuate UVB-induced damages in human dermal fibroblasts [J]. Naunyn Schmiedebergs Arch Pharmacol, 2012, 385(1): 95-102.

[27] KIM J A, LEE J E, KIM J H, et al. Penta-1,2,3,4,6-*O*-galloyl-β-*D*-glucose inhibits UVB-induced photoaging by targeting PAK1 and JNK1 [J]. Antioxidants, 2019, 8(11): 561.

[28] KIM H M, LEE D E, PARK S D, et al. Oral administration of *Lactobacillus plantarum* HY7714 protects hairless mouse against ultraviolet B-induced photoaging [J]. J Microbiol Biotechnol,

2014, 24(11): 1583-91.

[29] JUNG S K, HA S J, JUNG C H, et al. Naringenin targets ERK2 and suppresses UVB-induced photoaging [J]. J Cell Mol Med, 2016, 20(5): 909-19.

[30] PARK J E, PYUN H B, WOO S W, et al. The protective effect of *Kaempferia parviflora* extract on UVB-induced skin photoaging in hairless mice [J]. Photodermatol Photoimmunol Photomed, 2014, 30(5): 237-45.

[31] LI Z, NIU X, XIAO S, et al. Retinoic acid ameliorates photoaged skin through RAR-mediated pathway in mice [J]. Mol Med Rep, 2017, 16(5): 6240-7.

[32] LEE J K, KO S H, YE S K, et al. 8-Oxo-2'-deoxyguanosine ameliorates UVB-induced skin damage in hairless mice by scavenging reactive oxygen species and inhibiting MMP expression [J]. J Dermatol Sci, 2013, 70(1): 49-57.

[33] WANG S, ZHONG J, LI L. Protective effect of skin-derived precursors on photoaging in nude mice [J]. Australas J Dermatol, 2019, 60(1): e20-8.

[34] GONG M, ZHAI X, YU L, et al. ADSCs inhibit photoaging- and photocarcinogenesis-related inflammatory responses and extracellular matrix degradation [J]. J Cell Biochem, 2020, 121(2): 1205-15.

[35] LEE Y M, KANG S M, LEE S R, et al. Inhibitory effects of TRPV1 blocker on UV-induced responses in the hairless mice [J]. Arch Dermatol Res, 2011, 303(10): 727-36.

[36] SHIN M H, LEE S R, KIM M K, et al. Activation of peroxisome proliferator-activated receptor alpha improves aged and UV-irradiated skin by catalase induction [J]. PLoS One, 2016, 11(9): e0162628.

[37] CHOI S I, JUNG T D, CHO B Y, et al. Antiphotoaging effect of fermented agricultural byproducts on ultraviolet B-irradiated hairless mouse skin [J]. Int J Mol Med, 2019, 44(2): 559-68.

[38] LIM S H, JUNG S K, BYUN S, et al. Luteolin suppresses UVB-induced photoageing by targeting JNK1 and p90^{RSK2} [J]. J Cell Mol Med, 2013, 17(5): 672-80.

[39] JUNG H J, LEE A K, PARK Y J, et al. (2E,5E)-2,5-Bis(3-hydroxy-4-methoxybenzylidene) cyclopentanone exerts anti-melanogenesis and anti-wrinkle activities in B16F10 melanoma and Hs27 fibroblast cells [J]. Molecules, 2018, 23(6): 1415.

[40] YEO I, LEE Y J, SONG K, et al. Low-molecular weight keratins with anti-skin aging activity produced by anaerobic digestion of poultry feathers with *Fervidobacterium islandicum* AW-1 [J]. J Biotechnol, 2018, 271: 17-25.

[41] KANG S J, CHOI B R, KIM S H, et al. Beneficial effects of dried pomegranate juice concentrated powder on ultraviolet B-induced skin photoaging in hairless mice [J]. Exp Ther Med, 2017, 14(2): 1023-36.

[42] HATTORI N, MOCHIZUKI S, KISHI K, et al. MMP-13 plays a role in keratinocyte migration, angiogenesis, and contraction in mouse skin wound healing [J]. Am J Pathol, 2009, 175(2): 533-46.

[43] LIAO Y, IVANOVA L, ZHU H, et al. Cord blood-derived stem cells suppress fibrosis and may prevent malignant progression in recessive dystrophic epidermolysis bullosa [J]. Stem Cells, 2018, 36(12): 1839-50.

[44] ROHANI M G, MCMAHAN R S, RAZUMOVA M V, et al. MMP-10 regulates collagenolytic activity of alternatively activated resident macrophages [J]. J Invest Dermatol, 2015, 135(10):

2377-84.

[45] NISSINEN L M, KÄHÄRI V M. Collagen turnover in wound repair: a macrophage connection [J]. J Invest Dermatol, 2015, 135(10): 2350-2.

[46] WANG H, LI H, YAN Q, et al. Serum matrix metalloproteinase-13 as a diagnostic biomarker for cutaneous squamous cell carcinoma [J]. BMC Cancer, 2021, 21(1): 816.

[47] EL-HAWARY A K, YASSIN E, KHATER A, et al. Expression of matrix metalloproteinase-13 and Ki-67 in nonmelanoma skin cancer in xeroderma pigmentosum and non-xeroderma pigmentosum [J]. Am J Dermatopathol, 2013, 35(1): 45-9.

[48] XU N, ZHANG L, MEISGEN F, et al. MicroRNA-125b downregulates matrix metallopeptidase 13 and inhibits cutaneous squamous cell carcinoma cell proliferation, migration, and invasion [J]. J Biol Chem, 2012, 287(35): 29899-908.

[49] RAHMATI NEZHAD P, RIIHILÄ P, PIIPPONEN M, et al. Complement factor I upregulates expression of matrix metalloproteinase-13 and -2 and promotes invasion of cutaneous squamous carcinoma cells [J]. Exp Dermatol, 2021, 30(11): 1631-41.

[50] PIIPPONEN M, NISSINEN L, RIIHILÄ P, et al. p53-regulated long noncoding RNA PRECSIT promotes progression of cutaneous squamous cell carcinoma via STAT3 signaling [J]. Am J Pathol , 2020, 190(2): 503-17.

[51] FARSHCHIAN M, NISSINEN L, SILJAMÄKI E, et al. Tumor cell-specific AIM2 regulates growth and invasion of cutaneous squamous cell carcinoma [J]. Oncotarget, 2017, 8(28): 45825-36.

[52] DECICCO-SKINNER K L, JUNG S A, TABIB T, et al. Tpl2 knockout keratinocytes have increased biomarkers for invasion and metastasis [J]. Carcinogenesis, 2013, 34(12): 2789-98.

[53] MEIDES A, GUTSCHALK C M, DEVEL L, et al. Effects of selective MMP-13 inhibition in squamous cell carcinoma depend on estrogen [J]. Int J Cancer, 2014, 135(12): 2749-59.

[54] HATA H, ABE R, SUTO A, et al. MMP13 can be a useful differentiating marker between squamous cell carcinoma and benign hyperkeratotic lesions in recessive dystrophic epidermolysis bullosa [J]. Br J Dermatol, 2015, 172(3): 769-73.

[55] WANG N, XU Z W, WANG K H. Systematical analysis of cutaneous squamous cell carcinoma network of microRNAs, transcription factors, and target and host genes [J]. Asian Pac J Cancer Prev, 2014, 15(23): 10355-61.

[56] LIANG D, ZHANG Z. MicroRNA-27b-3p inhibits the proliferation and invasion of cutaneous squamous cell carcinoma by targeting EGFR and MMP-13 [J]. Oncol Lett, 2021, 22(4): 729.

[57] CIUREA M E, CERNEA D, GEORGESCU C C, et al. Expression of CXCR4, MMP-13 and β-catenin in different histological subtypes of facial basal cell carcinoma [J]. Rom J Morphol Embryol, 2013, 54(4): 939-51.

[58] SERINI S, ZINZI A, OTTES VASCONCELOS R, et al. Role of β-catenin signaling in the anti-invasive effect of the omega-3 fatty acid DHA in human melanoma cells [J]. J Dermatol Sci, 2016, 84(2): 149-59.

[59] ZAMOLO G, GRAHOVAC M, ŽAUHAR G, et al. Matrix metalloproteinases MMP-1, MMP-2, and MMP-13 are overexpressed in primary nodular melanoma [J]. J Cutan Pathol, 2020, 47(2): 139-45.

[60] PALKINA N V, SHVETSOVA Y I, KIRICHENKO A K, et al. Inhibition of matrix metalloproteinases 9 and 13 affects the degree of lymphocytic infiltration and the expression levels of microRNA miR-21 and miR-let-7b in melanoma cells *in vivo* [J]. Arkh Patol, 2015, 77(1): 41-7.

[61] LÓPEZ-OTÍN C, MATRISIAN L M. Emerging roles of proteases in tumour suppression [J]. Nat Rev Cancer, 2007, 7(10): 800-8.