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生长因子与皮肤创伤愈合

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摘要 皮肤创伤愈合是一种临床常见的病症, 包括急性和慢性两种类型, 伤口修复过程通常分为四个阶段: 止血期、炎症期、细胞增殖分化期和组织重建期, 各阶段的有序进行是伤口修复成功的关键。在伤口修复过程中, 生长因子发挥了至关重要的作用, 主要体现在调控血管再生, 调控细胞增殖、迁移、分化, 影响炎症与氧化应激, 调控胶原蛋白的合成, 调节基质的合成, 调节疤痕的形成六个方面。目前, 关于生长因子在皮肤创伤愈合中的综合作用研究较为有限, 而且现有的临床治疗手段也相对匮乏, 因此, 探究生长因子与皮肤创伤愈合的联系, 有助于寻找和分析新的有效治疗方案。该文采用图表归纳和文字分析的方法探讨了生长因子促进皮肤愈合的作用机制以及临床使用的伤口愈合类材料的优劣, 旨在为今后皮肤创伤愈合相关研究及新型伤口愈合材料的开发提供一定的参考。

关键词 生长因子; 信号通路; 创伤愈合; 创伤愈合手段

Growth Factors and Skin Wound Healing

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Abstract Skin wound healing is a common clinical condition, including acute and chronic types. The wound repair process is usually divided into four phases: hemostasis, inflammation, cell proliferation and differentiation and tissue reconstruction, and the orderly conduct of each phase is the key to the success of wound repair. In the process of wound repair, growth factors play a crucial role, which is mainly reflected in six aspects: regulating vascular regeneration, regulating cell proliferation, migration and differentiation, influencing inflammation and oxidative stress, regulating collagen synthesis, regulating matrix synthesis, and regulating scar formation. Currently, research on the integrative role of growth factors in skin wound healing is relatively limited, and there is a relative paucity of available clinical treatments; therefore, exploring the link between growth factors and skin trauma healing can help to find and analyze new and effective therapeutic options. In this paper, the mechanism of action of growth factors in promoting skin healing and the advantages and disadvantages of clinically used wound healing materials are explored by means of graphical summarization and textual analysis, with the aim of providing certain references for future research related to skin wound healing and the development of new wound healing materials.

Keywords growth factors; signaling pathways; wound healing; means of wound healing

皮肤是人体最大的器官, 易受到辐射、烧烫伤、挫伤和擦伤等多种创伤。创伤的正常愈合对健康至关重要, 如果开放性伤口无法愈合, 外界病原体的侵入可能引发感染, 严重时甚至危及生命。近年来, 皮肤创伤修复已成为医学研究的重点, 国内外学者的研究显著提高了我们对创伤修复基本机制的认识。伤口修复过程涉及多种细胞, 这些细胞在细胞因子和生长因子的严格调控下, 随着时间的推移发挥不同作用以促进愈合。随着科学技术的进步, 人们对皮肤创伤修复的期望也在提高, 不仅希望伤口能够正常愈合, 还希望修复后的皮肤美观且无疤痕。因

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此，深入研究伤口修复过程中的调控机制，特别是抑制疤痕形成的策略显得尤为重要。现代分子生物学的发展使我们对参与创伤愈合的细胞因子和生长因子的作用有了更深入的了解。这些生长因子包括血小板源性生长因子(platelet-derived growth factor, PDGF)、肝细胞生长因子(hepatocyte growth factor, HGF)、表皮生长因子(epidermal growth factor, EGF)、血管内皮生长因子(vascular endothelial growth factor, VEGF)、胰岛素样生长因子(insulin like growth factor, IGF)、成纤维细胞生长因子(fibroblast growth factor, FGF)、神经生长因子(nerve growth factor, NGF)和转化生长因子-β(transforming growth factor-β, TGF-β)。本文将总结这些生长因子的作用，并分析它们与受体结合后激活的下游信号通路。此外，随着对生长因子研究的深入，已经开发出多种有助于创伤修复的药物和材料，本文将在阐述生长因子作用后，简要解析这些药物和材料的相关作用。

1 创伤愈合的过程

一般而言，创伤修复可以分为四个时期：止血期、炎症期、细胞增殖分化期和组织重建期(图1)。在创伤后血管破裂并出血，伤口周围血管收缩、血小板凝聚，形成纤维蛋白凝块，从而使血液凝固并减少损伤部位的血液流出；止血期后，由于外界病原体的入侵而引起机体的免疫反应，即中性粒细胞、巨噬细胞、肥大细胞、T细胞等炎症细胞被招募到伤口区域，并与细胞因子相互作用发生炎症反应，从而实现对机体的保护；炎症期后的几周内，由炎症反应阶段剩余的炎症细胞、上皮细胞、真皮细胞通过自分泌和旁分泌等方式分泌细胞因子推动有创面再上皮化，促进血管的生成及肉芽组织的形成；细胞增殖分化期后的几周几月乃至几年，大部分内皮细胞、炎症细胞、成纤维细胞等细胞发生凋亡或从伤口处撤回，新生的血管逐渐成熟，角质形成细胞停止增殖和迁移并开始分化，伤口开始收缩，在前一过程中合成的III型胶原蛋白、纤维蛋白、纤连蛋白、透明质酸等物质被主要含I型胶原蛋白的细胞外基质所取代，从而完成重建。

2 创伤愈合的过程中的生长因子

在伤口愈合过程中，细胞之间的相互作用与细胞和细胞基质之间的作用至关重要，在伤口愈合的各个阶段受到多种生长因子和细胞因子的有序调控(表1)。许多研究表明，在不同类型的伤口愈合疾病的患者和动物实验中，许多生长因子如PDGF、FGF、EGF、FGF、TGF等可以促进伤口愈合。这些生长因子对于创伤愈合的作用可以归纳为六个方面：①调控血管再生；②调控细胞增殖、迁移、分化；③影响炎症与氧化应激；④调控胶原蛋白的合成；⑤调节基质的合成；⑥调节疤痕的形成。这些功能并不是孤立的，它们之间相互协调，密切相关，共同促进伤口的愈合(表2和图2)。

2.1 调控血管再生

血管再生是确保血液循环正常运行的关键，它为创面提供足够的氧气和营养，同时及时排出代谢废物，从而支持周围细胞的正常存活和功能。血管再生通过生长因子的调控，促使血管结构细胞进行一系列增殖、迁移和分化。生长因子结合其受体后，触发下游信号转导，确保血管再生的有序进行。具体而言，生长因子通过调控多条信号通路，如Ras/MAPK/ERK1/2、PI3K/AKT/mTOR、JAK/STAT和Wnt/β-catenin等，促进血管平滑肌细胞和内皮细胞的增殖与迁移[38-39]。此外，生长因子间的相互促进也增强了血管再生的效果。例如，PDGF通过PI3K/AKT信号通路调控HIF-1α，进而促进FGF和VEGF的表达，助力血管生成[40]。研究还表明，生长因子通过诱导基质金属蛋白酶(matrix metalloproteinases, MMPs)的活性进一步推动血管生成[41]。除了直接作用于血管组成细胞外，生长因子还可促进血管周围细胞(如基质细胞)的增殖。通过增加这些细胞的数量，它们能够保护血管周围环境的完整性，帮助形成健康的血管结构[42]。此外，内皮祖细胞的增殖与血管结构的形成密切相关，生长因子通过促进内皮祖细胞介导的管腔形成，支持血管的形成[43]。

2.2 调控细胞增殖、迁移、分化

创伤部位细胞的增殖、迁移和分化的正常进行是确保创伤修复的关键。生长因子与其受体结合后，激活一系列下游信号通路，从而促进周围组织中成纤维细胞、内皮细胞、平滑肌细胞和神经细胞的增殖与迁移，加速修复进程。生长因子通过激活PI3K/AKT通路、MAPK通路和JAK/STAT通路等，调节细胞周期以促进细胞增殖[44]。此外，具体

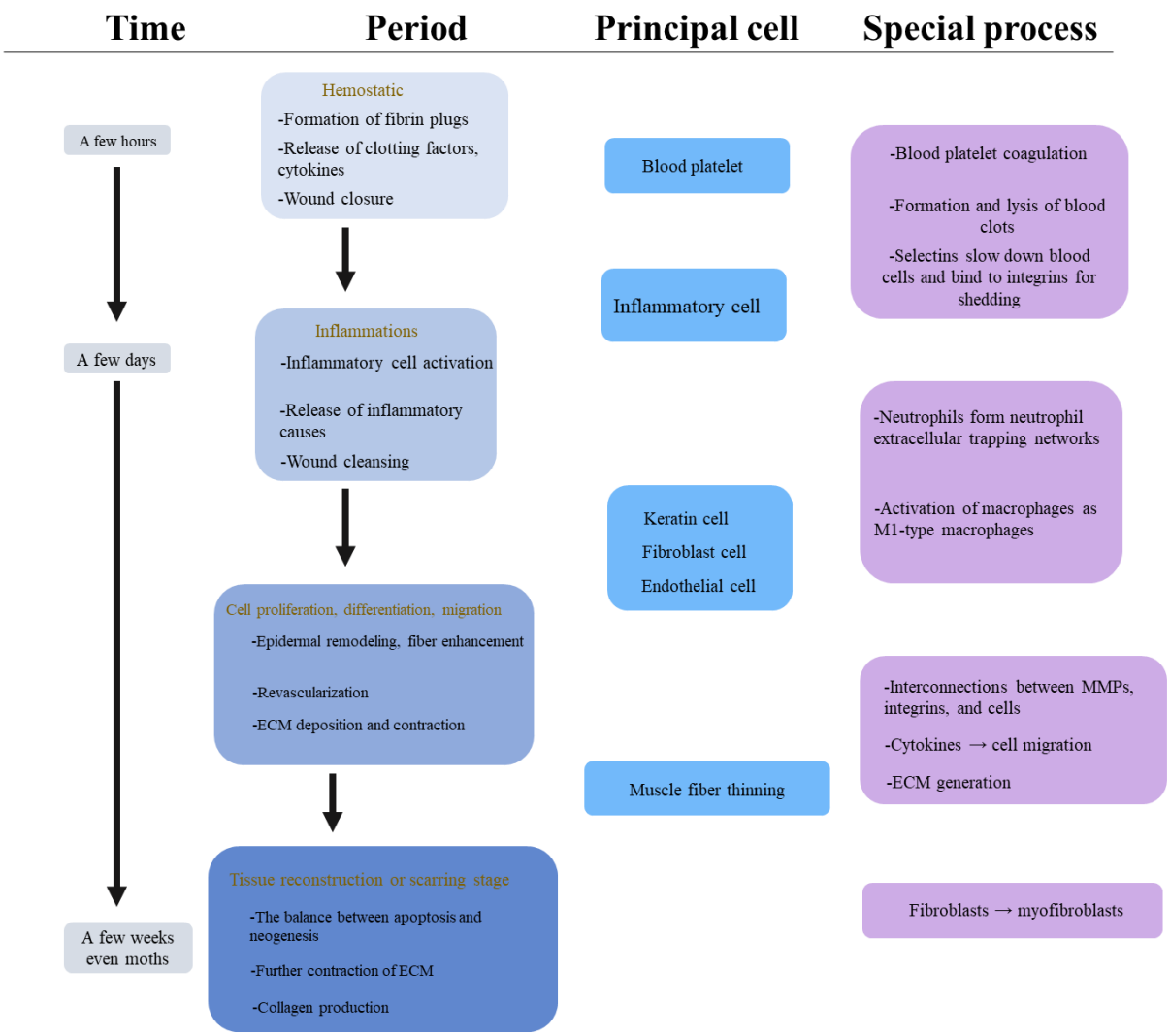


图1 创伤愈合的阶段

Fig.1 Stages of wound healing

而言，生长因子通过调节细胞膜的动态变化，促进细胞的伸展和移动[45]。一些研究发现，生长因子能够调节MMPs的活性，进一步促进细胞迁移[46]。研究团队如CHRISTINE等[47]、TIM等[48]的工作表明，FGF信号通过影响N-cadherin介导的细胞间黏附，调节细胞连接的稳定性，从而影响细胞的迁移能力，这种促进迁移的机制可能与微丝蛋白、肌动蛋白等的磷酸化与重组，以及黏附蛋白和整合素的表达与活性有关。HGF则通过促进表皮细胞的去分化、促进角质形成细胞迁移、促进腱源干细胞和抑制肌成纤维细胞分化来加速创伤愈合[49]。与此同时，IGF通过调节转录因子的表达和活性，影响细胞的分化方向，激活特定的转录因子来引导细胞命运。值得注意的是，IGF-I与胰岛素受体信号通路之间的交互作用与差异，对细胞命运和代谢产生重要影响[50]。

2.3 影响炎症与氧化应激

炎症反应的有序控制对于伤口修复至关重要。过弱的炎症反应可能导致机体无法抵御因创口暴露而引发的病原体入侵，从而引发感染；而过强的炎症反应则会导致机体应激，使受伤部位细胞功能受损，进而减缓创伤修复过程。生长因子对创口的炎症反应具有双重作用。在创伤修复的早期，生长因子通常通过激活NF-κB通路来增加炎症因子的释放水平，促进炎症反应；在创伤修复的中后期，生长因子通常通过抑制NF-κB通路来抑制过度的炎症反应[51]。除了调控炎症因子的释放外，生长因子还能够招募炎症细胞参与反应[52]。此外，IGF通过增强巨噬细胞

表1 创伤愈合过程中的生长因子

Table 1 Growth factors in wound healing

名称 Name	分泌细胞/组织 Secretory cells/tissues	基本作用 Basic functions
PDGF	Platelets, endothelial cells, macrophages, etc	Promotes cell proliferation and migration; involved in the process of tissue fibrosis; promote vascularization; associated with tumor development; associated with cell signaling pathway activation; etc
FGF	Fibroblasts, endothelial cells, etc	Involved in processes such as angiogenesis and cell proliferation and differentiation; important role in embryonic development; regulates multiple signaling pathways; involved in various diseases; diverse functions in evolution; etc
VEGF	Endothelial cells, smooth muscle cells, macrophages, etc	Regulates angiogenesis and vascular function; also plays an important role in neuroprotection; involved in various physiological processes such as trauma repair and immunomodulation; etc
HGF	Fibroblasts, mesenchymal cells, etc	Regulates cell migration and dissemination; plays an important role in organ development; promotes liver regeneration; neurotrophic; protective in the cardiovascular system, involved in cardiac remodeling; promotes invasion and metastasis in tumor cells; etc
EGF	Ciliated epithelial cells, fibroblasts, macrophages, etc	Stimulates cell proliferation and differentiation; plays an important role in gastric acid secretion and repair of kidney damage; plays an important role in the development and function of the heart; etc
IGF	Liver tissue, muscle tissue, bone tissue and other tissues	Promotes cell proliferation and differentiation and participates in the regulation of cell growth and development.; regulates blood vessel function; dysregulation of the IGF system may be associated with the development of certain diseases, such as tumors and diabetes; etc
NGF	Lymphocytes, fibroblasts, macrophages, and glial cells, among others	Involved in the development and maintenance of the nervous system; involved in the regulation of inflammatory responses; may improve spatial memory in older animals; etc
TGF-β	Immune cells, epithelial cells, fibroblasts, tumor cells, etc	Plays an important role in tumor development; plays an important role in immunomodulation and has been called “the master of immunomodulation”; plays a role in insulin secretion and insulin resistance; important in liver fibrosis; involved in the regulation of intestinal epithelial barrier function; influences cell cycle progression; etc

清除炎症介质和细胞碎片的能力，进一步抑制炎症反应[53]。EGF则通过与表皮生长因子的细胞质和核成分相互作用，调节角质形成细胞中的趋化因子表达，发挥抗炎和伤口愈合作用[54]。在创伤修复过程中，由于活性氧的大量生成，细胞会产生氧化应激。过度的氧化应激可能导致细胞凋亡，并引发连锁反应，造成大面积细胞死亡。生长因子激活的通路，如NF-κB和Nrf2-ARE通路，可以清除自由基，减少氧化应激，从而保障细胞存活[55]。

2.4 调控胶原蛋白的合成

胶原蛋白的合成有利于增强创口周围组织的机械强度和稳定性，这对后期创口的收缩闭合具有重要意义。尽管胶原蛋白是基质的一部分，但在创口恢复过程中发挥着极其重要的作用，因此需要单独进行讨论。生长因子在促进胶原蛋白合成中扮演关键角色，通过多种信号通路，包括MAPK通路、PI3K/AKT通路和TGF-β/Smad信号通路等影响其合成过程。激活这些信号通路能够促进胶原蛋白基因

表2 生长因子激活信号通路及功能

Table 2 Growth factor activation signaling pathway and function

生长因子 Growth factor	激活通路 Activation of signaling pathways		对应图2中的六大作用 Corresponding to the six roles in Fig.2
	公共通路 Public signaling pathways	特有通路 Special signaling pathways	
PDGF	PI3K/AKT, MAPK, JAK/STAT	VEGF [1]	Regulation of vascular regeneration
		Smad [12]	Regulates cell proliferation, migration, differentiation; regulates inflammation and antioxidant
		Wnt/β-catenin [3]	Regulates cell proliferation, migration, and differentiation; regulates inflammation and antioxidant; regulation of collagen synthesis; regulation of matrix synthesis
		TGF-β [4]	Regulation of collagen synthesis; regulation of matrix synthesis
		NF-κB [5]	Modulates inflammation and antioxidants; regulation of collagen synthesis; regulation of matrix synthesis
		Nrf2-ARE [4]	Modulates inflammation and antioxidants
FGF		Wnt/β-catenin B [6,9]	Regulates vascular regeneration; regulates cell proliferation, migration, and differentiation; regulation of matrix synthesis
		PLCγ [8]	Regulates vascular regeneration
		PKC [6]	Regulation of cell proliferation, migration, and differentiation
		TGF-β [7-9]	Regulation of substrate synthesis
		Smad [6]	Regulates collagen synthesis
		NF-κB [9]	Modulation of inflammatory response and antioxidant; regulation of matrix synthesis
		Nrf2-ARE [9]	Modulation of inflammation and antioxidant
VEGF		PLCγ, NOS [10]	Regulation of vascular regeneration
		Src, Notch [12]	Regulation of cell proliferation, migration, and differentiation
		NF-κB [12]	Regulation of cell proliferation, migration, and differentiation; regulates inflammatory response and antioxidant
		Nrf2-ARE [13]	Modulation of inflammatory response and antioxidant
		mTOR/AP-1 [13]	Regulation of matrix synthesis
		TGF-β [13], Wnt/β-catenin [15]	Regulates collagen synthesis
HGF		Integrin/ILK [16,19]	Regulation of cell proliferation, migration, and differentiation
		TGF-β1 [17,19]	Regulation of cell proliferation, migration, and differentiation; regulates collagen synthesis
		NF-κB [17,20]	Modulation of inflammatory response and antioxidant; regulation of matrix synthesis
		Nrf2-ARE [18]	Modulation of inflammatory response and antioxidant
EGF		TGF-β [21]	Regulation of angiogenesis
		Src [24]	Regulation of cell proliferation, migration, and differentiation
		NF-κB [22,24]	Regulation of cell proliferation, migration, and differentiation; regulates inflammatory response and antioxidant
		Nrf2-ARE [23,25]	Regulates inflammatory response and antioxidant

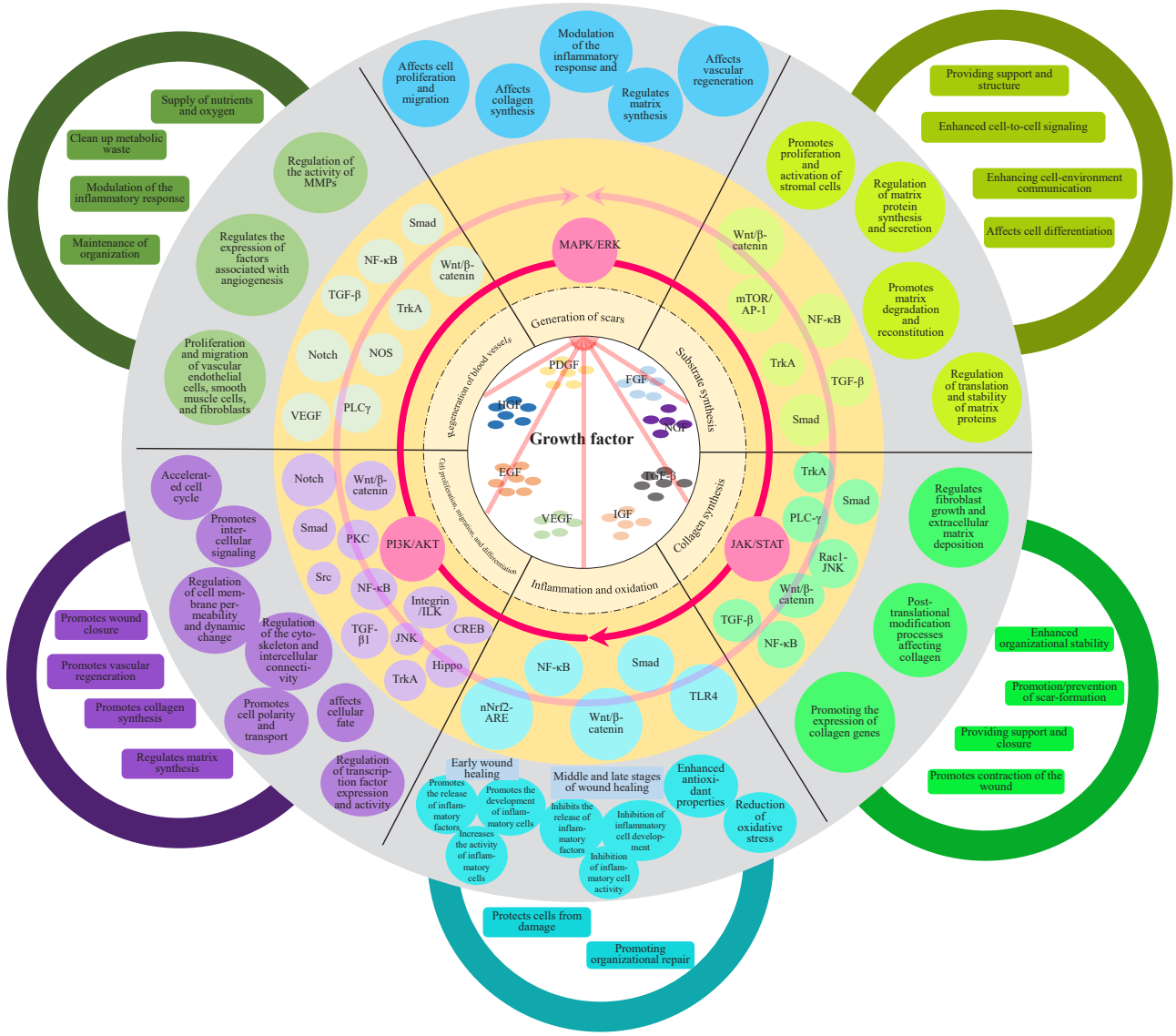
续表2

生长因子 Growth factor	激活通路 Activation of signaling pathways		对应图2中的六大作用 Corresponding to the six roles in Fig.2
	公共通路 Public signaling pathways	特有通路 Special signaling pathways	
IGF	PI3K/AKT, MAPK, JAK/STAT	VEGF [26]	Regulation of vascular regeneration
		NF-κB [27]	regulation of vascular regeneration; regulation of inflammatory response and antioxidant; regulation of collagen synthesis
		Nrf2-ARE [26,29]	Modulation of inflammatory response and antioxidant
		Wnt/β-catenin [28]	Regulation of vascular regeneration
		TLR4 [26,29]	Modulation of inflammatory response and antioxidant
NGF		Notch [30]	Regulation of vascular regeneration
		TrkA [30-31]	Regulation of vascular regeneration; regulates cell proliferation, migration, and differentiation; regulation of collagen synthesis; regulates matrix synthesis
		NF-κB [30]	Regulation of vascular regeneration; regulates cell proliferation, migration, and differentiation; modulation of inflammatory response and antioxidant
		Nrf2-ARE [31]	Modulation of inflammatory response and antioxidant
		JNK [32]	Regulates cell proliferation, migration, and differentiation; regulation of matrix synthesis
		CREB [32]	Regulates cell proliferation, migration, and differentiation
		Rac1-JNK [30-31]	Regulates collagen synthesis
		PLC-γ [31]	Regulates collagen synthesis
TGF-β		VEGF [33]	Regulation of vascular regeneration
		Smad [35,37]	Regulation of vascular regeneration; regulates cell proliferation, migration, and differentiation; regulation of collagen synthesis; regulation of matrix synthesis
		Wnt/β-catenin [34]	Regulation of vascular regeneration; regulates cell proliferation, migration, and differentiation
		Notch [36]	Regulation of vascular regeneration
		Hippo [34,36]	Regulation of cell proliferation, migration, and differentiation
		NF-κB [33]	Modulation of inflammatory response and antioxidant
		Nrf2-ARE [33]	Modulation of inflammatory response and antioxidant

的转录和翻译, 从而增加胶原蛋白的合成[56]。此外, 生长因子还通过调节与胶原蛋白合成相关的转录因子和调控因子, 如COL1A1、COL1A2和SP1等, 进一步增强胶原蛋白的合成[57]。胶原蛋白的合成和降解之间的平衡对于促进创伤愈合至关重要。胶原蛋白的过度合成会导致疤痕生成, IGF-1通过IGF-1R/AKT/mTORC1信号通路促进I型胶原和III的合成, 同时调节其降解, 从而维持这一平衡[58]。

2.5 调节基质的合成

基质是由细胞合成的支持结构, 为细胞的生长、迁移和信号转导提供必要的支持和框架, 并潜在地影响细胞增殖、血管再生和炎症反应。生长因子能够调节基质金属蛋白酶(MMPs)的活性, 这些酶在基质降解和重塑中起着关键作用。研究表明, 生长因子, 特别是TGF-β, 在调节MMPs活性以及基质金属蛋白酶的合成中发挥着重要作用[59]。此外, 生长因子可以调节细胞间的相互作用, 包括细胞–基质相互作用和细胞–细胞相互作用, 从而影响基质合成及细胞在伤口修复过程中的行为[60]。生长因子通过激活PI3K/AKT通路、MAPK通路和JAK/STAT通路



图片从内至外所涉及: 生长因子、六大作用、公共通路(MAPK/ERK、PI3K/AKT、JAK/STAT)、特殊通路、通路引起的生物学功能、最终影响。其中的六大作用中所有通路的效果都会影响疤痕的生成(通路在外圈由淡粉色圆箭头标出, 联系由中间的淡红色直箭头标出)。图2与表2共同阅读可促进理解。

The picture involves growth factors, six major actions, public pathways (MAPK/ERK, PI3K/AKT, JAK/STAT), specific pathways, biological functions induced by the pathways, and the final effects caused from the inside out. The effects of all of the pathways in the six major actions affect scarring (pathways are marked in the outer circle by light pink circular arrows, and connections are marked in the center by light red straight arrows). Fig.2 and Table 2 can be read together to promote understanding.

图2 生长因子在创伤愈合过程中的作用

Fig.2 The role of growth factors in the healing process of re-traumatization

等调节胶原合成, 增加基质的含量和稳定性。生长因子在基质蛋白的合成和分泌过程中发挥着重要作用, 许多研究已探讨了这一过程在多种类型细胞中的影响。例如, HUSSEY等[61]指出, 生长因子能够刺激细胞合成和分泌基质蛋白, 特别是在心肌损伤、修复和重塑过程中。同时, SVYSTONYUK等[62]提到, 细胞分泌的生长因子可以被基质蛋白纤维所固定, 形成浓度梯度, 从而影响细胞行为和功能。这些机制共同体现了生长因子在调节基质蛋白合成与细胞功能中的重要作用。

2.6 调节疤痕的形成

过度的炎症反应、过量的胶原蛋白合成及沉积、过度的细胞增殖以及血管再生受阻等因素, 都会对伤口愈合产生负面影响。研究显示, 持续和过

度的炎症反应是病理性疤痕形成的重要原因, 因此, 生长因子调控的炎症反应必须有序进行, 这是确保皮肤正常再生和功能恢复的关键因素[63]。过强的炎症反应会导致周围细胞经历应激, 进而引起胶原蛋白的过度合成和沉积, 促进疤痕的形成。此外, 过度的胶原沉积会导致皮肤异常增生, 妨碍血管、毛囊和腺体等结构的正常再生, 最终形成明显的疤痕。这些过程强调了在创伤修复中保持炎症反应的适度和胶原合成的平衡的重要性。

3 促进皮肤创伤修复过程的手段

3.1 以外源性生长因子为基础的促进创口愈合的材料

近年来, 许多研究将外源性生长因子应用于创口敷料, 以促进伤口修复。THAPA等[64]将VEGF-A、PDGF-BB和HB-EGF作为敷料直接覆盖创口, 结果表明这些生长因子通过促进伤口内肉芽组织的发育来改善伤口愈合。此外, 一些研究发现基因转移可以有效调节PDGF在伤口内的释放和表达, 从而促进愈合[65]。还有研究表明, 添加PDGF-BB的创口敷料可以调节炎症反应和其他细胞因子的分泌来促进伤口修复[66]。含FGF类材料在促进创口修复方面也展现了巨大潜力, 尤其是FGF-2在治疗压疮和糖尿病足等疾病中显示出良好的愈合效果, 这可能与其促进上皮间质转化的作用有关[64]。然而, 值得注意的是, 高剂量的外源性生长因子不一定促进创口修复, 甚至可能产生负面影响[68]。外源性的生长因子有一些不良反应且出现较多: (1) 剧烈疼痛, 外源性生长因子可能会给部分患者带来剧烈的疼痛和灼烧感; (2) 过度炎症反应, 导致伤口部位的湿热、肿痛等; (3) 氧化还原失衡, 可能会导致组织细胞中氧化还原平衡的紊乱, 从而影响伤口愈合; (4) 感觉神经病变, 可能会引起伤口部位的感觉神经损害, 导致异常疼痛、部分皮肤感觉丧失等症状; (5) 瘢痕形成, 可能会过度刺激胶原蛋白的沉积, 导致瘢痕疙瘩的形成。综上所述, 外源性生长因子作为主要成分或辅助成分的材料在创口修复中展现出巨大的潜力。然而, 这些材料通常价格高昂, 并且可能伴副作用, 因此不适合在日常生活中广泛使用。

3.2 以生物材料为基础的促进创口愈合的材料

近年来, 基于生物材料的创口愈合材料不断得到研发, 其中创口敷料尤为热门。水凝胶作为一种高生物相容性和可塑性的生物材料, 能够携带多种药物成分, 如生长因子、抗菌分子和炎症因子, 甚至可以递送细胞, 使其成为创面敷料研发的重点。此外, 水凝胶能够维持创面湿润, 有利于伤口愈合。纳米水凝胶敷料在伤口愈合中也展现出巨大的潜力, 能够观察伤口状态并提供治疗支持。综上, 水凝胶具有以下几个优点: (1) 具有良好的生物相容性和渗透性, 能够为伤口提供湿润的环境, 促进伤口愈合; (2) 多功能作用, 水凝胶可以结合抗氧化剂和抗菌剂等成分, 有助于加速慢性伤口的愈合; (3) 适应性强, 通过调节水凝胶的力学性能和自愈合特性, 可以提高其在伤口愈合过程中的效果; (4) 局部给药, 水凝胶可以作为药物载体, 实现伤口局部给药, 进一步促进伤口愈合。

3.3 以中药成分为基础的促进创口愈合的材料

传统中药在缓解炎症、促进血管生成和抗氧化方面的研究不断增多, 许多价格低廉的中药成分在创口修复中甚至表现出比生长因子类生物材料更强的效果(表3)。中药在伤口修复中的活性通常通过激活或抑制特定信号通路来实现, 包括促进血管再生、调节炎症反应和促进细胞增殖等方面。关于中药成分在创口愈合中负面影响的报道较少, 推测相比于生长因子的直接干预, 中药成分的多靶点调节可能具有更高的安全性和可控性。尽管中药成分具有多组分和多靶点的优势, 但仍面临一些挑战。(1) 中药作用机制尚未明确。由于有效成分复杂且影响因素众多, 目前的研究很少能完整阐明干预机制, 可能存在一定的风险, 因此需要进一步探索。(2) 中药由于成分复杂, 涉及的通路较多且繁琐, 因此目前的研究至局限于部分通路机理的阐述, 而缺乏对通路间相互作用的整合分析, 导致作用机制尚无理论和实验数据支持。(3) 虽然临床上已有多项中药干预创口愈合的实践, 但相关实验数据的系统整合和药物研发仍显不足。

4 结语与展望

伤口修复的分子机制复杂, 涉及多种细胞内和细胞间的信号转导过程, 各个环节相互影响, 最终协同实现损伤部位的修复。在这一过程中, 生长因子发挥着至关重要的作用, 且在不同时间可能展现出不同的功能。在止血期, 生长因子通过调控PI3K/AKT、MAPK/ERK和Notch等信号通路, 募集炎症细胞, 为

表3 中药通过调控相关信号通路干预创伤愈合的作用机制

Table 3 Mechanism of action of traditional Chinese medicine in intervening in wound healing by modulating related signaling pathways

中药 Traditional Chinese medicine	作用 Function	激活信号通路 Activation of signaling pathways
Panax ginseng/white and gum sponge [69]	Promotes angiogenesis; regulates cell proliferation, migration, and differentiation	β-catenin, *Rspo3* mRNA, *GSK-3β* mRNA, VEGF
Cabernet Franc (grape type) [70]	Regulates cell proliferation, migration, and differentiation; promotes angiogenesis; regulates collagen synthesis	IGF-1, PI3K, AKT, VEGF
Kaempferia galanga [71]	Reduces scar formation	TGF-β1, Smad7, collagen types I and III
Chinese bellflower [72]	Reduces scar formation; promotes angiogenesis; modulates inflammatory response and antioxidants	TGF-β1, VEGF, TNF-α, IL-6
Compound ANBP [73]	Reduces scar formation; promotes cell proliferation, migration, and differentiation	TGF-β1, Ski, Smad2/3
Root of herbaceous peony (*Paeonia lactiflora*) [74]	Regulation of inflammatory response and antioxidant; regulation of cell proliferation, migration, and differentiation	Nrf2, VEGF, TGF-β1
Coriaria nepalensis wall [75]	Regulates cell proliferation, migration, and differentiation; reduces scar formation	ILK, ITG-β1, TGF-β1
Scutellaria baicalensis Georgi [76]	Regulates cell proliferation, migration, and differentiation; reduces scar formation; promotes angiogenesis	TGF-β, Ang-1, VEGF, *Smad-2/3* mRNA, TGF-β/Smad-2/3, ERK, p-ERK, HSP27, p-HSP27

炎症反应奠定基础, 同时促进血管周围细胞的增殖、分化及基质的合成, 帮助血液凝固并为后续的血管再生打下基础。在炎症期, 生长因子通过影响NF-κB、Nrf-ARE、mTOR/AP-1等信号通路, 在早期增强炎症细胞的活性, 并通过调控细胞的增殖、分化和迁移增加炎症细胞的数量, 抵御外界病原体入侵。在炎症反应的后期, 生长因子则通过减弱炎症细胞的活性、诱导其迁出伤口区域, 以及抑制氧化应激, 最终保护细胞, 维持伤口微环境的稳定。在细胞增殖和分化期, 生长因子通过影响VEGF、NF-κB、Src等信号通路, 调节皮肤组成细胞(如上皮细胞和真皮细胞)的增殖、分化和迁移, 为重建期的修复提供支持。此外, 生长因子还通过调控Integrin/ILK、Wnt/β-catenin、TrkA等信号通路, 促进血管生成及肉芽组织的形成。在重建期, 生长因子主要通过调节TGF-β、Smad和mTOR/AP-1等通路, 控制伤口区域胶原蛋白、透明质酸和纤维蛋白等基质的合成与降解, 确保伤口正常收缩, 实现最终的修复。

综上所述, 本文将生长因子对伤口愈合的作用归纳为六个相互关联的方面, 维持伤口修复的有序进行。关于生长因子在特定时间段发挥特定作用的特点, 相关研究仍较为有限。因此, 未来应扩展和深入探讨生长因子在伤口修复过程中含量和功能的动态变化, 以及其激活的信号通路和受体细胞的时空效应。在伤口愈合药物开发方面, 外源性生长因子、水凝胶和中药活性成分各有其优势和不足, 建议有效利用中药的多活性成分和多药物靶点特性, 结合水凝胶, 进一步开发价格低廉且无毒的系统性药物, 以适应日常使用的需求。

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