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慢性创面的病因及发病机制的研究进展

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摘 要

慢性创面作为一类长期消耗性的皮肤系统疾病，是当前创面修复相关领域亟待解决的难题，给患者个人、社会带来了的沉重负担，该病的病因及发病机制复杂，涉及多方面因素，阐明其病因及发病机制有助于深入揭示慢性创面的致病机制并探究有效治疗靶点。本文就近年来慢性创面的病因及发病机制相关的研究进展进行综述，旨在为其分子机制及新的治疗靶点提供理论支持。

关键词

慢性创面，研究进展，创面修复，病因，发病机制

Advances in the Study of the Etiology and Pathogenesis of Chronic Wounds

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Abstract

Chronic wound, a long-term wasting disease of the skin system, is an urgent problem in wounds repair, which poses a heavy burden to patients and society. The aetiology and pathogenesis of this disease are complex and multifaceted, and their elucidation can help to shed light on the pathogenesis of chronic wounds and explore effective therapeutic targets. In this paper, we review the

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recent research progress on the etiology and pathogenesis of chronic wounds to provide theoretical support for the molecular mechanisms and new therapeutic targets.

Keywords

Chronic Wounds, Research Advances, Wounds Repair, Etiology, Pathogenesis

1. 引言

皮肤对环境形成了一个重要而有效的屏障，其在保护人们免于异生物、细菌和脱水等伤害的方面起到关键作用。当皮肤损伤发生时，身体会启动一系列复杂的事件来重建这种保护。创面愈合大致可分为四个阶段：1) 机体启动凝血机制，进行止血；2) 细胞因子释放、白细胞浸润引起炎症反应；3) 细胞因子启动增殖阶段，新的血管、上皮及细胞外基质(Extracellular Matrix, ECM)形成；4) 在数周至数月的时间内，随着 ECM 的重塑，创面收缩[1]。以上四个阶段是连续且相互重叠的。机体创面经历了修复过程后产生疤痕[2]。当慢性创面的修复过程受到破坏，会导致创面延迟或难以愈合[3]。延迟创面愈合涉及多方面的因素，如动静脉溃疡(占下肢慢性创面的一半以上，人群发病率为 1%~2% [4])、糖尿病(是慢性创面中致死的主要原因之一，全世界超 3.82 亿人患该病[5])、细胞老化(老化细胞容易受到感染发展为慢性创面[6])，以及压力性溃疡(占住院病人中的 10%，高发于老年人[7])、细菌感染(大多数慢性创面中含有一种以上的细菌，并产生协同效应[8])和缺氧(大部分慢性创面面临缺氧，其损害创面愈合过程[9])等因素[10]。

慢性创面作为一类长期消耗性的皮肤系统疾病，该病治愈难，病程较长，给患者个人及社会带来了的沉重负担[11]。阐明慢性创面病因及发病机制将有助于进一步揭示慢性创面的致病机制、探究新治疗靶点。慢性难治性创面的病因及发病机制复杂，涉及多方面因素[12]。国内外学者就慢性创面涉及的病因学、发病机制领域进行了大量的研究、探索，本文将以此为切入点，对国内外近年来在慢性创面领域的研究进行综述，以期为进一步阐明该病的分子机制及治疗靶点提供理论参考。

2. 病因

慢性创面的病因涉及多方面因素，当前国内研究认为慢性创面的病因主要包括：糖尿病溃疡、压力性溃疡和动静脉溃疡[13]。

2.1. 糖尿病溃疡

糖尿病溃疡是慢性创面延迟愈合的重要病因之一[14]。糖尿病相关的周围神经病变造成了结构上的弱化，增加了反复机械应力的溃疡风险，再加上灌注中断[15]。不愈合的糖尿病溃疡的典型特征是表皮创面边缘过度角化和副角化[16]。慢性创面边缘的角质细胞显示出 β-catenin 的异常核存在和 c-myc 的升高，这直接延迟了体外的迁移[17]。糖尿病创面边缘表皮还显示一些细胞周期、分化和生长因子受体信号传导受损[18]，毛囊缺乏[19]。这种异常的激活及创面边缘增殖的增加，抑制了的慢性创面闭合。此外，糖尿病患者持续的高血糖症会导致相关的代谢紊乱，损害白细胞功能，也会延迟创面愈合[20]，降低细胞增殖

能力、迁移能力，加速其凋亡、减少细胞外基质成分分泌[21]，损伤端粒[22]，诱发细胞衰老[23]，导致ECM 的非酶性糖化，诱发氧化应激[24]。当糖尿病患者的血糖控制欠佳时，会对微血管造成损害，从而导致局部组织缺氧、动脉血管病变和下肢神经病变，这些都是慢性创面发展的诱发因素[25]。高血糖会促进动脉粥样硬化的发展，从而影响循环营养物质到达创面，延缓创面愈合[26]。

2.2. 压力性溃疡

压力性溃疡也称压疮，也是慢性创面形成的重要病因。压力性溃疡常见于长期卧床的老年人，当身体某一部位长期过度受压时，在摩擦力的作用下容易形成皮肤和深部组织的溃疡。当组织压力超过毛细血管压力时，长期未缓解的压力或剪切力会导致缺血，组织缺氧和缺血再灌注损伤导致创面坏死[27]。骶骨、臀部和脚踝等骨质突出部位的皮肤特别脆弱，两小时的持续压迫可能就会引起这种情况[28]。当创面开始收缩时，粘着斑激酶/细胞外信号调节激酶会激活创面成纤维细胞释放的趋化因子配体 2，进而引发更大的炎症反应[29]，是慢性创面疤痕形成的主要驱动因素的理论。

2.3. 静脉溃疡

静脉性溃疡是较为常见的慢性创面的病因。持续的静脉高压引起局部组织的血液循环及吸收障碍，进而出现代谢产物堆积及皮肤营养改变，从而导致慢性创面的形成[30]。静脉瘀滞性溃疡占所有下肢慢性创面的一半以上，其中女性和老年人的发病率更高[4]。静脉溃疡往往较大且较浅，边缘通常不规则且不清晰，最常发生在内侧小腿上[4]，内踝及外踝的部位最为常见。慢性创面周围皮肤在局部形成色素沉着、呈皮炎改变；创面部位可出现肉芽组织生长，其表面可见纤维蛋白凝胶状坏死，伴有渗液及结痂。此外，慢性创面形成可继发于静脉血栓形成或瓣膜功能不全，在此过程中，血管的通透性增加，大分子物质可渗入血管间隙，诱导白细胞浸润引起炎症反应，进而组织炎性水肿阻碍营养物质、氧气及生长因子向创面组织的转移[31] [32]。

2.4. 动脉溃疡

动脉溃疡也是慢性创面的病因之一，较静脉溃疡略少见。动脉溃疡通常发生在骨突的远端，呈圆形，边界清晰[33]。动脉溃疡患者的皮温降低、苍白或发绀，创面的基底苍白、深浅不一，甚至可深及肌腱或骨骼。肢体血供不足常由动脉硬化、血栓栓塞或辐射损伤引起[34]，进而会引起局部组织的缺血、缺氧改变，进一步组织坏死形成慢性创面[35]。

3. 发病机制

慢性创面的发病机制复杂多变，据国内外最新研究提示，慢性创面的发病机制主要涉及炎症、缺血缺氧、细菌感染及细胞衰老等多方面因素[36]。

3.1. 炎症

慢性的、持续的炎症是慢性创面形成的重要发病机制[37]。炎症会对创面组织产生持续破坏，使急性创面经久不愈演变成慢性创面。慢性创面的特点是朗格汉斯细胞[38]、中性粒细胞、促炎性巨噬细胞[39]和蛋白酶数量增多，且数量与临床病变的严重程度有关。伴随着特定免疫细胞亚群的浸润增加，免疫细胞的功能受到影响，导致了创面的延迟愈合。其中中性粒细胞被过度激发，产生中性粒细胞外陷阱，具有细胞毒性[40]，延迟创面愈合[41]。在糖尿病小鼠模型中，研究者发现糖尿病小鼠体内的巨噬细胞对凋亡细胞的清除作用下降[42]，对细菌的吞噬作用减弱[43] [44]，抗炎状态的能力降低[45]。另外，在一项关于糖尿病溃疡发病机制的研究中发现，T 细胞受体多样性和 $CD4^+$ T 细胞的数量减少可能介导了溃疡的

发生发展[46]。总之，慢性创面免疫细胞的这些异常特征不仅介导了炎性级联反应，而且增加了机体对感染的易感性。由于慢性创面感染、炎症持续存在，使创面持续处于感染、炎症和不充分修复的循环中从而延缓了创面愈合。

3.2. 缺血

皮肤缺血已被证明是慢性创面的发病机制之一[47]。在创面修复过程中，血管新生极为重要的环节，创面修复所必需的营养物质可由新生的血管提供，从而促进细胞生长及创面愈合。血管生长受损和骨髓内皮祖细胞的动员减少是导致创面愈合障碍的因素。以往研究发现各种疾病引起的局部组织血供不足，可导致创面血管新生速度减慢，延迟创面愈合[48] [49]。特别是在糖尿病患者中，慢性不愈合的创面与血管生成和淋巴管生成紊乱有关[50]。血管生成紊乱导致缺氧，随后细胞因凋亡或坏死而死亡[51]。缺血组织的创面愈合，如远端皮瓣边缘，由于血液供应不足，在重建皮瓣手术中，缺血性组织损伤不仅会影响创面给愈合，还可能降低皮瓣的存活率。缺血和随后的组织缺氧会诱发促炎症状态，白细胞迁移到创面组织，产生大量炎症细胞因子和活性氧，进一步加剧了炎症，进而导致组织坏死和溃疡[52]。

3.3. 缺氧

局部组织缺氧是慢性创面形成的重要机制之一。局部组织缺氧会引起细胞膜破坏，促进炎症连锁反应[9]。缺氧的创面微环境的维持至关重要，它为血管生成、再上皮化、生长因子和细胞因子合成及释放提供了条件[53]。当慢性创面发生时，由于血管的破坏，局部氧气供应减少[54]，中性粒细胞和巨噬细胞的外渗至缺氧组织，随后以自分泌方式合成促炎症细胞因子，促进炎症的持续存在。缺氧延长了炎症时间，阻碍了创面愈合。缺氧损害创面再上皮化，慢性创面缺氧会加重创面感染、破坏血管生成、减少成纤维细胞的分化和增殖[53]。此外，缺氧会导致活性氧和促炎细胞因子的合成，会延缓愈合过程。过量活性氧的产生不仅造成氧化损伤，还干扰信号转导通路，引起丝氨酸蛋白酶、基质金属蛋白酶(Matrix Metalloproteinase, MMPs)和炎症细胞因子的高表达[55]。因此，缺氧是慢性创面形成的重要发病机制。

3.4. 细菌感染

慢性创面的另外一个重要发病机制是细菌感染。当前研究证实，在慢性创面中最常见的创面病原体为：铜绿假单胞菌和金黄色葡萄球菌[56]，创面的微生物的状况与愈合的结果密切相关[57]。细菌感染可引起白细胞趋化反应，分泌大量炎性因子、蛋白酶及 ROS，从而引起炎症级联反应[55]。大量的蛋白酶和 ROS 会降解生长因子和 ECM，阻碍细胞迁移、延缓创面愈合[31]。皮肤创面的病原体可形成多菌群(生物膜)，被包裹在细胞外聚合物质的保护性基质中，对抗生素和人体的防御存在抵抗力[58]。生物膜为细菌逃避人体免疫反应及抗生素作用提供了最佳环境[59]。有研究表明，创面组织中每超过 105 个细菌的生物负荷对各种急性和慢性创面以及创面的愈合都有不利影响[8]。以往研究发现，生物膜可明显延长患者的炎症反应时间，炎症渗出物会进一步稳固生物膜的结构[60]。此外，生物膜中细菌的耐药性也会增加[61]。因此，慢性创面中的细菌常形成生物膜，从而使创面处于炎症和难愈合状态[62]。创面缺氧会加剧细菌感染，感染和创面氧合水平呈负相关[55]。因此，细菌感染是慢性创面形成的重要机制，且与缺氧存在相互作用，这种复杂的相互作用进一步阻碍了慢性创面的愈合。

3.5. 细胞衰老

细胞衰老是涉及慢性创面的重要发病机制之一[63]。与细胞衰老相关的变化包括细胞迁移、粘附和功能反应的降低[64]。细胞衰老主要涉及中性粒细胞，衰老的中性粒细胞的呼吸作用降低，吞噬细菌的能力减弱，趋化性下降[65]。此外，中性粒细胞会产生大量的弹性蛋白酶，弹性蛋白酶会降解胶原蛋白、纤连

蛋白等重要的功能蛋白，导致慢性创面局部的纤连蛋白细胞黏附性降低，从而延缓和阻碍了慢性创面的愈合[66]。此外，衰老的皮肤创面更易受损，细胞萎缩，皮肤屏障破坏，水合作用降低[67]。衰老也会导致真皮基质的逐渐丧失，组织力学发生相应的变化，弹性丧失，对摩擦损伤的敏感性增加[68]。当发生创面损伤时候，一系列的分子和细胞变化会引起创面愈合障碍。在内外因素的作用下有丝分裂的细胞会发生衰老和停止增殖。衰老的细胞获得高分泌的表型，产生富含促炎症细胞因子和组织降解蛋白酶的分泌物，影响创面愈合[69]。

4. 慢性创面的治疗进展

慢性创面治疗基于对病因和发病机制的评估。局部清创，通过手术方式去除坏死组织[70]。然后用生理盐水或抗菌溶液冲洗创面，加用敷料[71]。现代敷料加入抗菌物质[72] [73]，具有材料属性。更为先进的疗法，包括负压治疗[74]。

最近的创面研究集中在抗菌剂和抗生物膜疗法。如纳米颗粒，其细胞毒性较低，促进创面愈合[75]。新兴的抗菌治疗方法，包括 CAP (Cold Atmospheric Plasma)等离子体[76]和生物活性玻璃[77]。针对特异致病菌的抗菌剂，如噬菌体疗法[78]。

实验研究为慢性创面的病因和发病机制提供新思路，为未来的预防治疗提供新途径。诸如抗衰老药物槲皮素，可以减少衰老细胞[79] [80]和抗炎[81]。此外，受体 CXCR2 可加速溃疡创面修复[82]。其他治疗策略包括给予干细胞[83]、生长因子[84]和基因疗法[85]。

5. 总结与展望

慢性创面愈合是一个复杂的、动态的过程，其病因及发病机制复杂，涉及多种因素及机制的综合调控，当调控机制异常时可引起慢性创面的形成。慢性创面具有高发病率和高复发率，因此，迫切需要提高对创面修复机制的病因及发病机制的认识。近年来，研究者们在关于其病因、发病机制及治疗方面做了大量的研究，然而，慢性创面愈合是一个相当复杂性的病理过程，仍需要更加深入的研究阐明其分子机制，从而更好地认识该疾病并寻找新的治疗靶点。新兴的伤口模型为进一步探索创面修复的分子和细胞特征提供了前所未有的机会，也将促进我们对慢性创面病因及发病机制的理解。

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