·综述·

ω–3多不饱和脂肪酸在创面愈合中作用的研究进展

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【摘要】创面愈合是创伤后机体功能康复的前提，创面不及时处理会发生感染，若炎症反应过度，会影响愈合速度和质量。ω–3 多不饱和脂肪酸（ω–3 polyunsaturated fatty acids, ω–3 PUFAs）在创面愈合和组织修复过程中起着重要作用，可抑制炎症反应、促进血管生成、调节神经系统、控制血糖水平、抑制微生物生长、加速创面愈合。本综述介绍了 ω–3 PUFAs 的特性，探讨了 ω–3 PUFAs 促进烧伤、创伤性脑损伤创面、糖尿病烧伤、糖尿病足溃疡创面愈合的机制及其给药途径。

【关键词】ω–3 多不饱和脂肪酸；创面愈合；水凝胶

Research progress on the role of ω-3 polyunsaturated fatty acids in wound healing

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【Abstract】Wound healing is the premise of body functional rehabilitation after trauma. If the wound is not treated in time, infection will occur. If the inflammatory process is excessive, the healing speed and quality will be affected. ω-3 polyunsaturated fatty acids (ω-3 PUFAs) play an important role in wound healing and tissue repair, which can inhibit the inflammatory response, promote angiogenesis, regulate the nervous system, control blood glucose levels, inhibit microbial growth, and accelerate wound healing. This review introduces the properties of ω-3 PUFAS and explored the healing mechanism of ω-3 PUFAS in promoting burn, traumatic brain injury wound, diabetic burn and diabetic foot ulcers and the routes of administration.

【Keywords】ω-3 polyunsaturated fatty acids; Wound healing; Hydrogel

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创面愈合是皮肤屏障功能恢复的复杂且动态的重叠阶段过程，其间不同类型的皮肤细胞和免疫细胞之间存在动态相互作用，提供特定条件支持创面愈合[1-3]。但在愈合过程中，创面易发生感染。糖尿病患者创面的病理过程更为复杂，受损的皮肤、肌肉、神经和血管伴有持续高血糖状态，使得糖尿病创面较正常创面更难愈合。传统治疗创面的方法主要包括彻底清创和控制感染等，采用生物复合材料可促进创面愈合。ω-3 多不饱和脂肪酸(ω-3 polyunsaturated fatty acids, ω-3 PUFAs ）是必需脂肪酸，可通过促进角化细胞增殖、诱导成纤维细胞分化、减少促炎细胞因子产生进而改善伤口愈合[4]。ω-3 PUFAs 可促进烧伤、创伤性脑损伤创面、糖尿病烧伤、糖尿病足溃疡创面愈合。本文就 ω-3 PUFAs 在创面愈合中的应用现状及作用机制做一综述，以期为 ω-3 PUFAs 的规范、广谱应用提供一定参考。

1 创面研究概况

创面是由各种内在病理因素和外在物理因素引起的，这些因素会损害皮肤组织结构的完整性[5-7]。创面愈合有 4 个重叠阶段，包括止血、炎症、增殖和重塑[8]。止血被定义为生物体的平衡防御机制，能够维持血液循环并在血管完整性被破坏的情况下防止失血。二十碳五烯酸（ eicosapentaenoic acid, EPA ）和二十二碳六烯酸（ docosahexaenoic acid, DHA ）可渗入细胞膜内，改变其流动性，使钙离子流入减少，抑制血小板活化，参与凝血酶产生，进而调节止血[9]。ω-3 PUFAs 对白色脂肪组织（ white adipose tissue, WAT ）抗炎和代谢的有益作用主要归因于脂肪酸与脂肪酸表达基因 G 蛋白偶联受体 120（ G protein-coupled receptor 120, GPR120 ）结合后，支架蛋白 β- 抑制蛋白 2（ β-arrestin2 ）被募集到 C 末端并内化，这种复合物干扰了炎症途径，如核转录因子（ nuclear transcription factor, NF ）-κB，从而缓解 WAT 炎症[10-11]。DHA 可促进细胞周期进展和细胞分裂，高浓度 DHA（ 10 μmol/L 及以上 ）可能对神经干 / 祖细胞（ neural stem/progenitor cells, NSPC ）的增殖能力有害[12-13]。肥大细胞可以促进 ω-3 环氧化物释放，调节肺动脉血管重塑，进而抵消肺动脉高压（ pulmonary hypertension, PAH ）发展，无法使用肺动脉扩张器有效治疗磷脂酶 A2 突变的 PAH 患者可以使用 ω-3 环氧化物促进肺血管重塑[14]。创面处理的主要目标是提供抵御细菌感染的物理屏障，保持创面部分处于湿润状态，进而加速愈合[15-17]。目前治疗创面的常规外科处理方法有清创、抗感染敷料包扎（ 包括生长因子输送、基因治疗和基于机械 / 压力的刺激 ）[18]、负压引流等。Duceac 等制造了一种壳聚糖 – 普鲁兰多糖复合材料，可调孔径和靶向特性，这些复合材料不仅可以作为药物输送装置，还能作为具有优异性能的现代创面敷料[19]。

1.1 ω-3 PUFAs及其药理作用

脂肪酸是细胞膜结构的关键组成部分，按其碳链长度及所含双键的数量和位置进行分类，含有一个以上双键的脂肪酸称为多不饱和脂肪酸，根据第一个双键从甲基位置进一步分为 ω-3 PUFAs 和 ω-6 多不饱和脂肪酸（ ω-6 polyunsaturated fatty acids, ω-6 PUFAs ）[20]。ω-3 PUFAs 主要包括 α- 亚麻酸（ alpha-linolenic acid, ALA ）、EPA、二十二碳五烯酸（ docosapentaenoic acid, DPA ）和 DHA，主要来源于鲑鱼、金枪鱼、凤尾鱼等脂肪鱼[21]。ω-3 PUFAs 对治疗严重创伤、降低失控炎症反应、缓解氧化应激与细胞凋亡、恢复免疫功能、促进神经发育、调节血小板活性等均有显著作用[10, 22-27]。日常摄入适量的 ω-3 PUFAs 可显著降低心血管死亡风险[28]。Innes 等研究证实，心血管疾病患病率低归因于 ω-3 PUFAs 的高膳食含量[29]。ω-3 PUFAs 在孕妇怀孕期间起着重要作用，能够确保正常怀孕的适当进展。研究者通过调查孕妇怀孕期间是否补充 EPA 和 DHA（ ω-3 PUFAs 指数 ）发现，儿童出生时 EPA 和 DHA 水平越高，神经发育越好，这提示 ω-3 PUFAs 能够对神经发育产生有利影响[22]。ω-3 PUFAs 可以有效降低创面的失控炎症反应。Poggioli 等研究发现，ω-3 PUFAs 对免疫细胞具有抑制作用并减少促炎症细胞释放[30]。

1.2 ω-3 PUFAs在创面愈合中抗感染的瓶颈问题

皮肤组织受伤后，皮肤微生物群易变得不平衡，被微生物感染。感染创面的微生物颇多，如铜绿假单胞菌、金黄色葡萄球菌、肺炎链球菌、曲霉菌等。Ye 等将制备的氧化铜（ CuO ）和氧化银（ AgO ）共改性氧化锌（ ZnO ）纳米复合材料敷在创面上，发现其能够有效消除金黄色葡萄球菌

和铜绿假单胞菌，进而促进创面愈合[31]。Ishihara 等发现 ω-3 PUFAs 衍生介质在控制炎症及其消退方面的体内活性在小鼠急性炎症模型中得到了最佳表征，DHA 衍生的溶剂素显著减少了大肠杆菌接种小鼠血液和腹膜渗出物中的细菌数量[32]。及时抗感染可促进创面愈合，因此，抗感染治疗在创面愈合的动物模型中显示出良好的前景。

1.3 ω-3 PUFAs在不同创面中促进愈合的作用机制

1.3.1 ω-3 PUFAs在烧伤创面愈合中的作用机制

烧伤是热蒸汽、火焰及热液等热力造成的皮肤及黏膜组织损伤。严重烧伤会导致显著的代谢变化，这使得营养支持尤为重要[33-34]。烧伤后的代谢状态特征是游离（血浆）脂肪酸可用性增加，增强了 ω-3 PUFAs 的有益作用。在烧伤幸存者中，低 ω-3 PUFAs 水平与感染和死亡率增加有关，故在烧伤患者治疗过程中可以补充 ω-3 PUFAs，从而减少炎症发生和感染、促进创面愈合[35]。Tingö 等通过研究证实，ω-3 PUFAs 可能通过增加白介素 -10（interleukin-10, IL-10）表达来影响炎症，IL-10 可通过抑制巨噬细胞活化和抑制白介素 -6（interleukin-6, IL-6）、白介素 -8（interleukin-8, IL-8）和肿瘤坏死因子 -α（tumor necrosis factor-α, TNF-α）等炎性细胞因子的释放和活性，在减少炎症方面起重要作用[36]。Tihista 等的试验发现，接受含有 DHA 和间充质干细胞（mesenchymal stem cells, MSCs）的壳聚糖 - 海藻酸盐治疗的烧伤患者重度脓毒症和脓毒性休克的发生率比未接受 ω-3 PUFAs 治疗患者低两倍，ω-3 PUFAs 可加速烧伤创面愈合[37]。上述研究表明了 ω-3 PUFAs 在烧伤、烫伤治疗中能减少炎症发生和促进伤口愈合，对烧伤、烫伤的治疗产生重要影响。

1.3.2 ω-3 PUFAs在创伤性脑损伤创面愈合中的作用机制

创伤性脑损伤（traumatic brain injury, TBI）常见于军事战斗、娱乐活动、车辆事故等。轻度 TBI 相关的损伤可能源于脑组织变形，这是由爆炸冲击通过脑和脑脊液传递的冲击波引起，或由头部快速加速 - 减速期间的脑压迫和扩张引起[38]。ω-3 PUFAs 具有抗氧化和抗炎作用，可以抑制 TBI 部位转变为促炎表型，从而减少脑损伤后的神经炎症。Lin 等研究证明，ω-3 PUFAs 能通过沉默信息调节因子（silencing information-regulating molecules, SIRT）去脱乙酰修饰高迁移率族蛋白 1（high mobility group box-1, HMGB1）/NF-κB 通路抑制神经炎症反应，ω-3 PUFAs 减小了病变面积、减轻神经元损伤和少突胶质细胞损失及凋亡，这与神经系统的改善有关[39]。以上研究表明，在 TBI 后立即服用 ω-3 PUFAs 可给神经系统提供保护作用，说明 ω-3 PUFAs 在治疗 TBI 方面具有潜力。

1.3.3 ω-3 PUFAs在糖尿病烧伤创面愈合中的作用机制

糖尿病烧伤患者的创面多属于开放性创面，血糖较高，此时受损处营养、温度和湿度环境有利于病原菌侵袭、定植与增殖，易发生创面感染[40-41]。转化生长因子 -β1（transforming growth factor-β1, TGF-β1）作为纤维化的有效调节因子，可协调伴随的葡萄糖转化为脂肪酸所需酶的表达减少，对成纤维细胞增殖起到了明显抑制作用，创面修复细胞的正常功能受到影响，导致糖尿病烧伤患者的创面治愈难度增大[42]。使用 ω-3 PUFAs 补充剂进行肠外免疫营养，制剂与抗氧化剂和氨基酸在内的其他佐剂联合使用，可减轻烧伤患者的严重炎症反应和调节免疫功能，降低发病和死亡风险。糖尿病患者重度烧伤后早期肠内喂养含 ω-3 PUFAs 的低脂饮食可避免感染并延缓肌肉退化，减少潜在致病菌[43]。总之，糖尿病患者皮肤具有创面难愈的特征，烧伤后可能发生水、电解质紊乱及应激性高血糖和创面感染，两者互相影响可加重病情。

1.3.4 ω-3 PUFAs在糖尿病足溃疡创面愈合中的作用机制

全球超过 20% 糖尿病患者存在糖尿病足溃疡，其中超过 10% 患者可能经历截肢，且有较高的复发率，显著增加了其 5 年内死亡风险（增加 2.5 倍）[44-45]。糖尿病皮肤溃疡由血管疾病、感染和神经病变共同引起，导致慢性不愈合溃疡的一个关键致病步骤是白细胞被困在受高血压影响的静脉循环中[46-47]。糖尿病患者伤口中血管新生过程十分迟缓，创面中血管表面积、分支连接数、总血管长度和总分支数均明显减少。血管生成可以有效支持伤口闭合，而血管病变正是导致糖尿病患者伤口难愈的诱因之一[47]。摄入 ω-3 PUFAs

可以改善老年人直立性压力的血压维持[48]。ω-3 PUFAs 可通过恢复巨噬细胞受损的可塑性来改善大鼠模型中的糖尿病伤口愈合[49]。用富含长链ω-3 PUFAs 的完整鱼皮肤移植物进行治疗，应用于糖尿病患者创面可以促进其愈合，从而有效治疗糖尿病慢性下肢溃疡[50]。

2 ω-3 PUFAs的给药途径

水凝胶是一种伤口敷料[51]。由于水凝胶敷料具有抗菌性、亲水性、生物相容性等特性，故其在药物递送、局部抗菌治疗、创面愈合等方面引起了重视[52-58]。近年来，部分学者将营养物质和水凝胶联合形成生物聚合物应用于创面治疗，生物聚合物被称为生物活性伤口敷料，包括羧甲基壳聚糖（carboxyl methyl chitosan, CMCS）、海藻酸盐、纤维素等，在伤口敷料中加入抗生素、抗氧化剂、纳米颗粒和生长因子，由于其内在特性，从而促进伤口愈合[59]。Hu 等通过非共价力和物理包埋将脂肪干细胞的外泌体包埋到水凝胶中，利用外泌体传递药物的机制加速糖尿病伤口愈合[60]。Pourtalebi Jahromi 等将多糖水凝胶平台作为脂质体和细胞外囊泡的载体，其在感染糖尿病伤口模型中的体内实验证实了水凝胶本身优秀的抗菌和促进伤口愈合的作用，这与干细胞衍生的细胞外囊泡（extracellular vesicles, EVs）的抗炎和血管生成作用协同作用有关[61]。Tsubosaka 等发现体外局部使用含 EPA 的明胶水凝胶可防止小鼠骨关节炎进展，并预防骨关节炎进展期间滑膜炎的进展，同时，EPA 可防止巨噬细胞浸润在滑膜组织中[62]。免疫组化分析结果显示，EPA 通过抑制 IL-1β 和基质金属蛋白酶（matrix metallo proteinase, MMPs）水平来预防骨关节炎进展。在小鼠骨关节炎模型中，含 EPA 的明胶水凝胶比单次注射 EPA 可以更有效地防止骨关节炎进展[62]。因此，将 ω-3 PUFAs 与以 CMCS 和海藻酸盐作为凝胶基体材料联合形成负载脂肪酸新型凝胶系统，可以减少病原菌感染，更好地促进局部微循环和肉芽组织生长，加速创面愈合[63]。

3 小结

创面恢复与创面周围微环境和患者自身营养有关。在创面愈合阶段通过补充 ω-3 PUFAs 营养成分，可达到显著效果。静脉注射 ω-3 PUFAs 脂质乳剂达到全身应用效果，可减少谷氨酸的兴奋性毒性释放，并抑制环氧合酶-2（cyclooxygenase-2, COX-2）和 IL-6 等炎症标志物，控制炎症反应。体外局部使用 ω-3 PUFAs 时，在体外 IL-1β 刺激下炎症转录因子表达增强，ω-3 PUFAs 展现了极强的抗炎作用。含有 ω-3 PUFAs 的明胶水凝胶比只含有 ω-3 PUFAs 的治疗药物更能有效防止炎症进展。目前，ω-3 PUFAs 在创面愈合方面已取得一定进展，但该研究领域仍存在较大空缺，并具有广阔的应用前景。本综述探索了 ω-3 PUFAs 调控烧伤、创伤性脑损伤创面、糖尿病烧伤创面、糖尿病足溃疡创面的愈合机制及其给药途径。不同患者对 ω-3 PUFAs 的反应不同，且个体化研究仍处于空白阶段，未来有待医疗技术的进一步发展及对创面的深入研究，将ω-3 PUFAs 广泛应用于临床变成现实，以便更好地服务于患者。

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