h综述h

干细胞原位激活再生促进皮肤软组织损伤修复的研究进展

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【摘要】 皮源短缺是大面积烧创伤患者面临的关键问题，现有的多种皮肤软组织损伤修复方法仍无法完全规避供体损伤的治疗困境，难以从根本上改善此类患者的预后。内源性干细胞具有自我更新、多向分化以及对损伤响应的特性，在皮肤损伤修复及无瘢痕愈合过程中发挥着重要作用。因此，如何招募、激活及促进内源性干细胞再生分化是目前原位组织工程的研究重点。部分生物材料因其自身具备的生物物理特性，可以通过招募、激活干细胞的再生促进创面修复。该文系统总结了干细胞原位激活再生促进皮肤损伤修复的研究进展，以期为临床上大面积皮肤软组织损伤修复提供新思路。

【关键词】 干细胞；　原位组织再生；　生物材料；　组织修复

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In-situ activation and regeneration of stem cells for promoting repair of skin and soft tissue injuries: a review

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【Abstract】 Shortage of skin is the bottleneck for treating large area wounds. Current metheds for repaining skin and soft tissue injuries still can′t entirely avoid donor site damage. These methods cannot fundamentally improve the prognosis of patients with extensive soft tissue injury. Because of self-renewal ability, multi-directional differentiation, and reaction to injury, endogenous stem cells play an important role in the process of wound healing and scarless healing. How to recruit, activate, and promote the regeneration and differentiation of endogenous stem cells has been a hot spot of in-situ tissue engineering. Because of biophysical characteristics, some biomaterials can recruit stem cells, and activate stem cell regeneration to promote wound repair. Based on the role of stem cells in the repair of soft tissue injury, this review systematically summarizes the research progress of stem cells in-situ regeneration, in order to provide new ideas for the repair of extensive skin and soft tissue injury in clinical practice.

【Key words】 Stem cells;　In-situ tissue regeneration;　Biomaterials;　Tissue repair

皮源短缺仍是大面积烧创伤修复过程中的临床难题，目前的皮肤软组织损伤修复重建技术无法从根本上完全规避供体损伤的治疗缺陷，且瘢痕增生挛缩等问题会进一步影响患者的生活质量。干细胞因其具有自我更新、多向分化及对损伤响应等特性，在创面修复过程中显示出较强的潜力。但传统干细胞疗法主要采用外源性干细胞移植的途径，存在存活率低、易遭受免疫系统攻击及制备困难等问题，使其在临床上的应用受到限制。干细胞原位激活再生即通过生物材料与体内微环境相互作用，促进并诱导内源性干细胞附着、迁移，将其募集到损伤或病变部位，同时协调干细胞的行为和功能，并支持其向成熟的细胞表型分化，从而实现受损组织的原位再生[1]。这种治疗策略无需外源性干细胞移植，方法简单，是一种更为直接的再生医学方法，具有广阔的临床应用前景[2]。现总结干细胞在皮肤软组织损伤修复中的作用，并对干细胞原位激活再生的机制及其研究进展进行综述。

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一、皮肤损伤修复过程

皮肤损伤修复主要分为4个阶段：(1)止血期：血小板活化后聚集形成血小板栓子，并激活凝血级联反应，引起血管收缩止血，血凝块形成临时的创面基质[3]。(2)炎症期：损伤细胞释放趋化因子、损伤相关分子模式(damage-associated molecular patterns，DAMPs)、过氧化氢等，募集中性粒细胞吞噬病原体[4]。骨髓源性单核-巨噬细胞迁移至损伤部位，通过平衡促炎与抗炎作用调节免疫反应，其中促炎细胞(如M1型巨噬细胞)负责清创，而抗炎细胞(如M2型巨噬细胞)对内源性干细胞的细胞外基质重塑、血管成熟和分化具有重要作用[5]。(3)增殖期：表皮细胞通过增殖和迁移完成再上皮化，成纤维细胞形成肉芽组织填充创面并伴有新的血管生成[6]。(4)重塑期：细胞外基质进行重塑，同时形成新生血管网，前期增殖过度的细胞发生凋亡[7]。

二、干细胞在皮肤损伤修复过程中的作用

干细胞具有自我更新与分化能力，可通过旁分泌作用分泌细胞因子和生长因子，以多种方式参与皮肤损伤修复

过程[8]。

1.脂肪间充质干细胞(adipose derived mesenchymal stem cells, ADSCs):ADSCs位于毛囊基底部皮下组织、真皮层、毛囊间真皮层和皮下组织,对于调节皮肤再生具有重要作用。ADSCs能分泌多种生长因子,如血管内皮生长因子(vascular endothelial growth factor, VEGF)、转化生长因子-β(transforming growth factor-β, TGF-β)等,可促进血管生成并进一步减少内皮细胞凋亡[9]。ADSCs通过自噬和旁分泌途径激活细胞再生和愈合过程。在皮肤损伤修复过程中,ADSCs能够迁移到受损部位,并向成纤维细胞、内皮细胞和角质形成细胞分化,同时也能通过其分泌物调节炎症反应,诱导创面上皮化,促进新血管形成和组织重塑[10]。此外,ADSCs通过释放各种生物活性分子促进细胞增殖和迁移,介导邻近或远距离的细胞间通信,从而在创面愈合过程中发挥作用[11]。

2.骨髓间充质干细胞(bone marrow mesenchymal stem cells, BMSCs):BMSCs可以调节创面床中的细胞间相互作用,还可以协调细胞外基质蛋白和生物分子之间的相互作用,包括趋化因子和生长因子[9]。BMSCs在创面愈合过程的各个阶段均起到辅助作用:在炎症期可以促进巨噬细胞向M2型极化,从而抑制炎症反应;在增殖期可以促使巨噬细胞募集角质形成细胞和成纤维细胞。BMSCs能提高成纤维细胞、表皮细胞和内皮细胞的增殖和分化潜能,促进血管生成,增加细胞外基质的重塑,从而促进创面愈合[12]。此外,在基质细胞衍生因子-1(stromal cell-derived factor-1, SDF-1)的作用下,内源性BMSCs向损伤部位迁移,释放碱性成纤维细胞生长因子(basic fibroblast growth factor, bFGF)、神经生长因子(nerve growth factor, NGF)和脑源性神经营养因子(brain-derived neurotrophic factor, BDNF),促进神经元再生[13]。

3.其他干细胞:表皮干细胞(epidermal stem cells, ESCs)能够迅速转变状态以实现有效的组织再生,具有强大的可塑性[14]。ESCs分泌的C-C基序趋化因子配体2(C-C motif chemokine ligand 2, CCL2)可影响巨噬细胞,通过角质形成细胞与巨噬细胞的相互作用促进组织修复[15]。ESCs在增殖期通过改变细胞迁移、细胞群体动力学和可塑性等促进再上皮化[16-17]。此外,ESCs可通过增加对称细胞分裂和减少分化适应环境,补充丢失的细胞[18]。严重损伤时,血管附近的ESCs可分化成血管内皮细胞,有助于血管生成[19]。

毛囊干细胞(hair follicular stem cells, HFSCs)通过促进再上皮化和改善血管生成加速创面闭合。当损伤发生时,邻近HFSCs向损伤部位迁移,产生过渡放大细胞(transit amplifying cells, TAC),随后这些细胞向终末分化细胞分化,参与创面床的再上皮化并恢复屏障功能[20]。尽管HFSCs修复创面的机制尚不清楚,但证据表明多种信号通路参与毛囊再生和创面修复,并发挥重要的调节作用,包括Wnt、BMP、Notch和SHH通路等[21-22]。

三、干细胞原位激活再生与皮肤软组织损伤修复

皮肤软组织损伤修复可以通过体外组织工程及原位组织工程实现。体外组织工程通过将支架与体外细胞和生物分子相结合,将满载细胞的组织构建体植入体内,以提供细胞外基质环境,从而促进组织再生[23]。植入的干细胞可以向损伤组织迁移,通过分泌细胞因子,调节免疫反应和炎症反应,增加血管新生,从而促进组织再生。体外组织工程具有以下局限性:(1)异体干细胞移植存在免疫排斥、肿瘤发生和病原体传播的风险,而自体干细胞分离、体外扩增和释放所需时间长[24];(2)干细胞采集、加工和移植的所有阶段所需条件均非常严格[25];(3)不适宜的创面微环境会导致干细胞移植和归巢效果不佳,成功率较低[26];(4)价格昂贵,运输及存储困难,临床应用受限[27]。

体外组织工程的局限也进一步推动了原位组织工程研究的进步,其无需体外构建及外源性干细胞植入,通过干细胞原位激活再生可以规避体外组织工程的缺点[5]。作为干细胞移植的替代方法,干细胞原位再生能够避免传统干细胞疗法的关键障碍,其主要优势在于:(1)无需体外细胞,操作简单;(2)仅依赖于生物材料在其自然体内微环境中与局部干细胞的相互作用,可充分发挥机体先天再生潜能,降低成本;(3)在损伤部位原位再生,调控障碍较少,质量稳定且可扩展[2]。

四、应用于招募及激活干细胞原位再生的生物材料

内源性干细胞在稳态条件下大多处于静止状态,并位于其生态位中。一旦发生组织损伤,生态位内或远处组织的生理和分子变化会激活干细胞的迁移和归巢,归巢后的细胞在损伤部位分化为成熟干细胞进行免疫调节,进一步促进组织修复[26]。用于原位再生的生物材料应能够招募内源性干细胞并引导其命运轨迹,同时不会引起有害的炎症反应,而设计生物材料的物理及化学特性就是控制其功能的核心。生物材料的物理特性包括弹性、硬度、结构以及材料的表面特性,如粗糙度、电荷和湿润性等。这些物理特性可以通过细胞与生物材料的相互作用改变局部组织微环境[28]。此外,不同的基质硬度还可影响干细胞的黏附、扩散和分化[29]。生物材料的化学特性包括生物材料的化学结构及生物信号分子,如蛋白质、矿物质、小分子药物和重编程分子等[30-33]。生物材料的化学性质影响免疫细胞的募集和免疫反应[34]。基于对内源性干细胞再生潜能的认识,目前一系列生物材料可用于干细胞原位再生,如纳米颗粒、水凝胶、3D打印支架等[35-37]。

生物材料的物理特性,如孔径、纤维尺寸以及微米/纳米模式等拓扑特征,都会影响其修复创面的效果。例如,纳米孔结构的丝素蛋白海绵在促进细胞附着和增殖方面表现出显著优势,这归因于其孔隙率更高、水渗透性更强[38]。聚合物纤维模型的相关研究表明,未对齐的纳米级纤维能够增强细胞生长和胶原合成,而微米级纤维则更支持细胞的组织化,抑制过度生长和生物合成[39]。生物材料的微观结构在促进组织再生和创面愈合过程中非常重要[40]。在安全性方面,生物材料降解副产物是需要考虑的重要因素之一。虽然一些易于生物降解的合成生物材料,如聚乳酸-乙醇酸和聚丙交酯,不具有细胞毒性,但其酸性降解副产物已被广泛认为不利于细胞迁移、增殖和血管生成[41]。而另一方面,有些降解副产物

如生物活性离子则可以促进组织再生。例如,在兔骨缺损模型中,微孔羟基磷灰石支架的降解会释放磷酸盐、钙离子、镁离子,从而促进新血管的形成[42]。目前,生物材料应用于激活干细胞原位再生的安全性和有效性尚需更多的研究验证。

五、生物材料刺激干细胞原位激活再生的机制

1.调控细胞外微环境并调节免疫反应:成体干/祖细胞存在于干细胞生态位的特殊微环境中,该生态位包含多种细胞,如成纤维细胞、内皮细胞以及基质成分。生态位及其成分通过直接相互作用或来自可溶性因子的信号线索严格调节干细胞的行为和功能[43]。生物材料植入后会吸附一系列血清蛋白,从而改变其表面特性。内源性免疫细胞吸附在蛋白上,并释放细胞因子和趋化因子启动炎症反应[44],同时细胞因子的释放会募集内源性干细胞,这是原位组织再生的关键步骤。初始附着后的内源性干细胞合成新生蛋白质并在生物材料表面沉积,同时通过分泌基质金属蛋白酶(matrix metalloproteinase, MMP)不断重塑局部细胞外基质[45]。新沉积的细胞外基质介导生物材料和内源性干细胞之间的双向信号转导。这些双向相互作用可以通过控制植入生物材料的生物物理和生化特性来调节,直接影响细胞反应和局部组织微环境[5]。

干细胞受生物化学和生物力学微环境的影响较大,其中生物力学因素对干细胞的增殖和分化具有重要影响。通过调节细胞微环境以及细胞内的信号转导,干细胞可以感知微环境中的力学信号,并将其转化为内力,重组和重排细胞骨架网络。这一过程通过机械转导影响干细胞的扩散、迁移和定向等行为,从而进一步调控干细胞的增殖和分化[46]。生物材料不同表面结构可以调节免疫反应。在比较亲水性或疏水性涂层表面免疫调节能力的研究中发现,亲水性涂层表面(如碱胺、丙烯酸、2-甲基-2-恶唑啉)促进白蛋白吸附,诱导抗炎细胞因子的分泌;相反,疏水性涂层表面(如1,7-辛二烯)则促进免疫球蛋白的吸附,导致局部巨噬细胞产生促炎信号[47]。此外,硅酸盐生物陶瓷支架中镁离子和钙离子的释放,通过诱导巨噬细胞抗炎反应,促进有利于组织再生的免疫调节作用[48]。

2.增强内源性干细胞动员与归巢:损伤部位通过增加损伤信号(如分泌的趋化因子、细胞因子或蛋白水解酶)刺激干细胞从生态位中排出的过程称为干细胞动员[49]。在组织修复过程中,骨髓来源的干细胞被动员到外周血中,以增加用于修复远处受损组织的再生细胞数量。被动员的干细胞感知损伤信号,从其生态位迁移到远处位点,参与组织修复的过程称为干细胞归巢[50]。

间充质干细胞(mesenchymal stem cells, MSCs)被局部移植到靶组织中,然后通过趋化因子梯度被引导至损伤部位。主要有5个步骤,即选择素的初始附着、趋化因子介导的激活、整合素调控的停滞、基质重塑因子辅助的渗透,以及趋化因子梯度引导的血管外迁移[1]。(1)初始附着与滚动:循环中的MSCs通过表面分子(如CD44、CD29/CD49整合素)与内皮细胞P-选择素结合(半乳糖凝集素-1或CD24也可能参与),启动沿血管壁的滚动过程。半乳糖凝集素-3与整合素介导细胞-基质黏附[51-53]。(2)趋化因子介导的激活:损伤组织释放的趋化因子,尤以SDF-1模拟肽为核心,激活MSCs表面的CXC趋化因子受体4(C-X-C motif chemokine receptor 4, CXCR4)。SDF-1由骨髓微环境细胞产生,损伤后局部浓度升高,通过SDF-1/CXCR4途径驱动MSCs向损伤部位定向迁移[49, 54-55]。生物材料(如负载SDF-1或其模拟肽的水凝胶/支架)可增强此募集过程[56-58]。(3)整合素介导的停滞与黏附:SDF-1等趋化因子激活MSCs表达的整合素,如极迟抗原4(very late antigen, VLA-4),使其与内皮细胞上的血管黏附分子-1(vascular cell adhesion molecule-1, VCAM-1)牢固结合,促使细胞停滞并形成迁移孔结构。VLA-4/VCAM-1相互作用对MSCs跨内皮迁移至关重要[26, 59-60]。靶向整合素的干预策略有助于MSCs在组织中的滞留[61]。(4)基质重塑与渗透:MSCs分泌MMP,降解内皮基底膜及细胞外基质以利于迁移。MMP(如MMP-2)的过表达增强侵袭能力,其与CXCR4协同促进迁移,生物材料可通过递送因子调控MMP表达,从而加速修复[62-64]。(5)趋化因子梯度引导的血管外迁移:MSCs最终受损伤部位释放的趋化信号,如炎症因子白细胞介素6(interleukin-6, IL-6)、IL-8、肿瘤坏死因子α(tumor necrosis factor-α, TNF-α)以及生长因子VEGF-A、血小板源性生长因子(platelet-derived growth factor, PDGF)、胰岛素样生长因子1(insulin-like growth factor 1, IGF1)等引导,穿透内皮屏障进入组织间隙,定向迁移至炎症或损伤微环境[65]。

3.诱导巨噬细胞向M2表型极化:免疫调节分子和归巢因子可以共同递送,以确保通过调节巨噬细胞向M2型极化来增强内源性干细胞的募集。例如,将肝素和P物质共价固定在聚丙交酯己内酯支架表面,通过巨噬细胞向M2型极化可抑制血栓形成,并募集MSCs促进大鼠皮下缺损的血管再生[66]。在没有归巢因子的情况下,多孔结构可以通过刺激M2型巨噬细胞极化提供干细胞募集能力,如34 μm微孔聚己内酯支架能够将大量巨噬细胞募集到支架表面,并诱导M2型巨噬细胞极化[67]。此外,α-半乳糖苷纳米颗粒介导内源性干细胞的归巢,通过局部补体激活使巨噬细胞极化为M2型促修复细胞。这些巨噬细胞分泌各种细胞因子,包括诱导新血管形成的VEGF和将干细胞归巢到损伤部位的细胞因子,从而促进受损组织修复和再生[68]。

六、总结与展望

机体具有先天组织修复能力,内源性干细胞可以分泌生长因子和细胞因子,调节炎症与免疫反应,促进血管生成,与其他细胞协同作用直接参与组织修复,同时分化成不同细胞以补充受损组织结构。干细胞原位激活再生利用干细胞的再生潜力恢复受损皮肤软组织的结构和功能,有望为皮肤软组织无瘢痕修复重建提供一种新的可能。其主要作用及机制在于通过生物材料的物理特性与化学特性调控微环境、触发内源性免疫反应,进而增强内源性干细胞的分化、增殖、动员与归巢,最终促进皮肤受损组织原位修复;还可以诱导巨噬细胞向M2型极化,协调受损组织的再生。

尽管干细胞原位激活再生的相关研究在组织工程和再生医学领域已取得进展，但目前相关技术转化为临床应用较少，主要原因为对干细胞再生过程的控制能力有限[5]。用于原位组织再生的生物材料具有与体内微环境相互作用并使其改变的能力，其安全性和有效性尚需进一步验证。此外，干细胞原位激活再生可能不适用于干细胞数量减少或存在干细胞功能障碍的组织。因此，未来需要深入探索各种生物材料的作用机制，以期实现其在皮肤软组织损伤修复领域的临床应用及发展。

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