

肩袖腱 - 骨愈合在组织工程学领域的研究进展

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摘 要

肩袖损伤后腱 - 骨界面原有组织遭到破坏, 大量纤维瘢痕组织新生填充, 腱骨界面缺失组成、结构以及力学等自身固有的典型移行渐变特征, 造成应力过于集中、界面失效, 引发肩袖再撕裂。目前, 种子细胞、支架和生物活性分子的三维修复方式是组织工程技术不断发展的方向。因此, 深入了解腱 - 骨界面结构组成及其修复过程发生机制, 积极寻找促进腱 - 骨愈合的组织工程学技术改善肩袖损伤疗效至关重要。基于目前对于腱 - 骨愈合的认识, 本文拟对近年来组织工程技术在促进肩袖腱骨愈合方面的研究进展予以系统综述与归纳总结, 旨在增进临床医务人员对肩袖损伤病理学机制的深入理解, 以期对肩袖损伤的临床诊疗提供新颖的治疗策略与思路。

关键词

肩袖损伤, 腱 - 骨愈合, 组织工程学, 间充质干细胞, 生物材料, 低氧浓度环境

Study Advances in Rotator Cuff Tend-Bone Healing in the Field of Tissue Engineering

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Abstract

In the aftermath of a rotator cuff injury, the initial tissues comprising the tendon-bone interface undergo destruction, giving rise to the formation of substantial fibrous scar tissue. The tendon-bone interface is characterized by a lack of inherent composition, structure, and mechanics. These

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characteristics are typically associated with processes of migration and gradual change. Currently, the three-dimensional repair approach involving seed cells, scaffolds, and bioactive molecules represents the evolving direction of tissue engineering technology. The field of tissue engineering technology is undergoing continuous development, with a focus on three-dimensional repair methodologies that utilize seed cells, scaffolds, and bioactive molecules. Therefore, it is imperative to comprehend the structural composition of the tendon-bone interface and the mechanism of its repair process. Moreover, there is an active need to search for tissue engineering techniques to promote tendon-bone healing to improve the efficacy of rotator cuff injuries. Based on current understanding of tendon-bone healing, this paper aims to provide a systematic review and summary of recent research progress in tissue engineering techniques for promoting rotator cuff tendon-bone healing. The objective is to enhance clinical practitioners' understanding of the pathological mechanisms underlying rotator cuff injuries, thereby offering novel therapeutic strategies and insights for the clinical diagnosis and treatment of such injuries.

Keywords

Rotator Cuff Injury, Tendon-Bone Healing, Tissue Engineering, Mesenchymal Stem Cell, Biomaterials, Low-Oxygen Concentration Environment

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1. 前言

腱-骨界面(Tendon-Bone Interface, TBI)由四层介于骨骼与肌腱组织间的渐变结构组成[1], 承担骨骼肌收缩产生的应力传导并维持稳定各肩关节的正常活动[2]。高度连续性和移行渐变性是腱-骨界面组织结构及力学传导的典型特征, 为界面不同组织间的稳定连接以及应力传导提供了可靠的保证, 避免腱-骨界面力学传导应力集中的发生, 降低界面失效发生的风险[3]。腱骨界面在肩袖损伤后伴随不同程度的结构破坏, 现有治疗手段均会在腱骨交界处新生大量纤维瘢痕组织取代天然肌腱组织, 肩袖组织结构的完整性和连续性遭受破坏, 难以实现牢固的腱骨愈合(Tendon-Bone Healing, TBH), 使交界处发生应力集中、界面失效, 造成肩袖再撕裂[4]。

组织工程学(Tissue Engineering, TE)在腱-骨愈合的研究主要包括以下几个方面: 种子细胞、生长因子、生物支架材料等[5], 如何有效安全地运用组织工程学促进腱-骨愈合已成为肩袖损伤修复治疗的关键和热点问题。近年来, 在大量学者的不懈努力下, 针对上述问题的研究已取得新的进展, 大量关于应用组织工程学还原天然腱-骨界面结构的文章已发表。因此, 本文将针对肩袖腱骨愈合在组织工程学方面的最新研究成果展开整理与综述工作, 以期推动肩袖损伤在组织工程领域不断开拓创新, 为肩袖损伤患者带来更加安全可靠、切实有效且长期稳定的临床干预策略。

2. 种子细胞

腱-骨愈合界面组织工程有两种来源的种子细胞[6], 一种是终末分化的成熟体细胞, 即能够直接补充损伤区域的功能细胞, 包括软骨细胞、成纤维细胞、成骨细胞等[7]; 另一种为未分化状态的干细胞, 其核心特征自我增殖及多向分化潜能, 可在特定微环境诱导下定向分化为功能成熟的终末细胞。干细胞根据细胞来源不同可分为胚胎干细胞、人类诱导多能干细胞和间充质干细胞, 胚胎干细胞的研究发展

受伦理限制而人类诱导多能干细胞的治疗效果又充满不确定性, 因此组织工程领域研究最多的种子细胞仍是间充质干细胞[8]。间充质干细(Mesenchymal Stem Cell, MSC)获取来源广泛, 可从骨髓(骨髓间充质干细胞, BMSCs)、脂肪(脂肪源性干细胞, ADSCs)和肌腱(肌腱来源性间充质干细胞, TDSCs)等部位获得[9]。

2.1. 骨髓间充质干细胞

骨髓间充质干细胞(Bone marrow derived Mesenchymal Stem Cells, BMSC)来源于骨髓组织, 可分化成多种类型细胞, 如脂肪细胞和成骨细胞等, 还能释放外泌体促进组织修复, 在人体临床研究和动物实验研究中均表现出良好的促腱-骨愈合能力[10], 是目前腱-骨愈合领域中研究最为广泛、最为重要的种子细胞[11]。史[12]等将负载羊膜间充质干细胞(hAMSCs)和脂肪干细胞(ADSCs)的生物支架植入大鼠后, 发现该支架在腱骨界面处不仅表现出良好的生物组织相容性, 还有利于肌腱-骨交界处胶原纤维的生成, 促进肩袖组织的修复再生。

2.2. 脂肪间充质干细胞

脂肪间充质干细胞(Adipose-derived Mesenchymal Stem Cells, ADSCs)是一种易从脂肪组织获取的干细胞[13], 分离出的 ADSCs 增殖速度快, 在成脂、成骨、成软骨和成肌腱方面具有很大的潜能[14]。Higa 等[15]发现将含 ADSCs 的支架植入前交叉韧带断裂重建术(ACL)兔中, 装载 ADSCs 的材料能够促进腱骨组织愈合。

研究发现, 力学刺激对软骨和肌腱的形成、稳态及功能意义重大[16], 合适的力学刺激有助于腱-骨界面生物发育并进行有效的力学传导, 避免发生应力集中[17]。利用组织工程技术研发出的生物反应器可以模拟人体生理器官的力学环境, 对细胞施加不同程度的力学刺激诱导细胞进行增殖、分化[18], 从而在体外形成用于修复的新组织[19]。董等[20]研发出具有磁响应特性的仿生包膜, 模拟天然包膜从而复制体内所经历的机械力, 用于骨修复。另外, 其他干细胞肝源性干细胞(LDSCs)、皮肤来源干细胞(SDSCs)、骨膜源干细胞(PDSCs)和尿源性干细胞(UDSCs)等在腱-骨界面修复中也表现出成骨、成肌腱细胞分化的潜力[21], 未来可作为组织工程替代的细胞资源。

3. 生长因子

生长因子是由炎症细胞、血小板和成纤维细胞产生的一种多肽信号分子[22], 又称多肽生长因子[23], 诱导细胞增殖分化并参与机体炎症反应, 对组织的修复和再生至关重要[24]。研究表明, 局部生长因子的使用有助于肩袖愈合, 如骨形态发生蛋白(BMP)、转化生长因子(TGF)、成纤维细胞生长因子(FGF)、血管内皮生长因子(VEGF)、血小板源性生长因子(PDGF)及胰岛素样生长因子 1 (IGF-1)等[25]。王等[26]观察到 TGF- β 的局部注射可有效地阻止肌腱疾病的进展。姚[27]等发现 dTDSC (脱细胞化的肌腱来源干细胞)包裹的肌腱移植通过增强 BMP-2 和 VEGF 介导的骨形成和血管生成, 促进大鼠前交叉韧带重建(ACLR)重建后肌腱组织的修复。王等[28]发现小鼠在注射含 BMP2 (骨形态发生蛋白 2)和 sVEGFR1 (可溶性血管内皮生长因子受体 1)水凝胶后, 肩袖界面出现大量排列有序的胶原纤维、纤维软骨及新生骨, 有效促进肩袖组织的愈合。

富血小板血浆(PRP)内富含血小板和诸多生长因子(如 VEGF、PDGF、TGF- β 和 IGF-1) [29], 在促进肌肉、肌腱、韧带和骨组织愈合过程中生物学优势明显[30], 是肩袖组织修复与再生领域的研究热点。大量临床和基础实验表明 PRP 治疗诱导腱骨愈合, 如张等[31]发现 PRP 联合转染 FGF-2 基因的 hAMSCs 有效增强兔关节的腱骨愈合; 陈等[32]通过评价多项荟萃分析发现使用 PRP 的患者肩袖发生长期再撕裂的情况明显减少, 临床疗效得到显著改善。不过 PRP 中生物因子作用机制及作用浓度尚未明确, PRP 的制

备方式及注射间隔时间、注射部位(腱周或腱内)也尚未统一,故 PRP 对肩袖损伤的具体疗效仍有待商榷[33]。此外,制备应用于生物活性物质的成本偏高,在临床实际工作中需考虑患者的经济条件。生长因子通过影响细胞增殖、分化,刺激胶原纤维和新骨的形成,增加新骨组织生成的数量,促进腱骨界面愈合,不过生长活性物质的作用发生机制和生物学效应较为复杂,未来还需科研人员结合多学科技术研发出在体内可调控生长因子持续、稳定释放的组织工程材料,尽早实现生物活性分子的精准治疗。

4. 生物支架材料

理想的生物支架材料应该具有良好的组织相容性、生物活性及力学性能以便种子细胞黏附增殖和分化,还应具备生物可降解性和临床可操作性等植入材料[34]特定,为组织修复再生提供良好的再生微环境和新生组织的结构支撑[35]。生物支架材料种类繁多,涵盖生物陶瓷、生物合金、高分子材料及其他复合材料[36],按照来源不同分为天然生物材料和合成高分子材料[37],天然材料包括天然高分子材料(如纤维素、壳聚糖)和经过特殊处理的天然组织(小肠黏膜下层、脱细胞基质),合成材料涉及人工合成高分子支架材料(如聚乳酸、超高分子量聚乙烯)及复合支架材料等[38]。如今为满足不同组织界面的结构特性,大量设计制备支架材料的技术应运而生,例如 3D 打印、脱细胞化、化学交联、物理吸附、冷冻干燥、纺织(例如针织或编织)、静电纺丝、冷冻干燥、溶剂浇铸法及挤压盐浸或熔压等[39]。杜等[40]通过 3D 生物打印技术制备的仿生多细胞支架可以模拟腱骨界面的层次结构及细胞组成,营造利于腱骨再生的良好微环境,促进腱骨界面组织的修复。多技术的巧妙应用能够将生物材料设计制造为水凝胶、纳米微粒、三维多孔固态支架、纤维网络等多种形式,还可以根据不同组织界面愈合的需求对材料表面进行修饰。如朱等[41]借助 3D 打印技术设计制备的负载温敏性胶原水凝胶的多孔钛支架复合系统促进 BMSCs 的增殖分化,帮助腱骨界面结构的恢复。白等[42]利用静电纺丝技术制备出的双三相微纤维支架(DTSs)生物力学特性良好,能够增强细胞分化、重塑脂质组学(如磷脂酰胆碱和磷脂酰丝氨酸等参与脂质代谢的重要成分)特征,促进肩袖肌腱-骨组织的愈合。

此外,有学者还在支架中添加种子细胞及生长因子等可调控的生物活性物质来模拟细胞外基质微环境[43],构建具备仿生拓扑结构的三维支架体系,通过表面功能化修饰与孔隙率梯度调控,实现细胞-材料界面生物信号的时空动态呈递,从而诱导定向细胞黏附、迁移及多谱系分化。例如袁等[44]研发出一种封装有 ADSCs 和 BMP-2 等生长因子的多孔透明质酸甲基丙烯酸酯水凝胶,重塑肩袖损伤大鼠模型的纤维软骨过渡区,通过对腱骨界面高度特异性结构特征的还原助力肩袖修复。适当的炎症反应有助于组织修复启动,反过来过度炎症会阻碍组织修复进展、延缓腱-骨界面的愈合,导致损伤部位病理性纤维化或疤痕结构的形成,降低损伤部位生物材料的预期功能[45]。因此腱-骨界面周围三维微环境的重建特别是体内免疫细胞引发的炎症反应对肩袖损伤的愈合至关重要[46]。充分认识巨噬细胞在腱骨愈合过程中发挥的调节作用,实现对巨噬细胞不同表型极化的精准调控,推动生物材料创新发展[47]。例如杜等[48]将具有免疫调节功能的多细胞支架用于肌腱-骨骼再生,表现出良好的生物相容性。功能性生物支架的研发是当前组织工程学发展进程中的核心关注领域,必须指出的是,多数新型生物支架仅在静态细胞培养下探讨修复效果,往往忽视了力学刺激对腱-骨界面愈合的影响。未来研究应结合交叉学科特点,利用组织工程技术研制出负载相关种子细胞及生长因子的生物支架材料,结合动态培养系统来控制环境中的力学刺激,制备出具有梯度变化的材料界面,加强支架对干细胞的调控,最终实现腱-骨界面的有效愈合。

5. 低氧浓度环境

氧气作为人体多种组织器官发育形成及维持的重要因素,在不同类别的组织间出现浓度变化[49],如

在骨组织的氧浓度介于 5.5%~15%之间,肌腱组织含氧量为<5%,而软骨中的氧分压为 1%至~5% [50]。腱-骨界面的氧含量与周围微环境中影响干细胞成骨分化、成肌腱分化等其他因素一直备受组织工程学者的关注。张[51]等发现涂覆 DFOA (去铁胺)的 PCL (可降解聚酯材料)支架通过有效模拟人体肌腱组织所处的缺氧环境,增强组织再修复能力。肩袖损伤引发腱-骨界面发生血供缺乏,进而出现周围环境氧含量不足。陈等[52]发现低氧环境能够增加 ALP (碱性磷酸酶)含量并增强 OCN (骨钙素)和 OPN (骨桥蛋白)等成骨相关因子的表达,提高 BMSCs 成骨分化能力,增加骨形成数量。如 Fredianto 等[53]观察到间充质干细胞(SH-MSC)进行缺氧预处理后 HIF-1 α 和 bFGF 基因表达增加,促进急性肩袖撕裂大鼠腱-骨界面的愈合修复。现已有学者根据肩袖损伤后组织极度低氧环境的病理改变,设计制备出在损伤局部缓释氧气的修复支架材料。邓等[54]发现引入释氧成分和免疫细胞的骨类器官相较于传统骨类器官表现出优越的骨再生和骨整合性能,可以更好地模拟骨修复环境。氧浓度对干细胞的生理功能影响深远,并且细胞所处的氧环境与腱-骨界面细胞、结构组成以及力学性能均呈现梯度变化的结构特征,故氧含量的不同对干细胞的分化作用仍需要深入研究。同时,鉴于肌腱和骨组织中含氧量存在的差异性[55],因而设计生物支架时还应探索各部位细胞向成肌腱、成软骨和成骨分化的最佳氧浓度。

6. 基因治疗

基因治疗通过修复、替换或调整患者体内缺陷的基因来治疗或治愈疾病,在腱-骨修复的研究主要集中在促进骨细胞增殖、分化和骨组织再生方面[56]。基因工程技术将特定基因加载至种子细胞内以可持续的形式分泌适量内源性治疗分子传递作用于局部组织,提高了成骨效果,避免了传统骨组织工程中整合外源性蛋白过量造成的致瘤和免疫风险[57]。目前最普遍的基因递送手段是使用基因载体包裹目的基因来隔绝体内核酸酶的破坏作用,同时基因载体易于进行化学改性,可以提升基因载体复合物的稳定性和对目标组织的靶向能力[58]。其中,非病毒载体比病毒载体具有安全性高、修饰方法多及导入方式便捷等优点,避免了病毒载体的免疫原性、致癌效应等不足,是一种理想的基因递送工具,具有广阔的应用前景,尤其以纳米粒子为代表的非病毒载体展现出巨大的研究潜力[59]。基因治疗现已取得了很大的进展,体外实验以及动物、人体研究中均提示基因治疗的有效性及安全性,为广大患者提供了更为有效的个性化治疗,在疾病治疗方面拥有巨大的发展潜力。钱等[60]发现负载 si-CD248 的脂质体对 CD248 进行靶向干预能够显著恢复 TSPC 的再生潜能,为改善骨质疏松患者的腱骨愈合效果提供了一种极具前景的治疗策略。不过,基因治疗这一领域还存在许多局限性及安全问题需要考虑,如脱靶效应、相关蛋白自身的免疫原性等治疗安全性、有效性[61]。鉴于目前基因技术发展的局限性,最终实现基因编辑产品在临床的应用仍面临着许多亟需解决的问题。唯有推动生物医学前沿技术发展,方可实现基因治疗从基础研究到临床转化的关键跃迁,奠定基因治疗作为未来创新型个性化治疗方案的战略地位。

7. 小结

肩袖损伤带来的肩关节局部疼痛、活动受限给患者的生活造成了诸多不便,而腱骨界面对肩袖组织的修复再生至关重要。腱-骨界面是由梯度变化的细胞、组织有序排列组成的特异性结构,多种因素协同参与调控腱骨的愈合过程。组织工程学在腱骨组织再生领域中有着很大的优势,为促进肩袖损伤腱骨的修复提供了创新性的治疗思路,例如种子细胞、生物支架、生长因子、低氧浓度环境、基因治疗等。如何将肩袖损伤已破坏的腱骨组织还原为最初梯度变化的界面结构仍是目前肩袖修复的重点和难点,同时组织工程学在腱骨愈合的研究大多停留在基础研究,还需研究者尽快推进实现临床治疗的转变。未来的研究需深入研究探索腱骨愈合的具体机制,充分利用组织工程技术设计制备出精准调控腱骨界面组织修复的生物材料,实现腱骨界面原有结构的精准还原及功能性愈合。

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