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· 综述 ·

水凝胶作为骨免疫调节性生物材料的研究进展

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【摘要】 随着对生物材料、免疫系统与骨骼系统关系研究的不断深入, 依据骨免疫学, 通过合理设计材料的性质可调节植入材料引起的宿主反应, 具有免疫调节性骨组织工程支架可诱导巨噬细胞及时从促炎 M1 型转换为抗炎 M2 型, 促进骨整合。水凝胶在骨组织工程中备受关注, 水凝胶组成的不同, 包括来源、组分含量及分子量、偶联连接蛋白、使用交联剂等均会影响免疫反应, 对水凝胶的理化性质进行改性亦可影响免疫反应, 如软光刻等处理水凝胶形成的不同表面微形貌, 加入酶敏感序列、酯键及使用动态共价化学等避免水凝胶降解过快或过慢, 添加制孔剂、3D 打印等制备具有互通大孔的水凝胶, 柔软可注射水凝胶等, 可减少促炎因子表达, 促进巨噬细胞分化为 M2 型及减少异物反应, 促进骨再生。然而骨免疫反应机制尚未阐明, 需要进一步研究不同理化性质的水凝胶对免疫调节的具体机制。

【关键词】 水凝胶; 理化性质; 骨免疫学; 骨再生; 免疫反应; 异物反应; 巨噬细胞; 交联

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【Abstract】 With the advances in understanding the relationships among biomaterials, the immune system and the skeletal system, the host responses elicited by implanted biomaterials can be balanced by properly designing material characteristics from the perspective of osteoimmunology. The immunoregulatory properties of bone tissue engineering scaffolds provide advantages for inducing macrophages from the proinflammatory M1 phenotype to the anti-inflammatory M2 phenotype and promoting osseointegration. Hydrogels are increasingly a focus in bone tissue engineering, and the immune response can be affected by different compositions of hydrogels, such as the sources, concentration, molecular weight, coupling with fibronectin, and the addition of cross-linking agents. Different physicochemical properties of modified hydrogels can trigger different host immune responses, modified by using soft photolithography to fabricate micropatterned hydrogels, adding enzyme-sensitive sequences, ester bonds and dynamic covalent chemistry to prevent rapid or slow degradation of the hydrogels, and adding porogens and 3D printing to modify the hydrogels with macroporous interconnective pore structures, soft and injectable hydrogels, etc. These optimized hydrogels can reduce proinflammatory factors, promote M2 macrophage polarization, and minimize foreign body reactions to evoke bone regeneration. However, the mechanism underlying the bone immune response is still poorly understood, and further study of the effects of hydrogels with different physicochemical properties on immune regulation is needed.

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目前临床中口腔骨缺损修复的常用方法是自体骨和骨替代材料移植,但自体骨可用性有限、骨替代材料组织利用率低及异物反应等使其临床应用具有一定局限性^[1]。理想的骨组织工程(bone tissue engineering, BTE)支架需具备包裹成骨细胞和成骨因子的三维结构,提供足够的力学性能,促进血管化。然而目前尚未开发出理想的BTE支架,多数BTE支架只能满足部分要求。水凝胶具备柔韧且多孔的三维结构,允许营养物质和氧气有效扩散,可携带并缓释细胞因子和药物,促进组织修复^[2]。水凝胶含水量>95%,可一定程度模拟天然组织微环境结构^[3],可注射水凝胶可微创使用,尤其适用于牙槽骨缺损等不规则缺损。依据骨免疫学观点,材料-免疫系统-骨骼系统相互影响,可通过交联、接枝、改变水凝胶组成等方式对水凝胶的理化性质进行改性,调节植入体内的免疫反应,促进骨愈合。本文将就不同改性水凝胶的理化性质对免疫反应,尤其是对巨噬细胞(macrophages)的影响作一综述。

1 骨再生与免疫

所有生物材料植入后均会引起宿主免疫反应,在骨组织再生中,可利用免疫反应增强生物材料与组织整合,这种生物材料-免疫系统-骨骼系统的相互作用即骨免疫学^[4],包括多种细胞、细胞因子和信号通路,对于材料介导的组织再生至关重要。当生物材料被植入骨缺损中后,蛋白质立即吸附在生物材料表面,形成富含生长因子、细胞因子的血凝块,能够将先天免疫细胞招募到损伤部位,在细胞募集之后,随之而来的急性和慢性炎症的严重程度取决于植入生物材料的类型^[5]。

在所有免疫细胞中,巨噬细胞是参与生物材料诱导免疫反应的最重要的效应细胞之一。巨噬细胞可通过Toll样受体(Toll-like receptors, TLR)及核因子 κ B(nuclear factor kappa B, NF- κ B)激活为不同的表型,大致可分为促炎型(M1型)和抗炎型(M2型)。在急性炎症的早期阶段,M1型占主导地

位,其通过分泌白细胞介素(interleukin, IL)、肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α)等促炎因子,引起局部炎症及促进破骨细胞分化^[6],M1及其分泌的因子在骨再生过程中是必不可少的,如白细胞介素-1(interleukin-1, IL-1)基因敲除的小鼠会出现骨生成延迟^[7]。M2型在后期占主导地位,分泌抗炎因子和促骨生成因子,如白细胞介素-4(interleukin-4, IL-4)、白细胞介素-10(interleukin-10, IL-10)及转化生长因子- β (transforming growth factor- β , TGF- β)、骨形态发生蛋白及血管内皮生长因子^[8]。

从促炎状态到抗炎状态的及时转换对骨成功愈合至关重要,如持续高水平的M1型反应将导致以纤维包裹和植入物隔离为特征的异物反应(foreign body reaction, FBR)和慢性炎症,延迟组织愈合^[9]。再生医学一个策略是开发优化生物支架,赋予其免疫调节特性,以精确的协调M1型与M2型极化^[10]。水凝胶中的化学性能包括连接蛋白、成分等,物理性能包括水凝胶的刚度、降解率、表面微形貌和孔隙大小等,均可调节巨噬细胞极化。

2 水凝胶的理化性能对免疫反应的影响

2.1 水凝胶的组成

水凝胶的性质很大程度上取决于其组成,水凝胶分为两大类,①天然水凝胶,包括多糖类、蛋白质类、脱细胞基质类;②合成水凝胶,包括聚乙二醇(polyethylene glycol, PEG)等。调节水凝胶组成,包括来源、含量、分子量,或进行接枝、交联等,均会引起免疫反应的变化。

明胶来源于I型胶原,保留了细胞识别的功能基团,具有较低的抗原性,明胶酶将明胶降解成多肽后,多肽进一步降解为氨基酸,具有很高的生物相容性^[11],可注射的明胶基微带水凝胶(gelatin-based microribbons),植入体内第3天可见M1型募集,第2周被M2型取代,并支持血管化,加速骨再生^[12]。

透明质酸(hyaluronic acid, HA)是一种糖胺聚

糖,通过透明质酸酶、软骨素酶、己糖氨基酶等酶以及活性氧降解为单糖^[13],HA通过表面受体CD44与细胞相互作用,影响细胞功能,这种作用依赖于HA的分子量,低分子量HA片段可导致巨噬细胞炎症因子表达升高。当HA被切割成更小的片段时,这些片段可诱导M1型反应激活^[14]。HA含羧基、羟基和乙酰基,可进行化学修饰,及通过氢键、离子相互作用、金属离子辅助行物理交联,从而改变材料的性质^[15]。

壳聚糖在中性水溶液中不溶解,限制了其应用。羧甲基壳聚糖作为壳聚糖的水溶性衍生物,具有优良的生物相容性、可控的生物降解性、良好的成骨能力^[16]。壳聚糖水凝胶由于其固有的抗炎和促进愈合的特性^[17],在大鼠牙周缺损模型中,与阿托伐他汀联合PEG相比,壳聚糖增强了与阿托伐他汀相关的抗炎作用^[18],显著促进牙槽骨愈合。乙酰化度(degree of acetylation, DA)为4%的壳聚糖水凝胶植入大鼠可诱导巨噬细胞向M2型极化,DA为38%壳聚糖水凝胶植入后诱导促炎因子如白细胞介素-6(interleukin-6, IL-6)分泌,不能促进组织再生^[19],然而DA为40%壳聚糖加入纤维蛋白水凝胶中后IL-6表达未上调,可能是因为由于纤维蛋白网络限制了壳聚糖与组织接触^[20]。

海藻酸盐及多数人工合成水凝胶,由于不含黏附蛋白,蛋白质吸附性低。有研究发现材料对巨噬细胞的影响与蛋白质吸附的厚度有关,吸附较厚蛋白质层会促进巨噬细胞向M1型极化,吸附较薄蛋白质层可促进M2型极化^[21],将PEG植入体内,有研究发现纤维包裹厚度降低^[22],也有研究发现纤维包裹厚度增加^[23],但黏附蛋白修饰的黏附蛋白水凝胶周围的纤维包裹均较薄^[24]。

海藻酸盐、HA及壳聚糖为天然多糖,允许离子相互作用,形成离子交联的动态水凝胶,这些水凝胶的性质可通过改变组分的分子量、Ca²⁺浓度或接枝短PEG来调整,如壳聚糖水凝胶中加入Cu²⁺可促进壳聚糖链间的形成氢键作用,随着Cu²⁺含量增加,水凝胶的交联度、孔径、抗拉强度均增加^[25]。不同的交联剂可能会引起不同的免疫应答,京尼平、戊二醛等化学交联剂被用于水凝胶的交联时会引起不同程度炎症反应。生物交联剂如谷氨酰胺转氨酶可催化明胶等蛋白质多肽发生分子内和分子间共价交联,不会促进炎症反应^[26]。

从仿生的角度,有机和无机成分的结合可制备类似骨组织材料,羟基磷灰石是骨的主要无机成分,具有非免疫原性、多孔表面等性能^[27]。将羟基磷灰石晶体、氧化镁晶体均匀固定于半胱氨酸

修饰的 γ -聚谷氨酸水凝胶,羟基磷灰石的加入显著降低了水凝胶的孔径并提高了机械性能,且通过缓释Mg²⁺,减少M1型浸润及增加血管生成^[28]。

2.2 水凝胶的表面微结构

材料表面微结构会影响细胞的附着和表型,合理设计“免疫导向”的微结构可调节巨噬细胞极化。目前可通过光刻技术、3D打印技术等使水凝胶形成特定的表面微形貌。水凝胶表面微结构可通过调节整合素介导的机械转导决定细胞命运,Vassey等^[29]采用高通量筛选以确定焦点黏附(微柱)和细胞伸长(微槽/脊)对巨噬细胞表型和功能的影响,发现微柱的面积及密度的组合可调节巨噬细胞表型。在更小、更密集的直径为5 μ m的微柱表面附着率最高且显示高M2/M1比率,在沟槽形表面显示出高M1/M2比率,然而不同形貌(微槽/脊、微柱)的甲基丙烯酸酯化明胶上的巨噬细胞的细胞形态无显著差异,无典型的M1或M2标记谱,但微形貌处理水凝胶中TNF- α 表达显著减少^[30]。

2.3 水凝胶的降解率

水凝胶的结构稳定性可提供一个物理屏障保护被包裹的细胞免受外来不利因素的影响,是理想的因子及药物释放动力学所必需的。巨噬细胞和淋巴细胞等会通过观察细胞间隙和动态细胞外基质迁移至靶部位发挥作用,HA、壳聚糖、胶原蛋白等天然聚合物与体液接触时可被酶迅速降解^[31]。相比2周降解50%的支架,1周降解50%的支架中M1比例增加^[32]。海藻酸盐及大多数合成聚合物,在人体缺乏特定的分解代谢酶,会导致M1长期高水平存在并形成纤维包裹^[33]。

大多数水解型水凝胶的降解机理是酯键的水解,可通过改变水凝胶中酯键数目控制降解速率^[34],其次,可将酶敏感序列嵌入缓慢降解水凝胶^[35]。再者,海藻酸钠主链可氧化生成氧化海藻酸钠^[36],与海藻酸盐相比,氧化海藻酸盐具有较高的活性和更快的降解率。最后,动态共价化学包括可逆加成反应(如希夫碱、硼酸盐及双烯加成反应)、可逆交换反应(如二硫和硫酯反应),通过将聚乙二醇双丙烯酸酯、二硫苏糖醇和硼砂溶液混合获得葡萄糖敏感的水凝胶,硼砂不仅作为可逆加成反应的催化剂,还与二硫苏糖醇反应形成了硼酸键,协同改变水凝胶降解率^[37]。

2.4 水凝胶孔径和孔隙率

孔径和孔隙率是细胞迁移、血管化以及支架与周围组织相互作用所需的重要支架结构特征,生物材料应该具有合适的孔径,较大的孔径有利于营养物质等交换,从而有利于成骨成血管及减

轻炎症反应,如孔径为100~200 μm 的水凝胶可促进成骨细胞增殖分化,160 μm 孔径中M2型标记物表达增加^[38]。使用二甲基亚砜调节低温过程中冰晶形成的孔径调节明胶支架的孔径,孔径增加后M2型标记物表达增加,同时需考虑过大的孔径会影响支架的机械强度。此外孔隙率也会影响免疫反应,非多孔支架在体内虽炎性细胞浸润最少,但其周围会形成较厚的纤维包裹影响愈合,多孔支架促进炎症细胞浸润,但主要为M2型^[39]。因此对水凝胶孔隙率和孔径,需综合考虑其对细胞迁移、血管化、免疫反应、水凝胶强度的影响。

2.5 水凝胶的硬度

细胞通过机械转导来感知和响应微环境,将机械信号转化为生化信号,从而调节生理过程,二维基质中成骨分化主要发生在硬度为30~40 kPa的水凝胶^[40],三维水凝胶中,水凝胶的高硬度需要高浓度的主链聚合物或高交联度来实现,不仅降解所需时间长,且需高水平的酶,不利于细胞迁移及基质改建,且可能会增强炎症反应,影响骨愈合^[29]。有研究证明缓释骨形态发生蛋白-2(bone morphogenetic protein-2, BMP-2)的可注射可降解的软水凝胶(0.5 kPa)植入体内可实现良好的骨再生^[41]。基质硬度会影响巨噬细胞极化及迁移速度,在高硬度水凝胶中,巨噬细胞迁移较慢且M1型比例明显升高,促炎因子表达增高,纤维包膜的厚度增加,低硬度则相反。此外,巨噬细胞对间充质干细胞分化具有重要调控作用,不同硬度谷氨酰胺转氨酶交联明胶中培养单一细胞时,高硬度水凝胶支持成骨分化,当二者共培养,低硬水凝胶中巨噬细胞倾向于极化为M2型,并促进间充质干细胞成骨分化,高硬度则相反^[26]。这可能解释了高硬度的凝胶在体内修复骨缺损效果欠佳的原因。

3 总结及展望

本文通过对现有研究的回顾,总结了不同改性方法处理水凝胶后其理化性质对骨免疫的调节作用。水凝胶的不同组成、来源、分子量等可影响巨噬细胞极化,通过接枝、交联等修饰水凝胶的不同理化性质,如含有细胞黏附位点、降解速率匹配骨生成速率、大孔径、柔软的水凝胶可降低促炎反应并减少纤维包裹厚度,促进骨生成。

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