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金属材料修复临界性骨缺损的实验研究进展

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摘要:金属支架材料是近年来新兴的骨组织工程支架材料之一,包括可降解金属支架材料和不可降解金属支架材料。金属支架材料生物相容性良好,耐腐蚀性强,力学性能优,相比传统支架材料,其机械强度更高,可为新组织生长提供良好的支撑,适用于临界性骨缺损(CSD)的修复,虽处于实验研究阶段,临床应用较少且时间较短,还有待进一步研究,但不可否认其在修复CSD方面具有巨大的优势和潜力,未来可能成为骨科治疗CSD的植入材料。笔者对目前常用的金属支架材料的种类及特性进行简要综述。

关键词:临界性骨缺损；　骨组织工程；　金属材料

Experimental research progress in repairing critical size bone defects with metal materials

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Abstract:Metal scaffold is one of the emerging bone tissue engineering scaffold materials in recent years,including degradable metal scaffold materials and non-degradable metal scaffold materials. The metal stent material has good biocompatibility,strong corrosion resistance and excellent mechanical property. Compared with the traditional stent material,the metal stent material has higher mechanical strength,which can provide good support for the growth of new tissues and is suitable for the repair of critical bone defects. Although it is in the experimental research stage,with few clinical application and,short time and still needs further study,it is undeniable that it has great advantages and potential in repairing CSD,and may become an implant material for orthopedic treatment in the future. In this paper,the types and characteristics of commonly used metal stent materials are briefly reviewed.

Key words:Critical size bone defect;　Bone tissue engineering;　Metal material

临界性骨缺损(critical size bone defect,CSD),是骨愈合中的一种极端情况[1],常由某种原因,如骨肿瘤切除、创伤、感染、结核、骨髓炎清创术等导致部分骨质丧失[2],直接影响血管重建和组织分化,最终导致自发性骨折,未经干预便进展到不愈合。CSD的经典定义是“在特定骨和动物物种中,活体动物不会自发愈合的最小骨缺损”,或“在动物的一生中骨缺损的骨再生面积小于10%”[3]。但缺损大小并不是代表CSD的唯一参数[4],人们发现,大多数物种的骨缺损长度超过直径的1.5倍或2.0倍时可以考虑为最小尺寸[5]。CSD常常合并软组织损伤,严重影响缺损部位的血供,导致骨折处畸形愈合或愈合过程中无连续性骨痂形成,产生骨不连,造成患肢功能障碍,降低病人的生活质量[6]。CSD在治疗上存在手术时间长,出现并发症概率高等风险。

目前CSD的主要治疗方法包括①自体骨移植:自体骨移植是修复CSD的“金标准”,可以达到理想的骨愈合效果。然而,自体骨取材困难、来源有限,且取骨将不可避免地增加病人的疼痛和感染的风险[7];②异体骨移植:异体骨取材容易,来源丰富,具有自体骨优良的组织学特性。但因物种间抗原差异,常引起免疫排斥反应,导致感染和肿瘤的发生;同时,样品制备、处理和储存成本较高,因此限制了临床应用[8-10];③骨组织工程:骨组织工程将种子细胞、生长因子与支架材料相结合,促进新骨的再生和重塑,为CSD的修复提供了新方法[11]。传统的支架材料,如羟基磷

灰石、磷酸三氢钙、聚己内酯、生物活性玻璃等,修复骨缺损效果良好,但因机械强度不够,修复大型动物承重骨 CSD 时易断裂;同时,其只有骨传导性和生物相容性,而不具备成骨性和骨诱导性,不能达到理想支架材料的全部性能[12]。

金属支架材料生物相容性良好,耐腐蚀性强,力学性能优,相比传统支架材料,其最大特点为机械强度更高,可为新组织生长提供良好的支撑,有效避免植入物与皮质骨间极低的骨内应力变和骨吸收,促进骨向植入物内生长,增强骨组织与植入物的结合强度,适用于 CSD,特别是承重部位 CSD 的修复[13],以及股骨和肱骨等长骨大段骨缺损的修复。笔者就目前金属材料修复 CSD 的相关研究做一简要综述。

1　不可降解金属材料对 CSD 的修复作用

1.1　钛(titanium,Ti)　Ti 因其良好的生物相容性、耐腐蚀性、骨整合性和优异的力学性能,使其能够在承重条件下用于永久性骨科植入物修复 CSD[14]。近些年,多孔钛金属支架因其良好的机械性能在动物体内用来修复 CSD 的实验中取得了一些积极的成果[15]。Zhang 等[16]用圆柱形多孔钛金属支架和羟基磷灰石支架修复兔桡骨 10 mm CSD,X 线检查和生物力学测试显示两种支架骨修复良好,12 周和 24 周时,两种支架材料内新生骨面积百分比差异无统计学意义,但术后 12 周生物力学测试表明,多孔钛金属支架的机械强度(107.3 ± 27.4)N 高于羟基磷灰石支架的机械强度(93.4 ± 21.2)N。Zhao 等[17]采用等离子体浸没离子注入技术制备表面改良的钛金属复合支架材料,将硅掺杂到钛表面的二氧化钛纳米管中。将该材料植入到大鼠股骨 CSD 处,观察 2 周,实验结果显示,掺杂硅的二氧化钛纳米管支架比二氧化钛支架和钛支架的机械强度分别提高了 18% 和 54%。研究表明[18],良好的机械性能可有效避免植入物与皮质骨间极低的骨内应变和骨吸收,促进骨向植入物内生长,增强骨组织与植入物的结合强度,促进 CSD 的修复。

除机械性能可影响骨愈合外,Woodard 等[19]研究发现,微孔对于生物材料实现良好的骨诱导也是至关重要的,具有相互连接的多孔结构有利于血管化和营养物质的交换,从而实现骨向内生长,通过生物锚固实现长期固定。研究表明,骨向内生长的最佳孔径范围为 100 ~ 500 μm[20],孔径大于 300 μm 可增强新骨和毛细血管的形成[21]。Li 等[22]将 3 种不同孔径(300 ~ 400 μm、400 ~ 500 μm 和 500 ~ 700 μm)的多孔钛合金支架在体外与人骨髓间充质干细胞共培养,结果发现 300 ~ 400 μm 支架组效果最好。随后将其植入山羊跖骨 30 mm 超 CSD 处,体内评价表明,随着时间的增加骨向材料内生长的量逐渐增多,骨修复良好,并且在实验期间没有发生植入物移位。Chang 等[23]将不同多孔钛(孔径 188 ~ 390 μm,孔隙率 70%)支架材料在体外与骨髓间充质干细胞共培养,在体内植入兔股骨 CSD 处,结果表明,钛 188 在初始阶段更倾向于促进细胞分化,而细胞增殖和骨向内生长偏向于钛 313 和钛 390。融合不同孔径优点的混合多孔钛支架的设计对 CSD 修复具有重要意义和应用前景。

1.2　钽(tantalum,Ta)　Ta 是一种稀有的过渡金属,在体内有高度耐腐蚀性和惰性[24]。20 世纪中期,钽就被用于医疗实践,并显示出良好的生物相容性和安全性,被认为是一种潜在的修复骨缺损的生物材料[25]。Ren 等[26]通过火器装置和手术随机在新西兰大白兔左或右胫骨作长 10 mm 的 CSD,将多孔钽支架材料植入骨缺损处。X 线观察显示:4 周后 CSD 周围纤维组织覆盖于多孔钽材料的表面,8 周后多孔钽材料表面产生骨膜反应,新的骨组织覆盖于多孔钽材料表面,16 周后骨缺损周围组织完全包裹于多孔钽材料表面,组织学评价显示:骨缺损周围出现的新骨已经长入了多孔钽支架内。在 CSD 动物模型中,多孔钽生物材料表现出骨向内生长,有利于骨缺陷的治疗。

Balla 等[25]提出,由于钽金属是一种惰性金属材料,在体内不能快速诱导成骨细胞的黏附和增殖,早期与宿主骨密切接触。为了提高其生物活性,需要对多孔钽金属材料进行表面修饰,使其能够为种子细胞的黏附、增殖和分化提供良好的生物界面,促进细胞外基质的生成和钙化,满足早期负重活动的要求。Zhou 等[27]研究显示,与未涂层的钽支架相比,磷酸钙聚乳酸(CaP-PLA)涂层的钽支架在模拟体液(SBF)环境中具有更高的表面生物矿化性能,且亲水性显著提高。Zhou 等认为,所制备的 CaP-PLA 复合涂层钽支架可用于诱导体内骨再生。Wang 等[13]在兔桡骨中段建立了 15 mm CSD 模型,实验组用 cyclo(-GDfK-)肽修饰的多孔钽支架,对照组分别为植入未修饰的多孔钽支架、异种松质骨支架,结果表明:经修饰的多孔钽支架与未经修饰的多孔钽支架相比,其支架界面和支架孔内骨形成更多;多孔 Ta 支架和异种松质骨的新骨体积分数相似;生物力学性能在三者中最优。经修饰的多孔钽支架具有增强节段骨缺损修复能力的作用,有望成为修复 CSD 的潜在材料。

2 可降解金属材料对 CSD 的修复作用

镁(Magnesium,Ma):是人体内第四丰富的阳离子,成人人体约含 1 mol(24 g)镁,60 % 以上积聚在骨骼和牙齿中[28]。镁作为支架植入材料修复骨缺损具有以下优点:①镁及其合金作为一种可生物降解的金属,在使用寿命结束后,可降解并通过新陈代谢排出体外[29];②镁(40 ~ 45 GPa)和天然骨(10 ~ 40 GPa)之间的类似弹性模量使应力屏蔽最小化[30];③镁是人体的一种重要元素,在人体新陈代谢中起着重要作用[31],Mg^{2+} 适度释放不会引起任何毒副作用[32]。此外,一些学者还对镁合金的生物相容性和骨传导性进行了研究,发现镁合金在骨中具有较高的矿物附着率和较高的骨量,镁支架材料周围具有较高的矿物密度,结果提示,Mg^{2+} 可促进新骨形成[33-34]。

与人体骨骼相似的力学性能和生物降解性表明镁及其合金有可能成为良好的机械承载装置。然而,因镁支架材料在人体内快速腐蚀降解,导致在组织完全愈合之前,镁支架机械性能降低,可能失去功效。为解决这一关键问题,常采用合金化和表面改性来控制降解速率[35]。Zhang 等[36]在使用小型猪胫骨平台外侧骨缺损模型来评价镁合金修复 CSD 的有效性时,分别用微弧氧化(MAO)涂层的镁合金支架和硫酸钙支架修复骨缺损。结果发现,植入 4 个月后,MAO 镁合金支架修复骨缺损的骨形态与正常骨相似,而硫酸钙支架修复骨缺损的骨形态异常,呈凹形,MAO 涂层镁合金支架材料的骨愈合率更高。Han 等[37]使用铸态、挤压态和 MAO 涂层的铸态镁锶(Mg-Sr)合金修复新西兰成年兔双侧桡骨 10 mm CSD 时发现,MAO 涂层的铸态 Mg-Sr 合金降解速率适中,介于另外两者之间,骨修复最好。表面粗糙的 MAO 涂层可促进细胞黏附[38]和增强植入物的骨整合。镁合金及改性的镁金属支架具有骨诱导、骨传导、可控降解性、力学性能优异等优点,这为生物可降解镁合金作为潜在的 CSD 修复替代材料提供了新思路[35]。

3 金属支架材料的不足

单纯的金属支架材料和传统的支架材料一样缺乏骨诱导性,需要进一步的修饰或者与生长因子联合应用。金属支架材料的临床应用时间相对较短,远期临床效果和并发症尚未知。未达到 CSD 标准的骨缺损可通过自体修复达到完全骨愈合,植入金属支架会造成二次损伤,加重软组织损伤,影响血运,并不会加快骨愈合时间甚至可能延长骨愈合时间。非承重部位的 CSD 可植入可降解性人工合成支架材料和镁合金支架材料,通过支架材料的降解程度和骨修复程度来修复骨缺损,骨修复效果优于不可降解金属支架材料,但如何控制可降解支架材料降解速率使与骨缺损修复程度相当还有待进一步深入研究[39]。

4 展望

近年来,金属支架材料的实验研究及临床应用越来越广泛。在国外,金属支架材料已成功应用于临床,如全膝关节置换术[40]、Paprosky Ⅲ型髋臼骨缺损的修复等,并取得了良好的临床效果。金属支架材料生物相容性好、耐腐蚀性强、机械强度高,虽然国内对金属支架材料的了解和应用相对较少,停留在实验研究阶段,有待进一步研究,但不可否认其在修复 CSD 时具有巨大的优势和潜力,未来可能成为骨科治疗 CSD 的植入材料。

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