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· 专家论坛 ·

含锌生物活性材料在口腔颌面部组织修复中的研究进展

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【摘要】 口腔颌面部组织修复是临床难题, 传统材料往往难以兼顾生物相容性、抗菌性、抗炎性、组织再生等多重需求。当前, 含锌生物活性材料因独特的生物学特性而成为研究热点, 为解决该临床难题提供新思路。本文阐述了含锌生物活性材料在该领域的最新研究, 首先阐述含锌生物活性材料发挥抗菌、抗炎、促组织再生的机制, 即在其降解过程中释放的锌离子通过干扰细菌代谢等途径有效抑制细菌生长、通过调控巨噬细胞极化与募集中性粒细胞以重塑免疫微环境、通过激活磷脂酰肌醇3-激酶(phosphatidylinositol 3-kinase, PI3K)/蛋白激酶B(protein kinase B, Akt)等信号通路促进成纤维细胞增殖以加速软组织修复、通过Wnt/ β -catenin等信号通路促进成骨分化。基于上述机制, 本文进一步阐述含锌生物活性材料针对颌面部骨缺损、骨折、牙周炎、种植体周炎、口腔黏膜病的设计策略, 分析如何调控锌离子的释放行为, 以实现抗菌、抗炎与促组织再生的功能。尽管含锌生物活性材料的研究已取得进展, 但仍然存在锌离子释放不精准、缺乏时序调控、长期生物安全性数据不足、临床转化标准不健全等问题。未来研究可聚焦于开发智能响应性锌离子控释材料、构建仿生生空调控系统、结合类器官/器官芯片等先进技术评估长期生物安全性、建立系统的临床转化评价体系等, 以期含锌生物活性材料在口腔颌面部修复领域的深入研究和临床应用提供研究思路。

【关键词】 含锌生物活性材料; 锌离子释放; 抗菌; 抗炎; 组织再生; 颌面部骨缺损; 骨折; 牙周炎; 种植体周炎; 口腔黏膜病

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Research progress of zinc-containing bioactive materials in oral and maxillofacial tissue repair XIA Dandan, LU Yupu. Department of Dental Materials, Peking University School and Hospital of Stomatology & National Center for Stomatology & National Clinical Research Center for Oral Diseases & National Engineering Research Center of Oral Biomaterials and Digital Medical Devices & National Medical Products Administration Key Laboratory for Dental Materials, Beijing 100081, China

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【Abstract】 Repair of orofacial tissue remains a clinical challenge, as conventional materials often fail to meet multiple requirements such as biocompatibility, antibacterial activity, anti-inflammatory effects, and tissue regeneration. Zinc (Zn)-containing biomaterials have recently emerged as a research focus due to their unique biological properties, offering new strategies to address this challenge. This article summarizes the latest research on Zn-containing bioactive materials in this field. It first elucidates the mechanisms by which these biomaterials exert antibacterial, anti-inflammatory, and tissue-regenerative effects. The Zn^{2+} released during degradation inhibits bacterial growth by interfering with bacterial metabolism, remodels the immune microenvironment by regulating macrophage polarization and re-



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cruiting neutrophils, promotes fibroblast proliferation to accelerate soft tissue repair by activating signaling pathways such as PI3K/Akt, and enhances osteogenic differentiation through pathways such as Wnt/ β -catenin. Based on these mechanisms, this review further elaborates on the design strategies of zinc-containing biomaterials for treating maxillofacial bone defects, fractures, periodontitis, peri-implantitis, and oral mucosal diseases, analyzing how to modulate the release behavior of Zn^{2+} to achieve antibacterial, anti-inflammatory and tissue-regenerative functions. Despite this progress, challenges remain, including imprecise Zn^{2+} release, inadequate temporal regulation, insufficient long-term biosafety data, and lack of standardized clinical translation protocols. Future research can focus on developing smart Zn^{2+} -controlled release systems, constructing biomimetic spatiotemporal regulatory platforms, assessing long-term biosafety using advanced technologies such as organoids or organ chips, and establishing systematic clinical translation evaluation frameworks. This review aimed to provide research frameworks for further development and clinical application of Zn-containing biomaterials in orofacial reconstruction.

【Key words】 zinc-containing bioactive materials; zinc ion release; antibacterial; anti-inflammatory; tissue regeneration; craniomaxillofacial bone defects; bone fractures; periodontitis; peri-implantitis; oral mucosal diseases

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口腔颌面部组织修复面临形态恢复与功能重建双重需求,其中软组织损伤常伴发瘢痕形成与创口感染,而硬组织缺损则多伴随颌面部畸形与功能丧失。在传统修复治疗中,自体组织移植虽被视为“金标准”,然而其供区并发症、移植组织远期吸收率高等问题仍不容忽视^[1];临床常用的修复材料普遍缺乏生物活性,可能因材料与组织界面的菌斑生物膜积聚而诱发炎症,无法引导组织再生^[2]。近年来,含锌生物活性材料在应对上述难题方面展现出显著优势。这类生物活性材料通过释放 Zn^{2+} 展现出抗菌、抗炎、促组织再生功能:在抗菌方面, Zn^{2+} 通过结合细菌金属酶活性中心,破坏病原体代谢稳态^[3];在免疫调节方面, Zn^{2+} 通过调控巨噬细胞极化,改善炎症微环境^[4];在促软组织再生方面, Zn^{2+} 可诱导成纤维细胞分化、加速细胞外基质沉积,促进创面愈合^[5];在促骨组织再生方面, Zn^{2+} 可促进间充质干细胞成骨分化,促进骨再生^[6]。当前,含锌生物活性材料在颌面部缺损、骨折、牙周炎、种植体周炎、口腔黏膜病、牙髓及牙本质相关疾病等口腔领域已有初步应用研究。该类材料通过骨钉与接骨板、引导骨再生(guided bone regeneration, GBR)膜、微针、可注射水凝胶、表面功能涂层及纳米颗粒等多种应用形式,实现抗菌、调节炎症微环境及促进组织再生。

本文阐述含锌生物活性材料在口腔颌面部修复的研究进展。首先,总结 Zn^{2+} 的抗菌、抗炎及促组织再生的作用及机制;随后,探讨含锌生物活性材料在口腔组织修复中的设计策略、应用效果、作用机制;最后,总结当前研究存在的挑战,展望未来发展方向,以期为该领域的深入研究及临床转化提供理论依据。

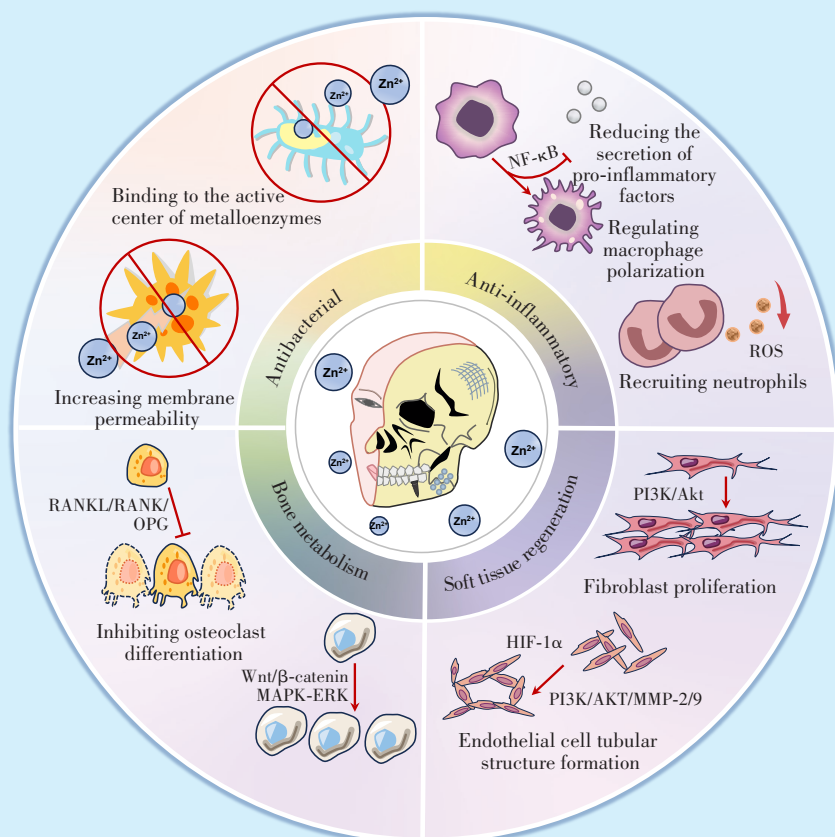
1 锌离子的生物学作用机制

作为人体内必需的微量元素之一,锌在多种生理过程中发挥着不可替代的作用。成年人体内锌含量约 2~3 g,主要分布于骨骼、牙齿、肌肉等组织中。作为 300 多种酶和 2 000 多种转录因子的必需辅助因子, Zn^{2+} 主要参与 DNA 合成、细胞增殖、免疫功能调节等生物学过程^[7]。研究表明,锌缺乏会导致口腔黏膜炎、味觉障碍、伤口愈合延迟等病理改变^[8-10],这为含锌生物活性材料在口腔颌面部修复的应用提供理论基础。

在抗菌方面, Zn^{2+} 可结合细菌金属酶活性中心干扰细菌代谢^[3],同时破坏细菌细胞膜完整性,诱导膜通透性改变,进而发挥杀菌作用^[11]。在调控炎症方面, Zn^{2+} 抑制核因子 κB (nuclear factor kappa-B, NF- κB) 信号通路活化,减少促炎因子分泌^[12],并促进巨噬细胞向 M2 型极化,增加抗炎因子分

泌^[13];此外, Zn^{2+} 还募集中性粒细胞,减少 ROS 积累,防止炎症持续^[14]。在促进软组织愈合方面, Zn^{2+} 通过激活磷脂酰肌醇 3-激酶(phosphatidylinositol 3-kinase, PI3K)/蛋白激酶 B(protein kinase B, Akt)信号通路促进成纤维细胞增殖^[15],并调控 PI3K-Akt-金属基质蛋白酶(matrix metallo proteinase, MMP)-2/9 和低氧诱导因子-1 α (hypoxia inducible factor-1 α , HIF-1 α)信号通路促进内皮细胞管状结构形成,利于血管生成^[16]。在骨代谢平衡方面,

Zn^{2+} 通过 Wnt/ β -catenin 和丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)-细胞外调节蛋白激酶(extracellular regulated protein kinases, ERK)等信号通路,上调成骨标志物表达^[17],并阻断核因子 κ -B 配体受体致活剂(receptor activator of nuclear factor kappa-B ligand, RANKL)/核因子 κ -B 配体受体(receptor activator of nuclear factor kappa-B, RANK)/骨保护素(osteoprotegerin, OPG)信号通路,抑制破骨细胞分化^[18](图 1)。



NF- κ B: nuclear factor kappa-B; ROS: reactive oxygen species; PI3K: phosphatidylinositol 3-kinase; Akt: protein kinase B; HIF-1 α : hypoxia inducible factor-1 α ; MMP: matrix metallo proteinase; MAPK: mitogen-activated protein kinase; ERK: extracellular regulated protein kinases; RANKL: receptor activator of nuclear factor kappa-B ligand; RANK: receptor activator of nuclear factor kappa-B; OPG: osteoprotegerin

Figure 1 Biological functions and mechanisms of Zn^{2+}

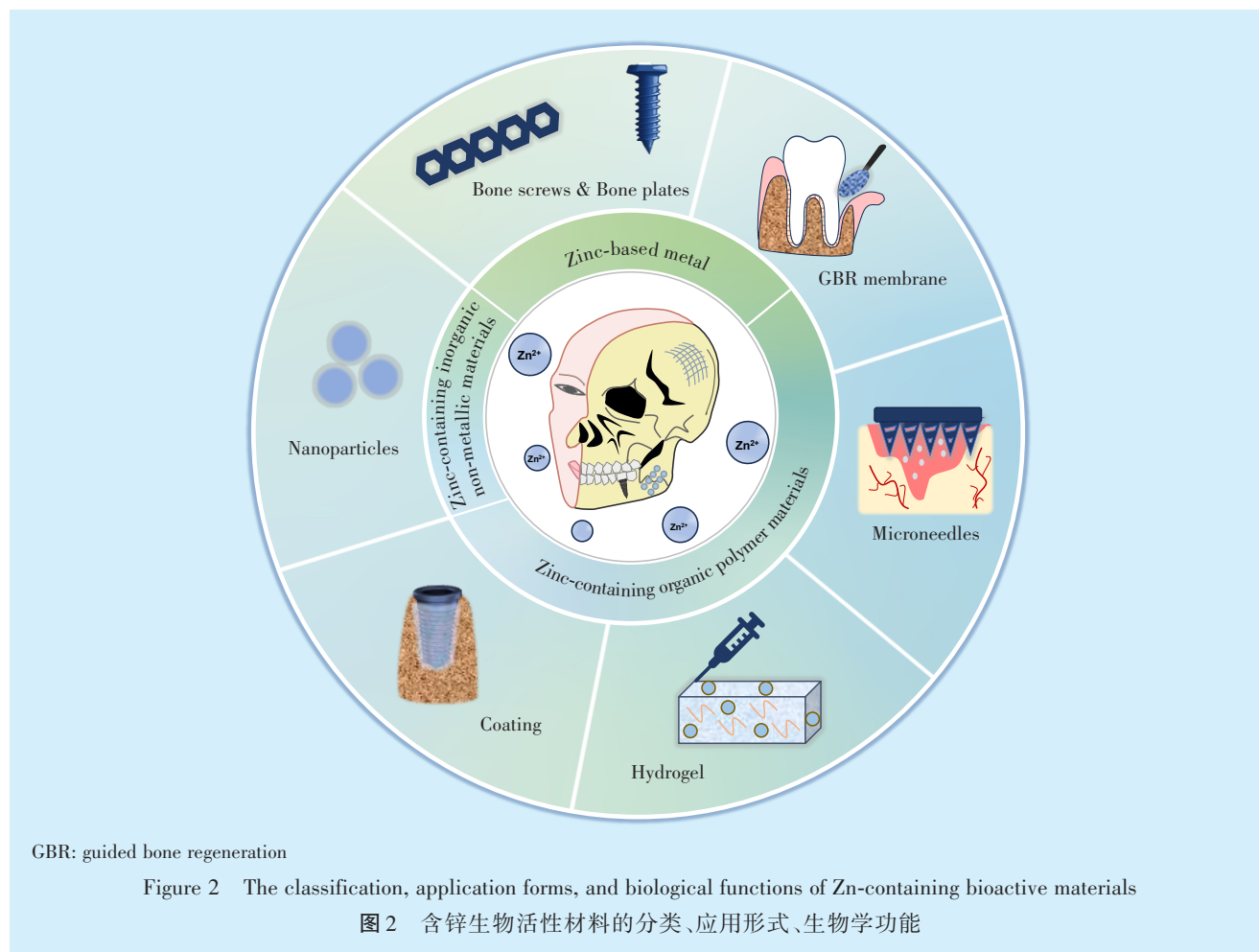
图 1 Zn^{2+} 的生物学功能及其机制

2 含锌的生物活性材料在口腔颌面部组织修复中的应用

近年来,含锌生物活性材料在应对口腔颌面部修复难题方面展现出显著优势。该类生物活性材料通过引入锌元素赋予材料体系特定生物学功能,如抗菌、抗炎、促组织再生。这类生物活性材料主要包括锌基金属(锌及锌合金)、含锌无机非

金属(如含锌生物活性玻璃)、含锌有机高分子材料(如含锌天然高分子、含锌合成高分子)。随着生物活性材料设计及制备技术的进步,含锌生物活性材料逐渐凸显出抗菌—抗炎—促组织再生多功能一体化,并以骨钉与接骨板、GBR、微针、水凝胶、涂层、纳米颗粒等多种应用形式,应用于颌骨再生、牙槽骨修复及黏膜愈合等领域,为口腔颌面

部组织修复提供解决方案(图2)。



在含锌生物材料的降解行为方面,不同材料体系的降解特性存在显著差异。锌及其合金主要通过腐蚀降解,其降解周期受成分、微观结构、植入环境等影响。数据显示,Zn-Li-Mn合金植入胃肠道4个月后体积降解率为11%^[19],纯锌植入腹主动脉1年后体积降解率为41.75%^[20]。含锌无机非金属材料主要依靠体液溶解作用降解,其降解速率与材料成分、结晶度、孔隙率、比表面积、植入部位等密切相关,其中含锌陶瓷在植入股骨缺损区域3个月后仍未完全降解^[21]。在含锌有机高分子材料中,Zn²⁺通过配位键物理负载或作为交联点化学键合于聚合物网络中,其降解主要依赖于高分子链的水解或酶解过程,降解时间相对较短,如含锌甲基丙烯酰胺胶(gelatin methacryloyl, GelMA)水凝胶在植入皮肤缺损区域后半个月即完全降解^[5]。上述含锌生物材料在降解过程中主要释放Zn²⁺及相应基材的离子或分子产物,从而发挥生物学功能。

值得注意的是,尽管Zn²⁺在高浓度下具有显著抗菌作用,但其对正常组织细胞的潜在毒性仍需审慎评估^[22]。因此,通过调控材料成分、微观结构、宏观形貌等调控降解行为,进而平衡其抗菌、抗炎与组织再生功能,已成为该领域的研究方向。

2.1 含锌生物活性材料在治疗颌面部骨缺损中的研究

研究表明,Zn可作为GBR膜应用于颌面部骨缺损修复。其中,300 μm孔径的纯Zn膜表现出最佳的成骨效果,其性能与无孔钛膜相当^[23]。合金化可进一步提高纯Zn的力学性能。具有优异力学性能的Zn-0.3Fe-0.05Mg(wt%)屏障膜能诱导巨噬细胞向M2型极化,促进早期血管化骨再生^[24]。表面修饰可进一步提高纯Zn的生物学性能,在激光蚀刻不对称纯Zn膜上修饰抗菌肽GL13K、速激肽SP,其中GL13K早期快速释放以防止伤口感染,SP则缓慢释放以调控免疫环境并促进骨再生^[25]。除

了锌基GBR膜外,锌还与聚合物结合以制备复合膜。例如,本课题组通过自组装在纯Zn膜表面制备矿化胶原蛋白的双层GBR膜,其可减轻 Zn^{2+} 的爆释,促进血管生成、巨噬细胞向M2型极化、成骨分化^[26]。本课题组还采用熔融沉积成型技术制备了具有不同Zn粉末含量(1 wt%、2 wt%、3 wt%)的聚己内酯/Zn复合支架。机制上, Zn^{2+} 通过调控Wnt/ β -连环蛋白与NF- κ B信号通路分别促进成骨分化并抑制破骨细胞形成。值得注意的是,Zn含量为2 wt%的支架表现出最佳的促成骨活性,而进一步提高含量至3 wt%时,其成骨效果略有降低^[27]。此外,含锌无定形磷酸钙的聚己内酯/GelMA复合膜释放 Zn^{2+} ,促进巨噬细胞黏附、巨噬细胞向M2型极化、牙槽骨再生^[28]。

2.2 含锌生物活性材料在治疗骨折中的研究

在下颌骨骨折及颧颌复合体损伤导致的口颌功能紊乱综合征患者中,血清 Zn^{2+} 水平降低3.09%,唾液 Zn^{2+} 水平下降更为明显(6.30%)^[29]。补锌可能成为口腔颌面部骨折的辅助策略。在口腔颌面部骨折治疗中,锌合金主要应用形式为接骨系统。其力学性能与临床常用的钛合金接骨板相当,能够在骨折愈合提供稳定的机械支撑^[30]。值得注意的是,锌合金具有更为优异的促成骨能力^[31]。研究表明,锌合金通过激活Wnt/ β -catenin、PI3K/Akt信号通路促进成骨分化,抑制生长因子受体结合蛋白2(growth factor receptor bound protein 2, GRB2)/ERK信号通路抑制破骨细胞分化,加速骨质疏松性骨折愈合^[32-34]。

在治疗口腔颌面部骨折中,Zn-Mg-Fe合金接骨系统展现出优异的综合性能。该植入物在植入3个月后的降解速率约0.183 mm/年,同期骨锌含量呈现先升高后降低的动态变化^[35];6个月后,Zn-Mg-Fe合金接骨系统仍保持良好的力学性能、生物相容性以及均匀且缓慢的降解行为^[31];在12个月时,其降解速率降至约0.065 mm/年,降解产物被骨骼替代,植入物长期稳定^[35]。目前,锌基合金在口腔颌面部骨折固定中的应用仍处于临床前探索层面。已有研究采用比格犬等大动物模型开展相关实验^[31, 35],相较于小动物模型更具临床参考价值,然而其促成骨、免疫调节等具体分子机制仍有待深入阐明;此外,锌基合金的降解速度仍然较慢,与骨组织的愈合速率匹配性仍需进一步优化。

2.3 含锌生物活性材料在治疗牙周炎中的研究

缺锌状态下,脂多糖(lipopolysaccharide, LPS)

促使巨噬细胞M1型极化、树突状细胞成熟、抑制调节性T细胞的抗炎活性,进而导致牙周慢性炎症^[36]。锌稳态有助于改善牙周微环境:一方面杀伤病原体、增强免疫细胞的防御能力;另一方面协调宿主细胞增殖与分化,维持骨代谢平衡^[37]。临床试验也证明含锌牙膏可抑制牙龈炎相关细菌,缓解牙龈炎症^[38]。然而,口腔环境的特殊性(如唾液持续冲刷、pH波动等)致使常规含Zn制剂的滞留时间短、疗效不持久,严重限制其临床疗效。因此,开发具有长效 Zn^{2+} 控释功能的新型生物活性材料成为研究热点。

在牙周炎治疗中,含锌生物活性材料主要的应用形式为水凝胶。相较于临床常用的抗生素凝胶,该材料可有效避免耐药性问题,同时还促进牙周骨组织再生^[39]。当前,含锌生物活性材料在牙周炎治疗的研究主要聚焦于金属有机骨架(metal organic framework, MOF)化合物的设计与应用,尤其是锌基沸石咪唑酯骨架(zeolitic imidazolate framework, ZIF)。该生物活性材料是由 Zn^{2+} 与2-甲基咪唑配位形成的一类金属有机框架材料,能够稳定释放 Zn^{2+} ,抗氧化应激并促进成骨分化^[40]。具体而言,采用共混法制备负载ZIF的GelMA复合水凝胶,该光固化水凝胶能稳定滞留于牙周袋内,持续释放的 Zn^{2+} 可降低牙周致病菌负荷、缓解局部炎症反应、促进牙槽骨再生^[41]。此外,本课题组采用共混法制备负载锌钴双金属有机框架(Zn/Co-MOF)的泊洛沙姆水凝胶,该生物活性材料可清除过量的活性氧(reactive oxygen species, ROS),通过Wnt信号通路加速成骨分化^[42]。为进一步增强含锌生物活性材料的综合治疗效果,Zn-MOF常与其他药物联合应用。例如,通过自组装构建Mino@ZIF-8纳米复合系统,该体系通过 Zn^{2+} 介导的AKT/糖原合成酶激酶3 β (glycogen synthase kinase 3 beta, GSK3 β)/核因子E2相关因子2(nuclear factor erythroid 2-related factor 2, Nrf2)信号通路纠正牙周组织的糖酵解-氧化磷酸化失衡,减轻氧化应激损伤^[43]。通过化学交联-共混法制备含槲皮素改性ZIF-8的复合水凝胶,该水凝胶可抵抗口腔液体冲洗,释放的 Zn^{2+} 和槲皮素可改善牙龈卟啉单胞菌LPS诱导的能量代谢障碍、氧化应激和自噬异常,增强牙周膜干细胞的成骨和血管生成能力^[44]。除水凝胶外,ZIF-8还通过表面功能化策略应用于牙周屏障膜。具有Janus结构的负载ZIF-8的静电纺丝膜不仅具备优异的力学性能,还具有抗菌活

性和组织再生能力^[45]。然而,上述材料体系缺乏环境响应特性,难以实现精准的 Zn^{2+} 控释。

目前,研究方向逐渐聚焦于开发智能响应性含锌生物活性材料(如 ATP、pH 响应等),以实现 Zn^{2+} 的特异性释放。例如, Mg/Zn-MOF 通过 ATP- Zn^{2+} 配位作用,表现出更高的 ATP 反应性,该生物材料通过抑制 NOD 样受体热蛋白结构域相关蛋白 3(nucleotide-binding domain, leucine-rich repeat containing family, pyrin domain-containing 3, NLRP3)/Caspase-1/Gasdermin-D 和 Caspase-11/Gasdermin-D 焦亡通路以减轻炎症浸润和胶原降解^[46];含多肽修饰 ZIF-8 的 GelMA 水凝胶在酸性条件下释放更多的 Zn^{2+} ,通过激活 FAK/PI3K/AKT 信号通路和增强 YAP 核定位以促进骨髓间充质干细胞成骨分化^[47];此外,以 ZIF-8 作为基础基质,通过 Ag_2S 纳米粒子封装与金纳米粒子锚定以构建 AgZ@Au ,随后掺入聚丙交酯-聚乙二醇-聚丙交酯水凝胶中。该复合体系在近红外光激发下产生光热效应,增强纳米酶的催化活性,并实现 pH 响应性 Zn^{2+} 释放,促进牙槽骨修复^[48],此设计整合光热治疗与离子释放的协同优势,为牙周组织工程提供新策略。

除 Zn-MOF 外,其他含锌生物活性材料也被用于构建功能性水凝胶系统。例如,将封装淫羊藿苷的 ZnAl -层状双氢氧化物纳米片与没食子酸修饰的羟基丁基壳聚糖复合,实现抗菌-抗炎-再矿化的时序性治疗功能,该水凝胶释放的 Zn^{2+} 通过调控 ZEB1 靶点诱导 M1 巨噬细胞向 M2 型转化,从而改善免疫微环境并促进组织再生^[49];通过溶胶-凝胶法制备含锌和钒的生物活性玻璃纳米颗粒,并随后将其整合至水凝胶微针系统,该体系释放的 Zn^{2+} 具有良好的抗菌与抗氧化特性,并通过抑制 Janus 激酶/信号转导与转录激活子(the Janus kinase/signal transducer and activator of trans-ions, JAK/STAT)和 NF- κB 等炎症通路治疗糖尿病牙周炎^[50];此外,利用羧甲基壳聚糖和氧化透明质酸之间的动态亚胺键和静电相互作用,以及 Zn^{2+} 之间的配体键合,构建可注射水凝胶 OC-Zn,该水凝胶可以通过释放 Zn^{2+} 发挥抗菌功能,以及促进牙周组织再生作用^[39]。

2.4 含锌生物活性材料在防治种植体周炎中的研究

在种植体周炎的防治中,含锌生物活性材料主要通过涂层形式对种植体表面进行功能化修饰,展现出良好的应用前景。含锌生物活性材料

不仅抑制牙周致病菌^[51-52],还通过调控巨噬细胞极化改善免疫微环境^[53],还可增强软组织封闭^[54-55]、促进血管生成并增强骨再生^[56-57],有效发挥抗细菌感染、免疫调节和组织再生功能。

在抗菌抗炎方面, $\text{ZnO/Zn}_3(\text{PO}_4)_2$ 杂化纳米结构涂层对种植体相关感染模型显示出良好的抗菌效果。机制上,该纳米结构可物理穿透细菌,释放 ROS 引发氧化应激、释放 Zn^{2+} 整合细菌内蛋白质和灭活酶,通过破坏细菌结构和代谢功能实现高效抗菌^[58]。聚多巴胺@ ZnO/Endothelin-1 多功能涂层对种植体相关感染模型也显示出显著的抗菌效果,其中 ZnO 释放的 Zn^{2+} 通过破坏细菌细胞膜完整性、干扰跨膜运输和葡萄糖代谢途径,导致细胞内金属离子稳态失衡和关键酶系统失活^[57]。基于锌指启发的肽金属酚醛纳米涂层对种植体相关感染模型显示出良好的抗炎效果,该涂层通过单宁酸- Zn^{2+} 配位网络实现成骨药物的高效负载与控释,调节 M1 巨噬细胞向 M2 型转化,减少炎性纤维组织包裹,提高种植体的长期稳定^[53]。

在软组织封闭方面,采用等离子体浸没离子注入技术在钛种植体表面构建锌功能层,该改性表面通过特异性激活转化生长因子- β (transforming growth factor- β , TGF- β)信号通路促进牙龈成纤维细胞增殖^[59]。通过水热处理在氧化锆表面构建 ZnO 纳米棒晶体涂层,该功能化涂层促进粘连蛋白 332 与整合素 $\beta 4$ 的特异性结合、激活 PI3K/Akt 信号通路增强口腔上皮细胞的黏附与增殖^[60]。在组织再生方面,通过微弧氧化技术在钛种植体表面构建含 Sr/Zn 的 TiO_2 微/纳米多孔涂层,该涂层有效调节成骨相关细胞之间的信号串扰,促进成骨细胞分化、微血管形成^[56]。

随着控释技术的进步,智能响应性(如超声响应、光响应)含锌生物活性材料为种植体周围炎的防治提供了新策略。例如,二维 MOF- MoS_2 异质结构中的局部电势差和压电极化可提供局部内部极化场,增强界面电荷转移,改善电子-空穴对分离和声催化活性。因此,该异质结构涂层可通过声催化作用促进 ROS 产生,有效抑制种植体周围感染,并稳定释放 Zn^{2+} ,增强骨-种植体界面的骨整合^[61]。 ZnO/黑色 TiO_2 异质结涂层在近红外照射下可抑制生物膜内的细菌生长,诱导巨噬细胞 M2 型极化,并通过 Wnt/ β -catenin 信号通路促进成骨分化^[62]。未来研究可进一步开发多刺激响应性含锌生物活性材料,进一步精准调控 Zn^{2+} 释放。

2.5 含锌生物活性材料在治疗口腔黏膜病中的研究

锌缺乏会影响牙龈成纤维细胞的生物学行为,导致细胞形态学异常、迁移能力下降、增殖速率降低、氧化应激加剧等^[63]。锌治疗能保护牙龈成纤维细胞免受氧化应激损伤^[64-65],并有效抑制口腔致病菌生长。因此,口服含锌制剂可作为口腔黏膜病的临床治疗手段之一^[66-67]。然而,口服锌制剂存在明显的局限性,如吸收效率不稳定、全身代谢负担等。局部应用含锌生物活性材料可实现 Zn^{2+} 靶向递送,在病灶部位维持有效浓度的同时还降低全身副作用。例如,临床应用热塑性含锌聚合物支架可持续释放 Zn^{2+} ,既发挥抗菌作用又促进腭黏膜愈合^[68]。目前,开发新型局部含锌生物活性材料已成为口腔软组织修复的研究方向。

当前,含锌生物活性材料在口腔黏膜病治疗中的主要应用形式为微针贴片。其中,含ZIF-8的微针贴片被广泛用于治疗口腔溃疡等黏膜疾病:基底层负载ZIF-8、尖端层负载曲安奈德与表皮生长因子的透明质酸微针可穿透口腔黏膜溃疡的真皮并溶解,实现抗菌抗炎与血管再生的协同作用^[69];负载ZIF-8和脂多糖预处理骨髓间充质干细胞外泌体(LPS-pre-Exos)的丝素蛋白微针可控制释放 Zn^{2+} ,进而抑制细菌、促进巨噬细胞向M2型极化、加速口腔溃疡愈合^[70];负载槲皮素修饰镁锌层状双氢氧化物纳米片的 γ -聚谷氨酸微针可缓释治疗成分,实现抗菌、诱导巨噬细胞向M2型极化、促进糖尿病口腔溃疡修复^[71]。

2.6 含锌生物活性材料在牙髓再生与牙本质矿化中的研究

临床上,以氧化锌丁香油水门汀和碘仿氧化锌糊剂为代表的含锌生物材料,凭借其良好的生物相容性与镇静止痛功效,长期以来被广泛用于暂时充填和盖髓治疗。随着对生物活性材料研究的深入,含锌材料在促进牙髓再生和牙本质矿化等方面的潜能日益凸显。例如,含锌玻璃离子水门汀抑制MMP活性并维持牙本质胶原基质的结构稳定性^[72],为治疗牙髓再生及牙本质矿化提供理论依据。含锌 β -磷酸三钙(Zn - β -TCP)通过诱导矿化,有效封闭牙本质小管。随后,将其与海藻酸钠-聚乙二醇糊剂复合,构建出具有良好操作性与生物活性的复合材料。该复合材料不仅表现出良好的矿化潜能,还兼具抗菌、促进牙本质形成的多重功能^[73],为治疗牙本质过敏提供新思路。此外,含

锌生物材料还可与其他活性成分联合应用,以进一步促进牙髓再生及牙本质矿化。具体而言,负载血管内皮生长因子与阿司匹林的含锌部分稳定水泥不仅展现出优异的生物相容性,还能持续释放活性因子,有效促进牙髓干细胞的矿化及成牙/成骨向分化,从而显著提升其诱导牙髓再生的能力^[74]。具有聚多巴胺修饰ZnO纳米颗粒涂层的聚四氟乙烯膜能有效缓解牙髓高压、阻隔微生物入侵,并通过诱导巨噬细胞向M2型极化,显著加速牙本质桥形成,同时保持牙髓组织完整性^[75],这一策略为活髓治疗提供了兼具机械屏障与生物调节功能的解决方案,展现出显著的临床转化潜力。

3 挑战与未来展望

含锌生物活性材料凭借优异的抗菌性、抗炎性、促组织再生能力,在口腔疾病治疗中展现出传统修复材料难以比拟的优势,为口腔修复领域提供新的治疗策略。然而,其临床应用仍面临诸多问题:首先, Zn^{2+} 的精确释放问题,现有材料体系表现出早期突释效应,即大量 Zn^{2+} 在初始阶段快速释放,这会导致局部浓度过高,在发挥抗菌作用的同时也可能产生细胞毒性问题。因此,如何平衡其抗菌浓度与细胞毒性阈值仍是研究焦点。其次,研究面临抗菌—抗炎—成骨的时序性调控难题。组织修复是一个动态、有序的生物学过程,理想的生物活性材料应模拟这一过程,即在早期高效抗菌并控制感染;随后,转而促进组织再生。然而,当前大多数含锌生物材料的释放模式无法实现与生物进程相匹配的智能切换,因而缺乏真正的仿生特性。此外,现有研究集中于体外或短期体内试验^[76],缺乏长期安全性试验及广泛临床验证。 Zn^{2+} 从生物活性材料中持续释放后,其在体内的代谢动力学(包括吸收、分布、半衰期、代谢和排泄)及是否存在肝、肾慢性蓄积风险等问题,尚待系统阐明;另一方面,含锌生物材料长期滞留于口腔环境,其对复杂微生物菌群稳态的潜在影响也亟待评估。

为精确调控 Zn^{2+} 释放,含锌生物活性材料的研究可聚焦于智能响应系统。例如,声/光/电响应性含锌生物活性材料可响应外源性刺激,精准释放 Zn^{2+} ;pH/酶响应性含锌生物活性材料根据病变部位的微环境变化,靶向释放 Zn^{2+} 。针对含锌生物活性材料的仿生问题,可采用表面改性、多组分协同策略等方法构建具有时序调控功能的生物材料,

实现抗菌-免疫调节-组织再生的级联效应。目前,含锌生物活性材料的研发正迎来技术革新,其中3D打印、类器官/器官芯片、人工智能等新兴技术为评估生物材料长期安全性提供新手段,这些技术能在人体试验前更有效地模拟生理或病理环

境,评估远期安全性。未来,可加快制定基于循证医学的含锌生物活性材料临床应用指南与专家共识,构建国内外统一的质量评价标准体系,以推动其临床转化及产业化进程(图3)。

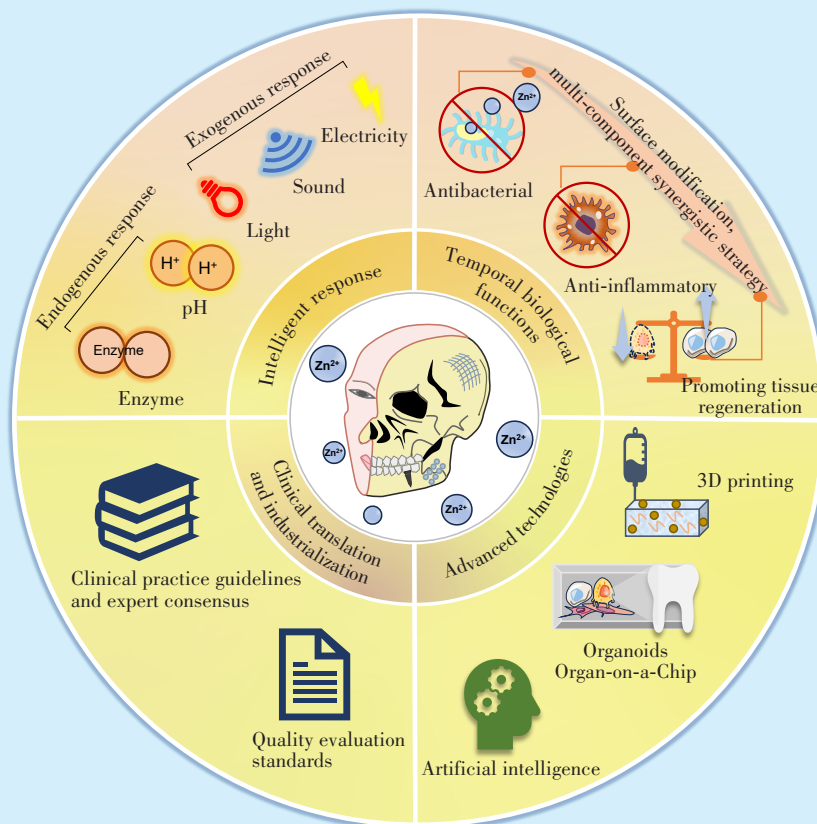


Figure 3 Future perspectives of Zn-containing bioactive materials for oral and maxillofacial tissue repair

图3 含锌生物活性材料在口腔颌面部组织修复的未来展望

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