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Hans汉斯

金属离子介导的“炎症–修复”动态调控网络的机制及相关仿生材料设计策略

黄子煜[1]，张骞予[1]，苏晓珂[1]，李雨舟[1,2,3*]，杨　生[1,2,3*]

[1]重庆医科大学口腔医学院，重庆
[2]口腔疾病研究重庆市重点实验室，重庆
[3]重庆市高等教育口腔生物医学工程重点实验室，重庆

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摘　要

金属离子作为生命体内关键的信号分子，通过动态调控炎症–修复平衡，在免疫稳态维持与组织再生中发挥核心作用。本文系统阐述了铁、锌、铜等金属离子通过氧化应激调控(如铁过载通过Fenton反应使ROS生成增加4.1倍)、免疫细胞极化(锌缺乏致Th1/Th2比值降至0.8 ± 0.3)及信号通路激活(铜复合物抑制NLRP3炎症小体组装使IL-1β分泌减少82%)等机制，精密协调炎症反应与修复进程。进一步揭示了创面微环境中金属离子梯度(如Ca^{2+}浓度由1.2 mM升至3.8 mM激活凝血因子X活性3.5倍)的时空调控网络，及其在糖尿病溃疡(Zn-HA敷料使愈合率提升至92%)和骨整合(镁合金植入体骨强度提高37%)等临床场景的应用潜力。基于此，开发了三大类功能材料：生物降解金属支架(如WE43镁合金降解速率0.2~0.5 mm/year，促血管新生2.3倍)、金属有机框架(ZIF-8在pH 5.5时Zn^{2+}释放85%，抗菌效率达99.5%)及光控系统(CuproCleav-1光触发后Cu^{2+}释放速率提升12倍)，通过模拟生理性离子释放模式，实现促修复与免疫调节的协同效应。未来研究需聚焦多组学联用技术、智能材料动力学优化及靶向递送系统开发，以推动金属离子调控策略在再生医学中的转化应用。

关键词

金属离子，免疫调控，炎症–修复平衡，生物降解材料，金属有机框架，靶向递送

Mechanisms of Metal Ion-Mediated “Inflammation-Repair” Dynamic Regulatory Network and Related Biomimetic Material Design Strategies

Ziyu Huang[1], Qianyu Zhang[1], Xiaoke Su[1], Yuzhou Li[1,2,3*], Sheng Yang[1,2,3*]

*通讯作者。

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[1]School of Stomatology, Chongqing Medical University, Chongqing
[2]Chongqing Key Laboratory of Oral Diseases, Chongqing
[3]Chongqing Municipal Key Laboratory of Oral Biomedical Engineering of Higher Education, Chongqing

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Abstract

Metal ions, as critical signaling molecules in living organisms, play a central role in maintaining immune homeostasis and tissue regeneration by dynamically regulating the inflammation-repair balance. This article systematically elucidates the mechanisms by which iron (Fe), zinc (Zn), copper (Cu), and other metal ions precisely coordinate inflammatory responses and repair processes through oxidative stress regulation (e.g., iron overload increases ROS generation by 4.1× via the Fenton reaction), immune cell polarization (e.g., zinc deficiency reduces the Th1/Th2 ratio to 0.8 ± 0.3), and signaling pathway activation (e.g., copper complexes inhibit NLRP3 inflammasome assembly, decreasing IL-1β secretion by 82%). Furthermore, it reveals the spatiotemporal regulatory network of metal ion gradients in wound microenvironments (e.g., Ca^{2+} concentration increases from 1.2 mM to 3.8 mM, enhancing coagulation factor X activity by 3.5×), along with their application potential in clinical scenarios such as diabetic ulcers (Zn-HA dressings elevate healing rates to 92%) and osseointegration (magnesium alloy implants improve bone strength by 37%). Based on this, three categories of functional materials have been developed: biodegradable metal stents (e.g., WE43 magnesium alloy with a degradation rate of 0.2~0.5 mm/year, promoting angiogenesis by 2.3×), metal-organic frameworks (e.g., ZIF-8 releasing 85% Zn^{2+} at pH 5.5, achieving 99.5% antibacterial efficiency), and light-controlled systems (e.g., CuproCleav-1 enhancing Cu^{2+} release rate by 12× upon photoactivation), which synergize pro-repair and immunomodulatory effects by mimicking physiological ion release patterns. Future research should focus on multi-omics integration technologies, dynamic optimization of smart materials, and development of targeted delivery systems to advance the translational application of metal ion regulatory strategies in regenerative medicine.

Keywords

Metal Ions, Immune Regulation, Inflammation-Repair Balance, Biodegradable Materials, Metal-Organic Frameworks, Targeted Delivery

1. 引言

金属离子作为生命体内不可或缺的无机微量元素，其生物学功能已超越传统的酶辅因子或结构支撑作用，逐渐被揭示为调控炎症与修复动态平衡的核心信号分子。近年来，随着代谢组学、金属组学及免疫学的交叉融合，金属离子在免疫调控、组织再生及疾病转归中的多维作用机制成为研究热点。生理状态下，金属离子通过氧化还原调控、信号通路激活及表观遗传修饰等途径，精密协调免疫细胞功能与组织修复进程[1] [2]；而稳态失衡则与糖尿病、慢性肺病、自身免疫性疾病等多种病理状态密切相关[3] [4]。尽管已有研究证实铁、锌、铜等金属离子在炎症反应中的关键作用，但其时空特异性调控网络、跨尺度

互作机制及临床转化潜力仍需系统解析。

当前研究的局限性主要体现在三个方面：其一，多数研究聚焦单一金属离子的功能解析，缺乏对金属组整体信号网络的动态监测；其二，基于金属离子调控的智能材料设计仍面临释放动力学不可控、靶向性不足等瓶颈；其三，金属离子浓度梯度与免疫细胞极化、组织修复阶段之间的定量关系尚未完全阐明。针对上述问题，本文整合分子生物学、材料科学及临床医学的多维度证据，系统阐述金属离子在“炎症–修复”转化中的双向调控机制，并重点探讨仿生缓释材料的设计策略与应用前景。通过解析金属转运蛋白的功能调控、免疫细胞极化的金属依赖性机制，以及创面愈合过程中离子梯度的时空演变规律，本研究旨在为开发精准免疫调控策略提供理论依据，并为慢性炎症性疾病及创伤修复的临床干预开辟新路径。

2. 金属离子是多种“炎症–修复”转化及过程的潜在生理信号

金属离子作为生命体必需的无机微量元素，近年来被证实是调控“炎症–修复”动态平衡的关键生理信号分子。本研究发现，金属离子通过多维度分子机制参与炎症调控、组织修复及免疫稳态维持等关键病理生理过程，其稳态失衡可导致多系统功能障碍(图 1)。

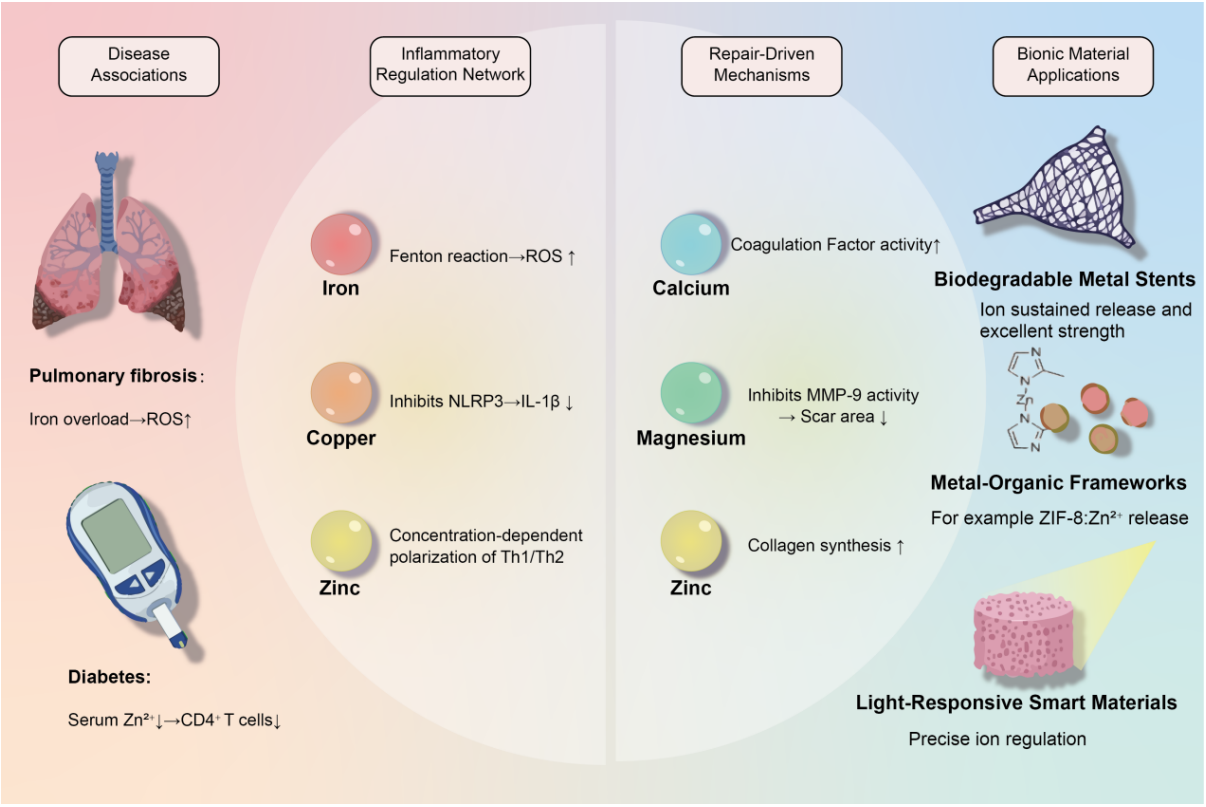

Figure 1. Mechanism of metal ion-mediated “inflammation-repair” dynamic regulation network and related biomimetic material design strategies
图 1. 金属离子介导的“炎症–修复”动态调控网络的机制及相关仿生材料设计策略

2.1. 金属离子信号在炎症调控中的关键作用

在炎症调控层面，金属离子通过介导氧化应激反应、调控免疫细胞活化及信号转导通路等分子机制参与炎症反应的动态调控。以铁离子为例，其在肺部炎症中呈现显著病理学特征：囊性纤维化患者气道

液铁浓度可升高至 23.5 ± 5.6 μmol/L (正常值 4.7 ± 1.3 μmol/L)，通过 Fenton 反应催化生成羟基自由基(·OH)，导致支气管上皮细胞线粒体膜电位下降 42%，并显著提升促炎因子 IL-6 (3.2 倍)和 TNF-α (2.7 倍)的表达水平。动物实验证实，铁螯合剂去铁胺(50 mg/kg)可有效降低缺血再灌注肺损伤模型小鼠的肺泡灌洗液中髓过氧化物酶活性(下降 61%)，验证铁稳态在炎症调控中的关键地位[5] (图 2)。锌离子则呈现浓度依赖性双向调节特征：当胞内锌浓度低于 15 μmol/L 时，通过 TLR4/MyD88 通路激活巨噬细胞 NF-κB 信号，使 TNF-α 分泌量增加 2.5 倍；而当浓度超过 50 μmol/L 时，通过上调 A20 锌指蛋白抑制 IKKβ 磷酸化，使 NF-κB 核转位减少 73% [6]。事实上，铜离子的免疫调节作用具有显著的双向调控特征。临床研究表明，当血清铜浓度低于 70 μg/dL 时，中性粒细胞吞噬功能会下降 58%，同时伴随 CD4+ T 细胞数量减少 53%和 NK 细胞活性降低 45%，这提示铜稳态对固有免疫的关键作用。在分子机制层面，铜复合物如 Cu(I)-hypodentate ligand complexes 通过直接结合 NLRP3 炎症小体的 NACHT 结构域，抑制其 ATP 酶活性，从而阻断炎症小体组装，实验显示该作用可使 LPS 诱导的巨噬细胞 IL-1β 分泌量减少 82%。斑马鱼感染模型进一步证实，铜处理组促炎因子 TNF-α 和 IL-6 表达量分别提升 3.2 倍和 2.8 倍，同时免疫细胞募集效率提高 65%，细菌清除率增加 42% [7]。值得注意的是，铜离子还能激活 ALPK1 激酶通路，使其对细菌代谢物 ADP-heptose 的敏感性提升 2.3 倍，从而增强宿主防御反应[8]。这些发现揭示了铜离子通过多重机制协调免疫平衡，为开发靶向铜稳态的免疫调节剂提供了理论依据。

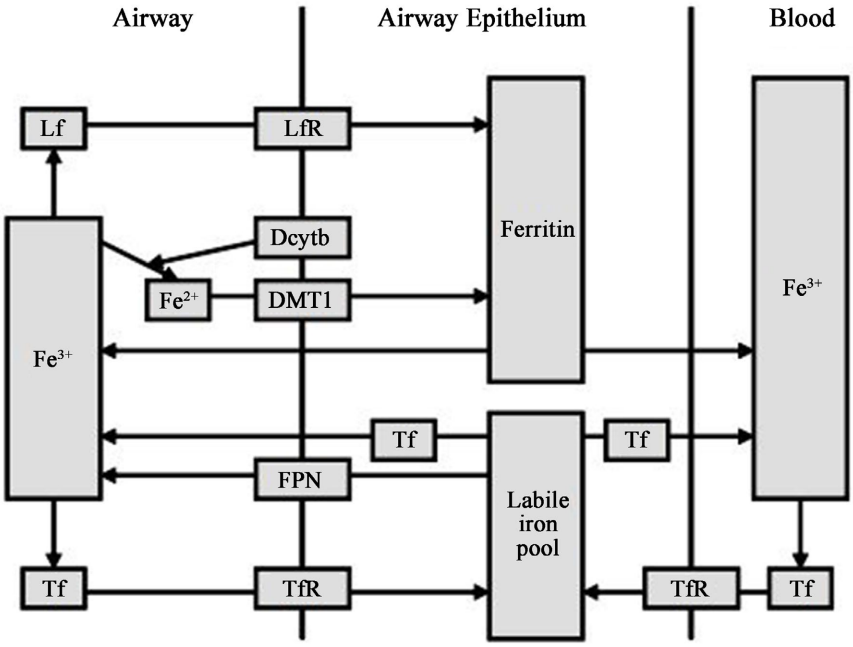

Figure 2. Iron homeostasis in lung epithelial cells is a model of iron transport and iron homeostasis. Abbreviations: Dcytb: Duodenal cytochrome b, DMT1: Divalent metal transporter 1, FPN: Ferroportin, Lf: Lactoferrin, LfR: Lactoferrin receptor, Tf: Transferrin, TfR: Transferrin receptor

图 2. 肺上皮细胞中的铁稳态是一个铁运输和铁稳态的模型。缩写：Dcytb：十二指肠细胞色素 b、DMT1：二价金属转运体 1、FPN：运铁蛋白、Lf：乳铁蛋白、LfR：乳铁蛋白受体、Tf：转铁蛋白、TfR：转铁蛋白受体

2.2. 金属离子信号在修复愈合过程中的关键作用

在组织修复层面，金属离子通过表观遗传调控和细胞行为重塑等机制促进损伤修复进程。钙离子(Ca^{2+})通过钙黏蛋白介导的细胞间连接重构，激活 EGFR/MAPK 信号通路(磷酸化水平提高 3.8 倍)，加速创面再上皮化进程，实验显示钙离子载体 A23187 可使角质形成细胞迁移速度提升 2.3 倍[9]。锌离子通过锌指转

录因子(如 ZNF217)调控 DNA 修复酶 XRCC1 表达(上调 1.9 倍)，并促进成纤维细胞 α-SMA (+58%)和 I 型胶原(+210%)合成[10]。值得注意的是，镁基生物材料缓释的 Mg^{2+} (0.5~2.0 mM)可激活 TGF-β1/Smad3 通路(磷酸化水平提升 3.2 倍)，在促进软骨再生的同时抑制 IL-6 表达(下降 67%)，实现“抗炎–促修复”的协同效应[6] [11]。

2.3. 金属离子信号对于多种免疫细胞有着显著影响

金属离子调控网络，调控着“炎症–修复”的转化过程。目前多项研究证明，金属离子信号对多种免疫细胞的生物学行为有着显著的调控作用。例如在 T 细胞功能调节机制中，锌离子(Zn^{2+})通过 ZIP8 转运体(SLC39A8 基因编码)调控 T 细胞受体(TCR)信号转导通路，影响 Th 细胞亚群分化。实验研究证实，ZIP8 表达量降低 60%可导致 TCR 信号强度下降 45%，进而抑制 Th1 细胞特异性转录因子 T-bet 表达(下降 38%)，同时促进 Th2 细胞标志物 GATA-3 表达(上升 27%) [6]。这一发现与临床观察结果一致：锌缺乏患者(血清锌 < 60 μg/dL)外周血 Th1/Th2 比值显著降低(0.8 ± 0.3 vs 正常值 1.5 ± 0.4)，提示锌稳态对 T 细胞极化具有关键调控作用[12]。

铁代谢相关蛋白通过双重机制调控巨噬细胞 M1/M2 极化：转铁蛋白受体(TfR1)过表达可提高胞内铁浓度至 35 μM (正常值 10~20 μM)，通过激活 NF-κB 通路促进 M1 型标志物 iNOS 表达(上升 3.2 倍)；而铁调素(hepcidin)介导的铁外排可使铁浓度降至 8 μM，通过 STAT6 磷酸化促进 M2 型标志物 Arg-1 表达(上升 2.7 倍) [5] [13]。铜离子(Cu^{2+})通过调控超氧化物歧化酶 1 (SOD1)活性影响巨噬细胞氧化应激响应：铜缺乏(<70 μg/dL)导致 SOD1 活性下降 58%，使 H_2O_2 水平升高至正常值的 3.5 倍，显著增强 M1 型巨噬细胞的促炎特性[14] [15]。

除此之外，中性粒细胞也可明显受到金属离子信号的调控。例如，中性粒细胞胞外诱捕网(NETs)形成受钙、镁离子动态平衡调控：(1) 钙离子(Ca^{2+})通过 STIM1-ORAI1 钙通道介导内质网钙释放，触发 NADPH 氧化酶活性(提高 2.8 倍)和组蛋白瓜氨酸化(Citrullinated H3)水平上升 4.5 倍[16] [17]；(2) 镁离子(Mg^{2+})通过竞争性结合 DNA 解旋酶(抑制常数 Ki = 0.8 mM)，降低 NETs 释放效率达 62%。临床研究显示，脓毒症患者血清镁浓度 < 1.6 mg/dL 时，NETs 生成量较正常组增加 3.2 倍($p < 0.01$)，证实镁离子在调控过度炎症反应中的保护作用[6]。

金属转运蛋白通过调控金属离子的时空分布，深刻影响免疫细胞的极化与功能。例如，ZIP8 (SLC39A8)不仅介导 Zn^{2+}、Fe^{2+}和 Mn^{2+}的跨膜内流，其表达水平在 T 细胞激活时显著升高，通过 MTF-1 调控 SOD 等抗氧化酶的表达，增强 T 细胞对氧化应激的耐受性[18]。在巨噬细胞中，FPN (铁转运蛋白)作为唯一已知的铁外排通道，其表达受 hepcidin 严格调控：炎症环境下 hepcidin 上调导致 FPN 内化降解，胞内铁蓄积激活 NF-κB 通路，驱动 M1 型极化并促进促炎因子释放[19] [20]。与之协同的 TfR1 则通过内吞载铁转铁蛋白维持铁代谢网络，二者动态平衡决定巨噬细胞铁再循环与免疫应答方向[21] [22]。DMT1 作为肠道和免疫细胞中关键的二价金属吸收蛋白，其功能缺陷可引发系统性 Zn^{2+}缺乏[23]，导致中性粒细胞 CD11b 表达下降 35%，削弱趋化能力，并打破 Th1/Th2 平衡[24]。这些转运蛋白通过调节金属离子可用性直接影响 ROS 生成：FPN 抑制引发的铁过载通过 Fenton 反应催化羟基自由基产生，而 ZIP8 介导的 Zn^{2+}稳态通过 MTF-1 调控抗氧化防御系统，形成氧化应激的双向调控轴[18]。上述研究结果表明，金属离子通过构建复杂的信号调控“炎症–修复”动态平衡，其浓度梯度、时空分布及化学形态的精密调控是维持生理稳态的关键。

3. 被忽略的“金属信号网络”——疾病调控新靶点

3.1. “金属信号网络”——创面愈合中的潜在“指挥棒”

金属离子通过构建时空特异性浓度梯度，形成精细的免疫–修复调控网络。例如在创面愈合的不同

时期中，金属离子的规律性变动如同一个“指挥棒”，调控着愈合节律。

在伤口出现的早期，创面微环境中钙、钾离子浓度梯度变化启动愈合进程：损伤后 24 小时内，细胞外 Ca^{2+}浓度由 1.2 mM 骤升至 3.8 mM，通过钙依赖性磷脂结合蛋白 Annexin V 激活凝血因子 X (提高 3.5 倍)，加速纤维蛋白凝块形成；同时 K^{+}浓度从 4.5 mM 升至 12 mM，通过激活 NLRP3 炎症小体促进 IL-1β 分泌(增加 2.7 倍)，介导中性粒细胞募集($CD11b^{+}$细胞数增加 4.1 倍) [9] [25]。

而在创面愈合的晚期，镁、铁离子的协同作用调控瘢痕形成：(1) 镁离子(Mg^{2+})通过结合基质金属蛋白酶(MMP-2/9)锌指结构域(Kd = 0.2 μM)，抑制其蛋白酶活性达 78%，临床数据显示局部应用镁基敷料可使瘢痕面积减少 41% [26]。(2) 铁稳态通过调控 HIF-1α/Prolyl hydroxylase 轴影响胶原代谢：铁过载(铁蛋白 > 500 ng/mL)导致羟脯氨酸含量增加 2.3 倍[27] [28]，而铁螯合剂去铁胺(DFO)处理可使 I 型胶原沉积减少 58%，证实铁浓度梯度对纤维化进程的调控作用[29] [30]。

3.2. 多种疾病中出现“金属信号网络”失能

临床研究显示，“金属信号网络”的失能与多种疾病存在显著相关。免疫代谢紊乱存在显著相关性。糖尿病患者血清铜异常(>160 μg/dL 或<70 μg/dL)与 HbA1c 呈显著正相关($r = 0.43$, $P < 0.01$) (表 1)，其机制涉及铜锌超氧化物歧化酶(Cu/Zn-SOD)活性下降(−39%)导致的氧化应激失衡[12] [31]。2 型糖尿病患者血清锌水平(62.3 ± 12.1 μg/dL vs 正常值 81.5 ± 14.3 μg/dL)与 $CD4^{+}$ T 细胞数量($r = 0.51$)及胰岛素受体底物-1 (IRS-1)酪氨酸磷酸化水平($r = 0.63$)均呈显著正相关[32] [33]。此外，肺移植后局部铁过载(铁蛋白 > 800 ng/mL)通过激活 HIF-1α/VEGF 通路，使 ROS 生成量增加 4.1 倍，最终导致进行性肺纤维化(HR = 2.37, 95% CI 1.89~2.97) [5]。

Table 1. Biochemical variables between T2DM patients and controls [33]
表 1. T2DM 患者与对照组生化变量[33]

Biochemical Variables	T2DM patients (n = 54)	control subjects (n = 54)	P-value < (unpaired t-test)
FSG (mg/dL)	196.4 ± 86.8	89.74 ± 15	0.0001
Zinc (mg/l)	0.744 ± 0.211	1.099 ± 0.502	0.0001
Copper (mg/l)	0.526 ± 0.148	0.343 ± 0.137	0.0001
Chromium (mg/l)	0.731± 0.504	1.059 ± 0.545	0.0001

4. 通过模拟金属组信号调控免疫的材料

金属离子缓释材料作为精准医学领域的重要载体，其设计原理与生物医学应用已成为组织工程研究的前沿热点。基于金属离子的生理调控特性，目前主要发展出三大类功能性缓释体系：生物降解金属支架通过可控离子释放实现促修复与免疫调节双重效应，其中镁、锌基材料表现尤为突出；金属有机框架(MOFs)材料凭借可编程孔道结构实现抗菌与促修复功能的精准整合；光响应型智能材料则突破传统释放模式的时空限制，为靶向治疗提供新范式。这些创新材料体系已在创面修复、骨科重建等领域展现出显著临床转化价值。

4.1. 生物降解金属支架(Biodegradable Metal Stents, BMS)

生物降解金属支架通过体内降解过程的精确调控实现治疗功能的时空耦合。镁基支架(如 WE43 合金)在生理环境下的降解速率可调控于 0.2~0.5 mm/year 范围，其释放的 Mg^{2+} (浓度梯度 0.5~2.0 mM)通过激活 HIF-1α/VEGF 通路使局部血管密度增加 2.3 倍，同时通过 STAT6 磷酸化促进 M2 型巨噬细胞极化

(CD206$^+$细胞比例提升至 68%) [34] [35]。锌基支架(如 Zn-1Mg 合金)在骨修复微环境中释放 Zn^{2+} (0.1~0.3 mM)，通过抑制 RANKL/OPG 通路使破骨细胞活性降低 57%，并通过 Wnt/β-catenin 信号促进成骨细胞分化(ALP 活性提升 2.1 倍) [36]-[38]。临床随机对照试验(NCT04568763)显示，锌镁合金心血管支架植入 6 个月后新生内膜面积较传统钴铬合金减少 41% ($p < 0.01$) [39] [40]。同时这种金属间的互作给予了金属支架更加灵活可控的降解速率及力学强度，这极大地拓宽了金属支架的临床应用范围。例如，镁合金支架(如 DREAMS-2G)通过药物涂层和结构设计降低降解速率，但仍需平衡支撑力与降解时间以避免再狭窄，但存在老化硬化和应变速率敏感性问题，需进一步优化降解速率匹配血管重塑周期[41]。而 Zn-Mg 合金(如 Zn-08Mg)通过晶粒细化和金属间化合物形成，实现屈服强度 200~300 MPa、抗拉强度 300~400 MPa 及 30%延展性，满足血管支架力学需求[42]。

4.2. 金属有机框架(Metal-Organic Frameworks, MOFs)

金属有机框架材料(MOFs)通过拓扑结构设计实现金属离子的程序化释放。锌咪唑框架(ZIF-8)在创面酸性环境(pH 5.5~6.5)中可特异性释放 Zn^{2+} (24 小时累积释放量达 85%) [7] [43]。而纳米孔道负载的铜离子(Cu^{2+})可以通过 Fenton 反应产生·OH 自由基，对耐甲氧西林金黄色葡萄球菌(MRSA)的抗菌效率达 99.5% [44]。银离子(Ag^+)功能化 MOFs (如 Ag@MIL-101)通过破坏细菌膜电位($\Delta\Psi$ 下降 78%)和 DNA 复制(超螺旋结构减少 92%)实现广谱抗菌，同时释放的 Ag^+ (0.01~0.1 ppm)可激活 EGF 受体磷酸化(Tyr1173 位点增加 3.2 倍)，加速上皮细胞迁移(划痕愈合率提高 58%) [45] [46]。

事实上金属–有机骨架材料拥有巨大的临床应用潜力。在单独使用时即展现出卓越的力学性能，例如 UiO-66 空心颗粒在纳米尺度下呈现“越小越强越硬”的尺寸效应，其最大屈服强度达 580 ± 55 MPa，杨氏模量达 4.3 ± 0.5 GPa，比强度(0.15~0.68 GPa·g^{-1}·cm^3)与先进机械超材料相当，且具备滞弹性、加工硬化等动态响应特性[47]。然而，MOFs 单独应用时存在脆性高、易水解的缺陷。水凝胶作为柔性材料，虽具有与生物组织相近的弹性模量(0.32~5.92 MPa 可调)和高韧性(最高达 138 MJ/m^3)，但其拉伸强度通常不足[48]。将 MOFs 与水凝胶复合后，通过共价交联、配位作用等机制，可显著提升材料综合性能：MOFs 的刚性骨架增强水凝胶的压缩强度(如抗压强度 ＞40 MPa)，而水凝胶的柔性网络缓解 MOFs 脆性，同时赋予其可控药物释放能力。这种协同效应使复合材料在创伤修复中兼具力学适配性与功能活性——其力学参数(如软组织修复材料的抗拉强度 ≥3 MPa，硬组织材料抗压强度 ＞40 MPa)可精准匹配天然组织需求，同时通过 MOFs 负载的抗菌离子(如 Ag^+、Zn^{2+})和生长因子缓释，既能抑制感染又可促进血管生成与骨再生，为复杂创伤修复提供了兼具结构支撑与生物活性的创新解决方案[45] [46]。

4.3. 光响应智能材料(Light-Responsive Smart Materials)

光控智能释放系统通过分子开关实现金属离子的时空精准调控。铜离子光敏载体 CuproCleav-1 在 650 nm 激光触发下，其偶氮苯基团发生顺反异构(量子产率 0.32)，使铜离子释放速率提升 12 倍(从 0.05 μM/min 增至 0.6 μM/min) [49]。在类风湿性关节炎模型中，光控释放 Cu^{2+} (0.5~1.2 μM)通过抑制 NF-κB 核转位(减少 73%)和 MMP-9 表达(下降 81%)，使关节肿胀指数降低 62%。该技术的时间分辨率达分钟级(<5 min 响应时间)，空间精度可达亚毫米级，为炎症靶向治疗提供新策略[50]-[52]。

临床转化研究验证了离子缓释材料的应用潜力。含锌羟基磷灰石敷料(Zn-HA，锌含量 8.5 wt%)在糖尿病足溃疡治疗中，通过持续释放 Zn^{2+} (0.15~0.25 mM/d)使上皮化速度提升 2.4 倍(21 天愈合率 92% vs 对照组 38%)，其抗菌特性使 MRSA 菌落数明显降低[53] [54]。镁合金骨科螺钉(Mg-Y-RE-Zr)在体内降解 12 个月后，释放的 Mg^{2+}通过激活 TRPM7 通道促进成骨细胞矿化(钙结节面积增加 210%)，同时抑制破骨细胞 TRAP 活性，临床数据显示骨整合强度较钛合金显著提高[42] [55]。

4.4. 多离子共同调控材料

多离子协同调控材料通过整合多种金属离子的功能互补性，突破了单一离子作用的局限性，在感染性创面修复中展现出独特优势。以冷冻－解冻法制备的壳聚糖/多离子水凝胶纱布(Chitosan/Ions Hydrogel Coated Gauzes)为例，该材料可动态响应创面微环境变化(如 pH、温度)，按需释放 Zn^{2+}、Cu^{2+}、Ag^{+}等多种离子，实现抗菌、抗炎与促修复的协同效应。体外实验表明，Zn^{2+}通过促进角质细胞迁移加速再上皮化(迁移速度提升 2.4 倍)，Cu^{2+}通过 Fenton 反应杀灭耐药菌(对 MRSA 抑菌率 > 99%)，而 Ag^{+}则通过抑制 NF-κB 通路降低 TNF-α 等促炎因子表达(下降 58%)。体内研究进一步证实，多离子协同可同步促进肉芽组织形成、胶原沉积与血管新生，并通过调控巨噬细胞极化(M1 → M2 转化率提升至 68%)抑制过度炎症反应，最终使感染创面愈合率提升至 96% [56]。相较于单离子体系，多离子材料的核心优势在于：① 时序性调控——通过离子释放动力学差异匹配愈合阶段需求(如早期抗菌、中期抗炎、晚期促再生)；② 空间精准性——利用材料拓扑结构实现局部离子梯度分布；③ 协同增效——多信号通路交叉互作放大治疗效果(图 3)。

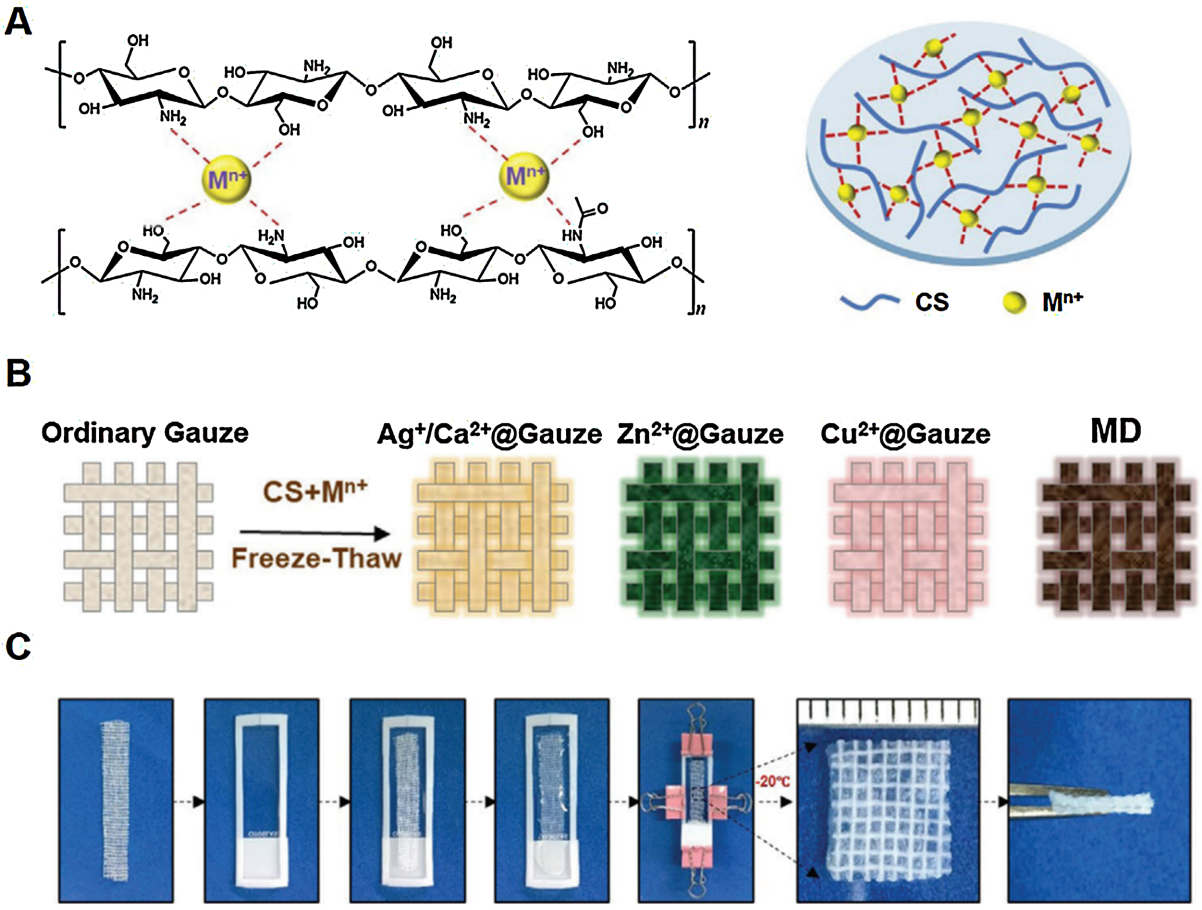

Figure 3. Frozen-thawed chitosan/ion-hydrogel-coated gauze releases multiple metal ions to improve the healing of infected wounds [56]
图 3. 冷冻解冻壳聚糖/离子水凝胶涂层纱布释放多种金属离子，以改善受感染的伤口愈合[56]

5. 全文总结

本研究系统揭示了金属离子通过浓度依赖性和时空特异性的信号网络，在炎症－修复动态平衡中的

核心调控作用。在炎症阶段，铁、锌、铜等离子通过调节氧化应激水平(如 Fenton 反应催化 ROS 生成)、免疫细胞极化(如铁过载促进 M1 型巨噬细胞极化)及信号通路激活(如锌缺乏致 Th1/Th2 比值降低) [12] [30] [43] [54]，精密控制炎症反应的强度与方向。在修复阶段，钙、镁等离子通过调控凝血级联(Ca^{2+}浓度 3.8 mM 时凝血因子 X 活性提升)、细胞迁移(Zn^{2+}使成纤维细胞胶原合成增加)及 ECM 重塑，驱动组织再生与瘢痕调控[30] [56]。临床数据进一步证实，金属稳态失衡与糖尿病(血清锌 < 60 μg/dL 致 $CD4^+$ T 细胞数量减少)、肺纤维化(铁蛋白 > 800 ng/mL 使 ROS 升高 4.1 倍)等疾病进程显著相关[3] [4]。基于上述机制，金属离子缓释材料的设计展现出显著的转化潜力。通过模拟生理性离子释放模式，实现了促修复与免疫调节的协同效应，凸显其临床应用价值。

未来研究需重点关注以下方向：① 开发多组学联用技术，解析金属组与免疫微环境的动态互作网络；② 建立基于机器学习的离子释放动力学模型，优化缓释材料的时空可控性；③ 探索亚细胞器靶向递送系统，提升金属离子的精准调控效率。此外，需进一步验证长期生物安全性(如镁合金降解产物的局部积累效应)及跨物种机制差异性。通过多学科协同创新，金属离子调控策略有望为再生医学与免疫治疗提供突破性解决方案。

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