

二维无机材料调控病损皮肤组织再生的研究进展

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摘要: 二维无机材料作为一类具有单原子层或多原子层的无机超薄纳米片, 呈现出高比表面积、高导电性和/或高光热转换效率等特点。这些独特的理化特性赋予其促凝血、抗菌、抗炎和抗氧化等生物效应。近年来, 鉴于降解和代谢问题, 该类材料被应用于调控病损皮肤组织, 如全层皮肤缺损、烧烫伤及糖尿病创面等, 展现出加速伤口愈合、减轻感染及改善炎症微环境的显著效果。本文围绕二维无机材料的特有结构和生物效应, 系统性阐述了其在伤口愈合中的应用及相关作用机制, 并展望了二维无机材料在皮肤修复领域面临的挑战和前景。

关键词: 二维无机材料; 皮肤修复; 微环境调节; 综述

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Advances in Regulation of Damaged Skin Regeneration by Two-dimensional Inorganic Materials

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Abstract: Two-dimensional (2D) inorganic materials, as a class of inorganic ultrathin nanosheets with single or several atomic layers, exhibit high specific surface area, high electrical conductivity and/or photothermal conversion efficiency. These unique physicochemical properties confer procoagulant, antibacterial, anti-inflammatory, and antioxidant biological effects. In recent years, in view of degradation and metabolism issues, these materials have been explored for modulation of diseased skin tissues, such as full-thickness wounds, burns and diabetic wounds, demonstrating remarkable effects in accelerating wound healing, alleviating infections and improving the inflammatory microenvironment. This review focuses on the unique structure and biological effects of 2D inorganic materials, systematically describes their applications in wound healing and related mechanisms, and looks forward to current challenges and prospects of 2D inorganic materials in the field of skin repair.

Key words: two-dimensional inorganic material; skin repair; microenvironmental regulation; review

近年来, 以硅酸钙、磷酸钙及生物玻璃等为代表的生物活性无机材料, 已被广泛应用于人体组织修复^[1-4]。它们在生物体内降解时释放大离子, 如

Ca^{2+} 、 Mg^{2+} 、 Cu^{2+} 、 Zn^{2+} 、 Si^{2+} 等, 发挥抑菌、促细胞黏附、促血管生成等积极的生物效应^[5-8]。最近, 不少研究聚焦于另一类具有类似生物效应的新型二

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维无机纳米材料。它们是仅具有单原子层或多原子层的无机超薄纳米片^[9],包括石墨烯及其衍生物、硼、黑磷(BP)、过渡金属二硫化物(TMD,如MoS₂、WS₂)和过渡金属碳/氮化物(MXenes)等。这类材料的超薄特点和二维形态学特征使其在生物医学领域展现出独特的优势^[10]。例如,超薄原子厚度为材料提供了高机械柔韧性,使其在生物传感和皮肤穿戴设备方面获得了突破性应用^[11-12];显著的近红外(NIR)吸收能力为光热治疗提供了新策略^[13-15];高比表面积可使其在药物递送系统中发挥更好的控释效果^[16],也有利于细胞黏附、增殖与迁移等;出色的导电率和可调带隙使其可模拟人体皮肤的多种功能^[17]。这些特性使二维无机材料成为制备可穿戴式、贴肤医疗设备的理想选择^[17-18]。

同时,二维无机材料也可作为功能性调节成分,用于修复各类病损皮肤组织。数据表明,大面积烧伤、全层伤口,以及由糖尿病、肾病等慢性病引发的皮肤溃疡,严重损害着皮肤屏障的生理功能,甚至可能并发感染而危及生命^[19]。据统计,在发达国家,约有1%~2%的人口面临伤口难以愈合的问题,其治疗费用约占医疗总支出的1%~3%^[20]。皮肤病损带来的巨大经济压力迫使创面愈合领域飞速发展。伤口愈合是一个动态且受精细调控的过程,主要分为四个重叠阶段:止血、炎症、增生和重塑^[21]。糖尿病、细菌感染等许多因素导致过量产生活性氧(ROS)和炎症因子,对细胞和组织造成不可逆氧化损伤,从而抑制血管生成和肉芽组织形成,减缓伤口愈合进程^[22-24]。目前,皮肤移植、光疗、电刺激疗法、生长因子治疗及富血小板血浆填充疗法等在临床上被用作治疗皮肤创伤的主要手段,但这些方法普遍存在医疗成本高、治疗效果欠佳和患者依从性差的问题^[25-26]。因此,迫切需要开发具有有效抗菌和抗氧化功能的新生物材料,以促进皮肤组织修复。

已有研究表明,二维无机材料可与细菌细胞膜作用产生物理损伤并发挥抗菌活性,主要有两种分子机制:一种是通过如“刀片”般锋利的边缘直接切割细胞膜;另一种是通过与膜脂质之间的强吸引力破坏脂质分子^[27-28],使细胞质渗漏和DNA释放,从而灭活细菌^[29]。利用自身卓越的光动力学特性,二维无机材料吸收NIR光辐射生成ROS,诱导细菌氧化应激,并将光能转化为热能,改变病原微生物膜的通透性,显著影响细菌结构和物质交换,从而杀死细菌^[30-32]。一些二维无机材料还能够有效抑制细胞因子分泌,调节伤口周围的炎症微环境^[16]。例如,MXenes纳米片依靠其表面丰富的亲水基团,通过

与白细胞介素-6(IL-6)分子形成氢键,吸附并诱导IL-6分子的二级结构由 α -螺旋“拉伸”为 β 片,从而表现出卓越的细胞因子去除能力^[33]。凭借抗菌、抗炎、抗氧化等多种生物性能,二维无机材料在促进伤口愈合方面展现出巨大的应用潜力。因此,本文旨在概述二维无机材料在调控皮肤病损修复进程中的作用,并探讨其所面临的潜在机遇(图1)^[34-37]。

1 二维无机材料调控病损皮肤修复

1.1 石墨烯及其衍生物

石墨烯是一种由碳原子以六边形蜂窝状紧密堆积而成的二维片材(图2(a)),其厚度小于10 nm^[38-39]。其中所有碳原子都是sp²杂化,有利于和脂质分子产生极强的分散相互作用,克服膜内脂质分子之间的自吸引力,从而展现出优异的抗菌特性^[40]。然而,石墨烯的单层结构易破裂,具有疏水性和惰性,并且合成功能化材料技术受限,制备成本高,这些问题严重限制了其临床应用。其衍生物氧化石墨烯(GO)和还原氧化石墨烯(rGO)引入了羟基、羧基、环氧基等,能够通过共价键或非共价键与生物分子附着,并且更容易实现材料的功能化(图2(b))。Zhang等^[41]结合季铵化壳聚糖(QCS)和rGO的优势,利用 β -环糊精(CD)和金刚烷之间的主客体相互作用设计了一款可注射的自修复导电超分子水凝胶(图2(c))。当水凝胶中rGO-CD质量分数达

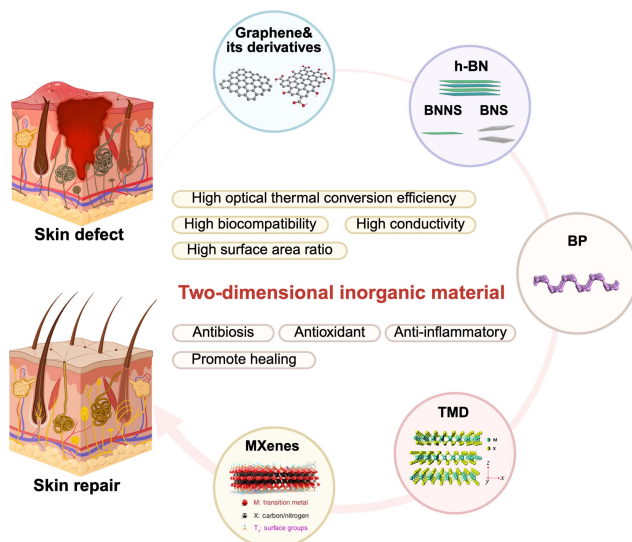
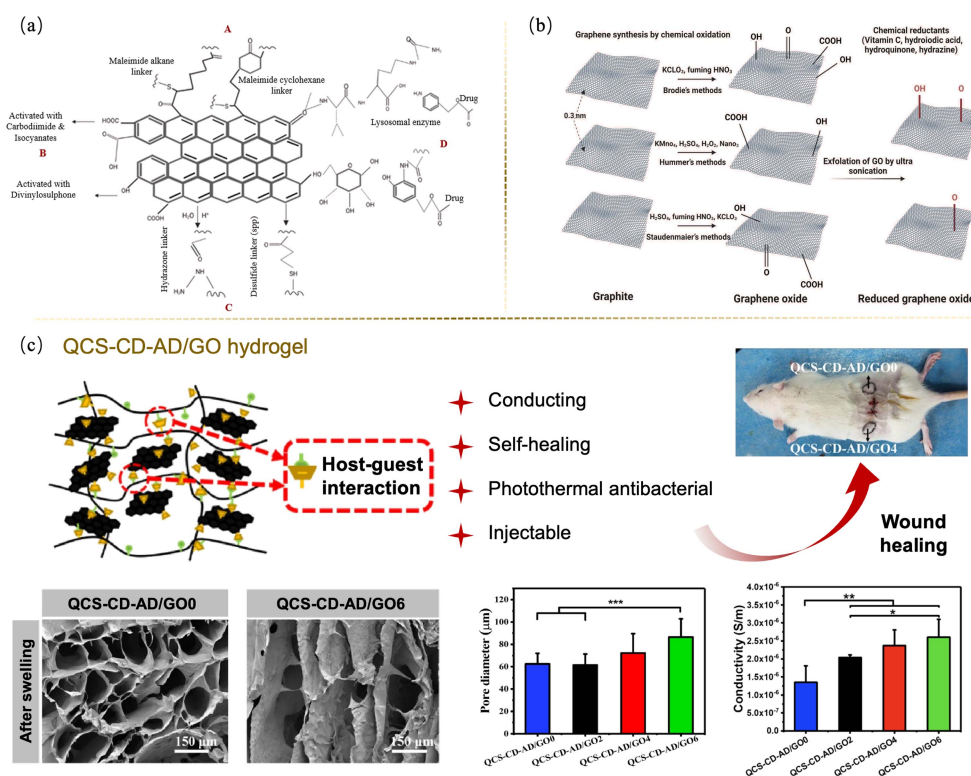


图1 二维无机材料调控病损皮肤再生^[34-37]

Fig. 1 2D inorganic materials regulating regeneration of damaged skin^[34-37]

BP: Black phosphorus; h-BN: Hexagonal boron nitride; BNNS: Boron nitride nanosheet; BNS: Boron nanosheet; TMD: Transition-metal disulfide. Created with BioRender.com. Colorful figure is available on website

图 2 石墨烯及其衍生物调控病损皮肤修复^[39, 41]Fig. 2 Regulation of graphene and its derivatives for the repair of damaged skin^[39, 41]

(a) Structure of functionalized graphene^[39]; (b) Conversion of graphene to GO/rGO^[39]; (c) QCS-CD-AD/GO supramolecular hydrogel promoting bioelectrical signal transmission to repair full-thickness skin defects^[41]. QCS-CD-AD: Quaternized chitosan- β -cyclodextrin-adamantane.

Colorful figures are available on website

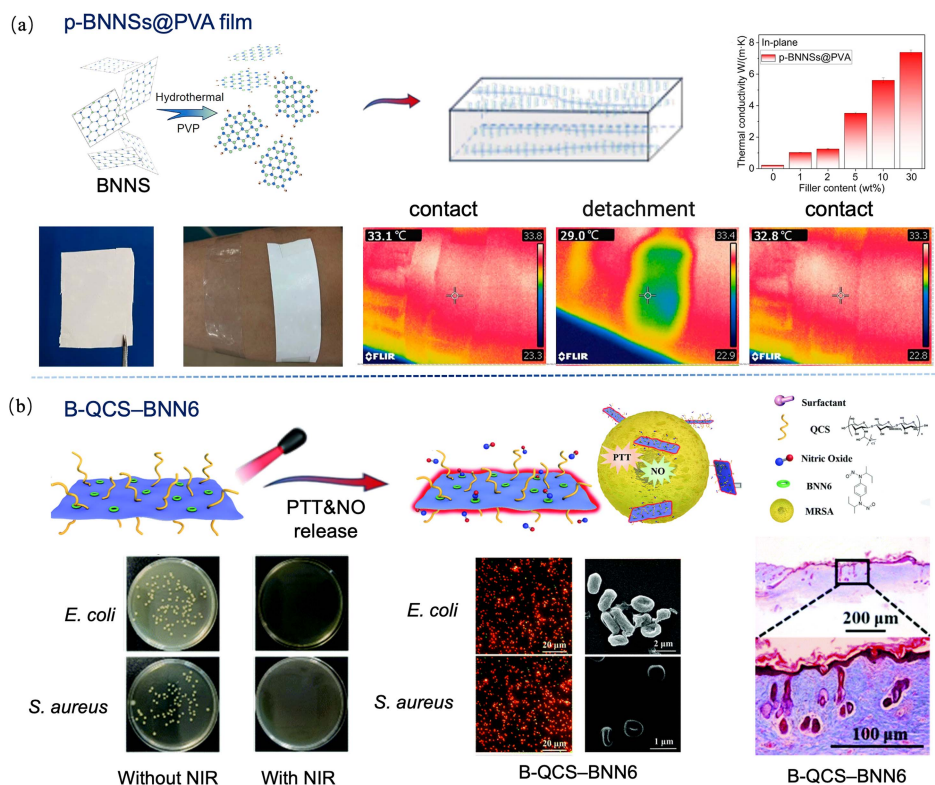
到 0.6% 时, 表现出 $(129 \pm 33)\%$ 的最高溶胀比。溶胀后的水凝胶导电率为 $0.07 \sim 0.11 \text{ S/m}$, 在皮肤组织的导电率范围内。相较于不含 rGO 的水凝胶, 这种材料可有效促进生物电信号传输, 从而促进全层皮肤缺损小鼠伤口愈合。然而, 相关研究表明石墨烯及其衍生物也可能对正常细胞造成损伤^[42]。其主要毒性机制为高浓度 GO 促进 ROS 产生, 并诱导氧化应激。ROS 稳态失衡可能会诱导细胞内蛋白质失活或线粒体功能障碍等, 最终导致细胞凋亡或坏死^[43]。当疏水性石墨烯质量浓度高于 $75 \mu\text{g/mL}$ 时, F-肌动蛋白丝状拉伸呈现异常形态, 且其与细胞膜之间的强疏水相互作用阻碍了必需的营养素和蛋白质的吸收, 从而引发细胞骨架功能障碍。相比之下, 经硝酸氧化的功能性石墨烯对细胞骨架结构和丝蛋白延伸的完整性没有明显不利影响^[44]。此外, 从分子水平研究石墨烯的细胞毒性发现, 石墨烯激活 RAW 264.7 噬菌体细胞中的活化蛋白激酶(MAPK)和转化生长因子 β (TGF- β), 同时进一步激活 Bcl-2 蛋白家族, 触发线粒体凋亡^[45]。因此, 如何降低石墨烯基材料的体内细胞毒性是未来研究的重要方向。

1.2 硼基二维材料

另一种典型的二维无机材料是六方氮化硼(h-BN)。与石墨烯相比, h-BN 具有更高的稳定性, 在

室温下不易与酸和碱反应。但 h-BN 的化学惰性、低剥离效率和较差的界面相容性, 大大限制了其应用^[46]。Chen 等^[47]针对高温环境下伤口愈合困难的问题, 采用固相熔盐法结合水热剥离的策略, 成功制备了稳定且具有亲水性的聚乙基氮化硼纳米片(p-BNNSs@PVA)。研究发现, 当 p-BNNSs 的质量分数为 30% 时, 材料的热导率达到 $7.38 \text{ W/(m} \cdot \text{K)}$, 是纯 PVA 薄膜的 33.44 倍(图 3(a))。采用静电纺丝技术将 p-BNNSs@PVA 制成纳米纤维薄膜, 其轻薄柔软的特性可增强与皮肤接触的舒适度, 高导热性可促进皮肤伤口散热, 高比表面积和孔隙率可促进空气交换和加速伤口愈合, 是一种理想的可用于皮肤修复的高级医用材料。

硼是人体正常生理活动所必需的微量元素之一, 由其构成的硼纳米片(BNSs)作为一种二维无机材料在病损皮肤修复中发挥了独特的优势。Lv 等^[48]将 BNSs 用于治疗耐甲氧西林金黄色葡萄球菌感染的伤口, 采用液相剥离和静电吸附法制备表面功能化正电荷 QCS 的改性 BNSs(B-QCS), 可以有效捕获带负电荷的细菌。通过 π - π 堆叠和疏水作用力将一氧化氮(NO)供体 N,N' -二仲丁基- N,N' -二亚硝基-1,4-苯二胺(BNN6)加载到 BNSs 上, 可使材料在 NIR 光照射 5 min 内按需释放 NO(图 3(b))。

图 3 硼基二维材料调控病损皮肤修复^[47-48]Fig. 3 Regulation of boron-based 2D materials for the repair of damaged skin^[47-48]

(a) p-BNNSs@PVA film with high thermal conductivity promoting heat dissipation of skin wounds^[47]; (b) B-QCS-BNN6 transferring NO to achieve efficient antibacterial effect^[48]. BNNSs: Boron nitride nanosheets; QCS: Quaternized chitosan. Colorful figures are available on website

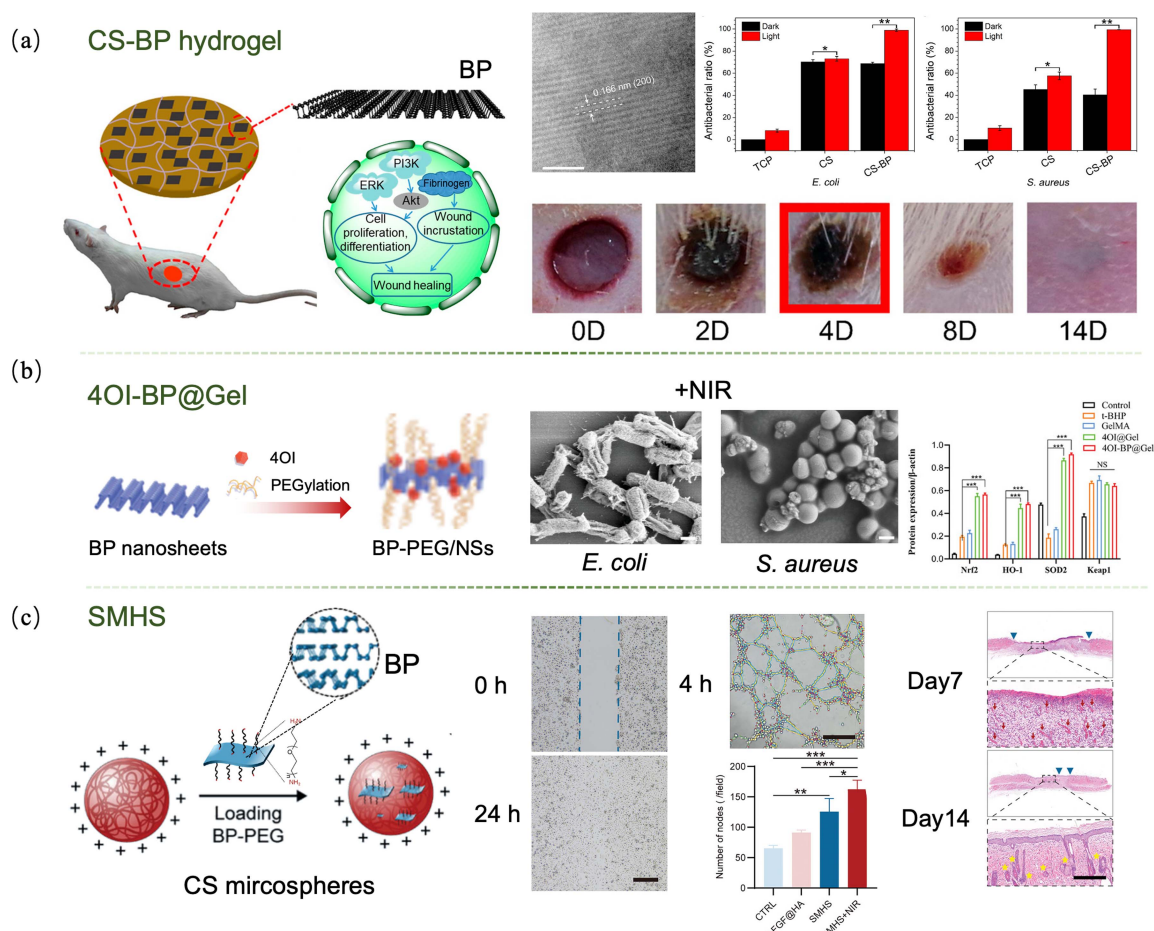
研究表明, NO 是一种内源性双原子自由基, 广泛参与血管生成、免疫反应、抗氧化应激以及抑制血小板黏附和聚集等多种病理生理过程^[49]。基于 NO 的有效疗法需要在特定时间内精准输送适宜剂量, 其治疗效果依赖于输送浓度和持续释放时间^[50]。在 808 nm、2.0 W/cm² 激光照射下, B-QCS-BNN6 纳米片可以在 10 min 内快速释放约 2.25 $\mu\text{mol/L}$ 的 NO。随后, 残留的 NO 以持续稳定的方式释放。得益于 BNSs 的高光热转化特性, 利用 NIR 光照射的开关和功率调控, B-QCS-BNN6 纳米片可精确控制 NO 的释放浓度。这种 BNSs 与 NO 供体的协同作用显著提高了抗菌效率(>99.9%)^[48]。二维无机材料助力药物可控释放的策略能够将药物浓度维持在有效且安全的治疗窗内, 大幅降低药物中毒风险, 为未来药物开发提供了全新的策略和思路。

1.3 黑磷纳米片

BP 是磷的一种层状同素异形体, 结构中的弱范德瓦尔斯力保证其极易被剥离成超薄的二维黑磷纳米片(BPNS)。BPNS 的带隙具有厚度依赖性, 从多层的 0.3 eV 到单层的 2.0 eV, 能够吸收整个电磁波谱的能量。该特点是迄今为止已知的其他二维材料无法比拟的^[51]。Mao 等^[52]以 BPNS 和壳聚糖为原料, 通过静电相互作用制成的杂化水凝胶(CS-BP

hydrogel)可在 10 min 内迅速杀死 98.90%的大肠杆菌和 99.51%的金黄色葡萄球菌(图 4(a))。这是由于 BPNS 独特的电子结构, 具有产生单线态氧(¹O₂)的强大能力, 可以对细菌的细胞膜、蛋白质甚至 DNA 造成损伤, 从而达到抗菌目的^[53-54]。该研究也表明, BPNS 通过激活磷酸肌醇 3-激酶(PI3K)、蛋白激酶 B 磷酸化(Akt)和细胞外信号来调节激酶(ERK1/2)信号通路, 进而促进伤口部位成纤维细胞的增殖和分化, 增强纤维蛋白原的表达并加速伤口结痂^[52]。组织学分析显示在伤口愈合过程中, BPNS 不会对大鼠的主要脏器造成明显损伤, 表明其可以成为一种安全的伤口愈合治疗材料^[52]。

BP 因其低毒性、高生物降解性和高光热转换效率^[55], 在糖尿病伤口愈合的应用中展现出极大的潜力。Ding 等^[56]将 4-辛基衣康酸盐(4OI)修饰的 BPNS 掺入甲基丙烯酰胺明胶水凝胶中, 在 NIR 光照射下, 水凝胶快速凝胶化, 在伤口上形成膜, 并提供高光热疗法和光动力疗法功效, 其抗菌率达 90%以上, ROS 清除率达 51.9%, 第 14 天时伤口愈合率达 99.64%(图 4(b))。Luo 等^[57]则将含 BP 的甲基丙烯酰胺壳聚糖微球与含碱性成纤维细胞生长因子的甲基丙烯酰胺透明质酸微球结合, 制成自组装微球水凝胶支架(SMHS)(图 4(c))。由于存在 BP, 当 NIR 光

图 4 黑磷纳米片调控病损皮肤修复^[52, 56-57]Fig. 4 Regulation of black phosphorus nanosheets for the repair of damaged skin^[52, 56-57]

(a) CS-BP hydrogel enhancing fibrinogen expression to accelerate wound scab formation^[52]; (b) 4OI-BP@Gel with high antibacterial effect promoting diabetic wound healing^[56]; (c) SMHS promoting wound healing in diabetic rats^[57]. CS: Chitosan; BP: Black phosphorus; 4OI: 4-octyl itaconate; SMHS: Self-assembled microsphere hydrogel scaffold. Colorful figures are available on website

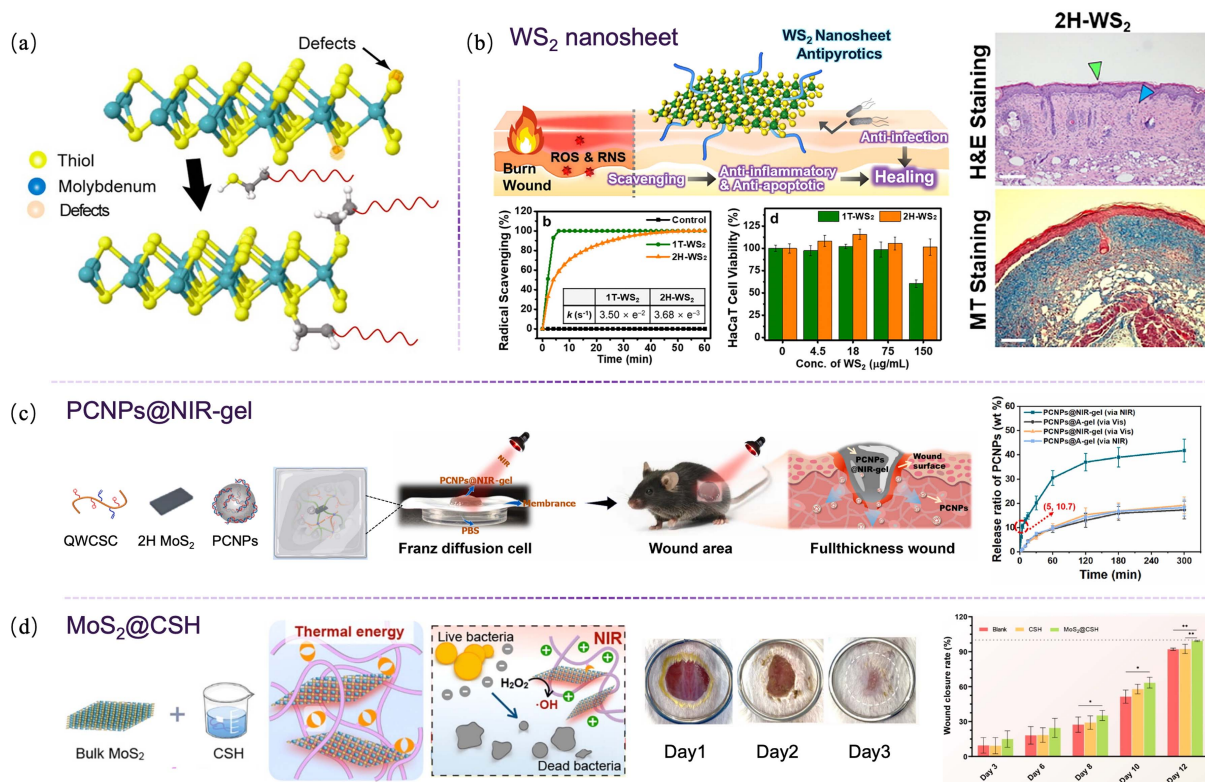
照射糖尿病大鼠皮肤伤口时, 材料的降解和药物释放行为得到了明显提高。在生理环境下, BP 可自然降解为 PO_4^{3-} 或 HPO_4^{2-} , 其降解产物大量存在于生物体内, 因此 BP 被认为是一类具有良好生物相容性的二维无机材料^[58]。但值得注意的是, 细胞质中堆积的磷酸盐阴离子可能会影响细胞三磷酸腺苷(ATP)水解并诱导细胞程序性死亡^[59]。因此, 深入探讨 BP 与生物环境之间的相互作用在未来研究中尤为重要。

1.4 过渡金属二硫化物

随着石墨烯等二维层状纳米材料的兴起, TMD 这类新型二维材料也引起了广泛关注。TMD 的通式为 MX_2 , 具有三明治结构, 过渡金属层(如 Mo、W、Tb、Ti、Zr 等)位于两层硫系元素(如 S、Se、Te)之间(图 5(a))^[37, 60]。TMD 有三角棱柱(2H)相和八面体配位(1T)相两种常见晶体结构相。这两个相显示出完全不同的电子特性, 2H 相表现为半导体, 而 1T 相表现为金属^[61]。So 等^[37]采用聚(ϵ -己内酯)-b-聚乙二醇对不同相的二硫化钨(WS_2)纳米片进行剥离和功

能化, 将其作为一种具有抗氧化性和生物相容性的生物材料, 用于治疗深度烧伤创面修复(图 5(b))。研究发现, 不同浓度的 1T- WS_2 纳米片和 2H- WS_2 纳米片都能快速有效地清除细胞外自由基, 且在第 8 次循环后仍然可以保持稳定的清除活性。通过测定不同相材料在 HaCaT 人角质形成细胞中的生物相容性发现, 2H- WS_2 纳米片的浓度不影响细胞活力, 均保持在 100%。而 150 $\mu\text{g/mL}$ 1T- WS_2 作用 48 h 后, 细胞存活率下降至 60.4%。这说明 2H- WS_2 因其特殊的晶体结构, 相比于 1T- WS_2 具有更好的生物相容性, 这可能是治疗深度烧伤创面更好的选择^[37]。

此外, TMD 的厚度也会显著影响其性能。二硫化钼(MoS_2)是目前研究最广泛的二维 TMD 材料。研究表明, 单层片状 MoS_2 纳米片的杨氏模量(~ 270 GPa)显著高于较厚块状 MoS_2 的杨氏模量(~ 240 GPa)^[62]。此外, 当 MoS_2 由块状形态减薄至单层时, 其光致发光性能显著增强, 带隙从间接转变为直接, 进而表现出强大的二阶非线性光学响应^[60-63]。

图 5 TMD 调控病损皮肤修复^[37, 64, 66]Fig. 5 Regulation of TMD for the repair of damaged skin^[37, 64, 66]

(a) Structure of TMD^[37]; (b) 2H-WS₂ nanosheets for treating deep burn wounds^[37]; (c) PCNPs@NIR-gel accelerating full-thickness skin healing in diabetic mice^[64]; (d) MoS₂@CSH repairing skin wounds of various shapes and sizes^[66]. TMD: Transition-metal disulfide; PCNPs: Polydeoxyribonucleotide nano-vectors particles; CSH: Chitosan hydrogel. Colorful figures are available on website

Sun 等^[64]用 MoS₂ 纳米片(MoS₂NS)引发 QCS 共聚反应后, 与聚(*N*-异丙基丙烯酰胺)形成交联网络, 负载核酸载体后形成复合水凝胶(PCNPs@NIR-gel) (图 5(c))。MoS₂NS 不仅可以促进自由基聚合以充当水凝胶基质中的物理交联位点, 还可以通过 NIR 光热转换提高水凝胶温度。当温度超过共聚物临界溶液下限温度时, 温度敏感链段发生相变, 触发水凝胶体积收缩, 释放核酸载体, 并将核酸有效递送至伤口部位, 促进其细胞内化并加速糖尿病小鼠全层皮肤缺损的愈合过程^[64]。值得注意的是, 当 MoS₂暴露于氧气中时, 易被氧化形成 MoO₄²⁻和 SO₄²⁻, 并在此过程中失去其内在特性^[65]。针对这一问题, 在超声分散条件下, 使用阳离子聚合物壳聚糖和多酚以增强剥离 MoS₂NS 的结构稳定性和生物相容性, 其光热转化特性加速了氧化剂和邻苯二酚之间的氧化反应速率, 实现溶胶-凝胶转变, 从而形成了由光热驱动的原位模塑可注射水凝胶(MoS₂@CSH) (图 5(d))。该水凝胶可应用于各种不规则形状、大小和深度的皮肤伤口, 有望成为一类颇具临床应用前景的新型伤口敷料^[66]。

1.5 过渡金属碳/氮化物

MXenes 是一类相对较新的二维纳米材料, 近

年来逐渐成为材料领域研究的焦点。它的通式为 M_{n+1}X_nT_x, 通过选择性蚀刻其 MAX 相的原子层进行合成^[67]。MAX 相可以由三元碳化物和氮化物、可靠的溶液以及有序的双过渡金属结构组成^[68]。MXenes 具有较大的比表面积、优异的电子传导和转移能力、丰富的边缘和缺陷位点以及过渡金属可变价态, 因而表现出较高的 ROS 清除活性和止血能力。Li 等^[69]将 Ti₃C₂ MXenes 纳米片作为人工非酶抗氧化剂, 引入到多巴胺水凝胶伤口敷料中 (图 6(a))。结合温和的光热刺激, 该材料极大地促进了人脐静脉内皮细胞增殖, 并通过清除 ROS 以保持细胞内氧还原稳态, 显著加速感染糖尿病伤口愈合^[69]。有研究表明, MXenes 清除 ROS 的机制可以概括为 MXenes 的边缘或缺陷位点为自由基提供或夺取电子, 使其失去孤对电子而淬灭^[70]。MXenes 的特殊结构也赋予了材料强大的止血能力。在 Wu 等^[71]的报道中, 含 0.5% (质量分数) GO/MXene 的 3-羟基丁酸-共羟基戊酸酯(PHBV)复合膜的血小板吸附能力比纯 PHBV 膜强 5 倍, 凝血时间为 379 s, 是纯 PHBV 膜的 1/3 (图 6(b))。该复合膜优异的止血性能在伤口愈合中极具应用价值。

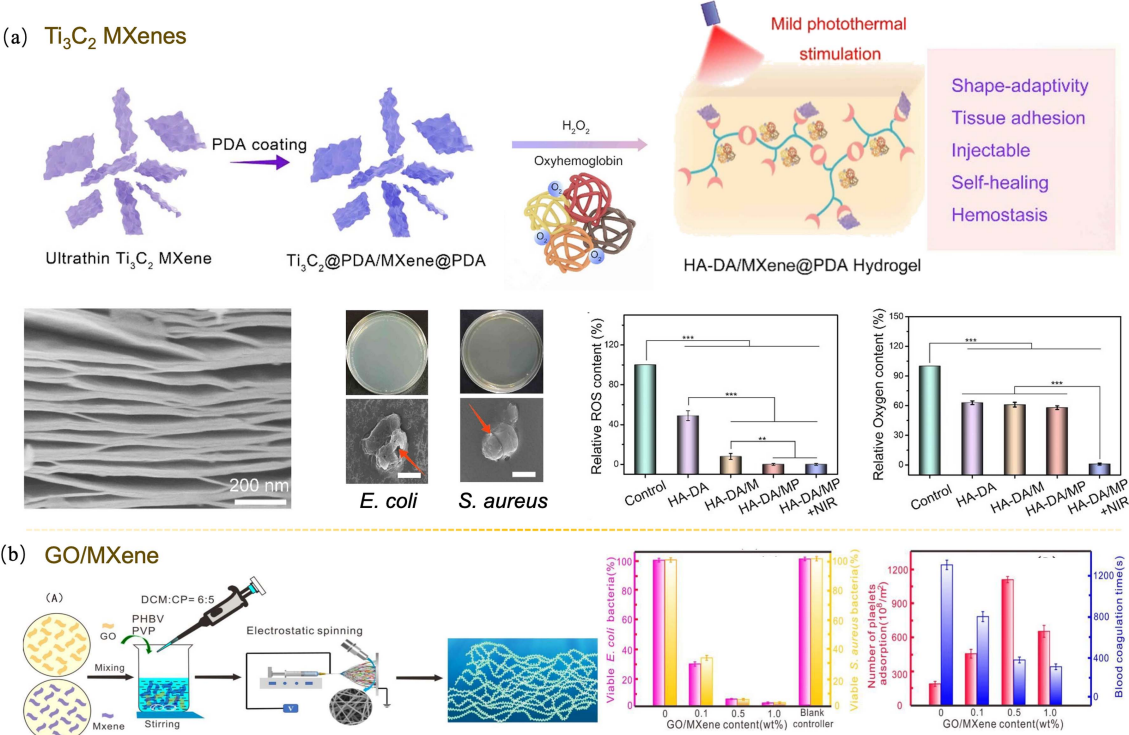


图 6 MXenes 调控病损皮肤修复^[69, 71]

Fig. 6 Regulation of MXenes for the repair of damaged skin^[69, 71]

(a) Ti_3C_2 MXenes nanosheet accelerating wound healing in diabetes^[69]; (b) GO/MXene laminate with excellent hemostatic properties^[71].
Colorful figures are available on website

此外, MXenes 中大量的离域电子赋予其良好的导电性, 使其能够作为外源性电场刺激应用于伤口愈合。通过模仿皮肤受损时跨上皮电位差诱导的内源性直流电场^[72], MXenes 能够调节成纤维细胞与上皮细胞的增殖及分化过程, 同时激发巨噬细胞和中性粒细胞迁移, 进而有效减轻水肿反应, 加速伤口从炎症期过渡到后期增生阶段^[73-74]。

2 展望

目前, 二维无机材料已成为组织再生修复领域的研究热点之一。凭借其独特的结构特性, 二维无机材料在调控病损皮肤修复过程中展现出抗菌、抗炎、抗氧化及止血等多种特性(表 1)和机制优势(表 2)。

表 1 二维无机材料在促进病损皮肤修复中的特性

Table 1 Characterization of various 2D inorganic materials in promoting the repair of diseased skin

Material	Characteristic	Ref.
Graphene/GO/rGO	QCS-CD-AD/GO supramolecular hydrogel rGO-CD: 0.6% (in mass) Swelling ratio: 129% Conductivity: 0.07–0.11 S/m Wound closure rate: 98.3%	[41]
Boron-based 2D materials	p-BNNSs@PVA thin film p-BNNSs: 30% (in mass) Thermal conductivity: 7.38 W/(m·K)	[47]
	B-QCS-BNN6 Bacterial inactivation rate: >99.9% (under NIR irradiation)	[48]
BP nanosheets	CS-BP hydrogel <i>E. coli</i> inactivation rate: 98.90% <i>S. aureus</i> inactivation rate: 99.51%	[52]
	4OI-BP@Gel Bacterial inactivation rate: >90% ROS clearance rate: 51.9% Wound healing rate: 99.64% (under NIR irradiation)	[56]
	SMHS Degradation product: $\text{PO}_4^{3-}/\text{HPO}_4^{2-}$	[57]

续表 1

	Material	Characteristic	Ref.
TMD	WS ₂ nanosheet	Cell viability of 2H-WS ₂ : 100% Cell viability of 1T-WS ₂ : 60.4% (150 µg/mL, 48 h)	[37]
	PCNPs@NIR-gel	Swelling ratio: 169% Bacterial inactivation rate: >99.9% (under NIR irradiation)	[64]
	MoS ₂ @CSH	Bacterial inactivation rate: ~100% (under NIR irradiation)	[66]
MXenes	Ti ₃ C ₂ MXenes nanosheet	DPPH clearance: 80% (2 mg) Wound closure rate: 98.8%	[69]
	GO/MXene laminate	GO/MXene: 0.5% (in mass) Coagulation time: 379 s	[71]

表 2 二维无机材料修复各类病损皮肤的作用机制

Table 2 Mechanisms of 2D inorganic materials for the repair of various types of diseased skin

Material	Type of skin defect	Mechanism	Ref.
QCS-CD-AD/GO supramolecular hydrogel	Full-thickness wounds	Bacterial cell membrane damage Modulation of immune cells Reduction: IL-6 Up-regulation: VEGF	[41]
p-BNNSs@PVA thin film	High-temperature environment	Out-of-plane thermal conductivity (TC): 7.38 W/(m·K) The higher TC, the faster heat dissipation	[47]
B-QCS-BNN6	MRSA infection	Bacterial cell membrane damage Controlled release of NO	[48]
CS-BP hydrogel	Bacterial infection	Producing ¹ O ₂ Promoting formation of the fibrinogen Activation: PI3K, Akt, ERK1/2	[52]
4OI-BP@Gel	Diabetic ulcers	High PTT (photothermal therapy) and PDT (photodynamics therapy) efficacy Up-regulation: Nrf2, HO-1 Activation: KEAP1–Nrf2	[56]
SMHS	Diabetic ulcers	Enhancing M2 activation Bacterial cell membrane damage Promoting collagen deposition	[57]
WS ₂ nanosheet	Deep burn	Up-regulation: CAT, GPx, antimicrobial peptides Reduction: TNF-α, IL-1β, IL-8, IL-6 Reduction: caspase-8, caspase-3, PARP	[37]
PCNPs@NIR-gel	Diabetic total skin defects	Bacterial cell membrane damage Up-regulation: VEGF, α-SMA Reduction: TGF-β, MPO Enhancing M2 activation Promoting collagen deposition Activation: PI3K-Akt, cAMP	[64]
MoS ₂ @CSH	Irregular wounds	Increase: CD31 Up-regulation: TNF-α	[66]
Ti ₃ C ₂ MXenes nanosheet	Diabetic ulcers	Enhancing M2 activation Scavenging ABTS ⁺⁺ Increase: IL-10, CD31 Up-regulation: TNF-α, HIF-1α, VEGF, α-SMA	[69]
GO/MXene laminate	Skin hemostasis	Presence of hydroxyl groups and terminal oxygen Free radical polymerization of ester bonds	[71]

然而,二维无机材料在临床应用中仍面临严峻挑战,这主要源于材料本身及其制备工艺可能引发的生物毒性、生物相容性差以及生物降解性不足等问题,这些安全性顾虑是当前阻碍其真正步入临床实践的重大障碍。二维无机材料利用自身锋利的边缘和光热转化特性可有效抗菌,但在杀死细菌的同时对人体正常细胞带来的毒性不容忽视。如前所述,某些未经处理的二维无机材料,其边缘的切割效应可能会直接对细胞膜造成伤害,或者导致产生过量的 ROS,进而引发正常细胞死亡。不过以往的研究似乎并未充分探讨这些二维无机材料可能具有的潜在细胞毒性。另外,材料在体内滞留会加重其潜在细胞毒性的长期危害。因此,可控的生物降解性是二维无机材料安全应用的必要条件。有研究表明,原始石墨烯在血浆中缓慢降解^[75],在过氧化物酶的作用下仅部分降解成二氧化碳。相比之下,高含量氧原子有助于 GO 在光-芬顿反应介导下表现出更好的降解性。而 h-BN 在 100 h 的光-芬顿反应条件下几乎完全降解,相比于碳基材料具有更好的降解性和更低的细胞毒性。但 h-BN 水分散性差,其生物相容性需要通过化学功能化提高。实际上,MoS₂ 的体内降解速率快于 WS₂。然而,其在血液中形成的蛋白质电晕是否会影响其生物降解过程,目前尚未得到充分研究^[76]。Ti₃C₂ 具有较高的稳定性,但目前对于伤口愈合的 Ti₃C₂ MXenes 材料的降解性研究不足^[77]。因此,开发适用于生物医学的可降解 MXenes 材料变得十分必要。相比之下,BP 独特的电子结构能够使电子转移到表面,物理吸附 O₂,这会导致 BP 的层依赖性氧化,促进其进入细胞和组织,为 BP 的体内生物降解奠定了基础^[78]。更重要的是,BP 的最终降解产物为 PO₄³⁻,可参与细胞正常新陈代谢,且无毒无副作用,可能是最有潜力和希望应用于病损皮肤修复临床治疗的二维无机材料。

为了加速推进二维无机材料的临床应用,实施大量标准化的动物实验是至关重要的步骤。然而,当前研究大多局限于小型啮齿动物,缺乏对二维无机材料在高级哺乳动物中的长期毒性、药代动力学、免疫原性和体内分布的深入研究,而这些研究能够更准确反映二维无机材料的实际治疗效果和代谢途径。此外,研究人员还需要密切关注临床环境中人体皮肤伤口微环境的变化,深入探索二维无机材料促进伤口愈合的潜在机制,以确保其在多变的临床条件下能够充分展现治疗效果。

材料的制备方法在很大程度上也影响着材料结构、生物效应及其在生物医疗市场中的开发和应用。目前,通过超声处理直接在有机溶剂中剥离块状晶

体以获得超薄层状二维纳米片的液相剥离法,是应用较广泛的制备方法之一。这种方法操作简单、成本低,可实现大规模生产。然而,通过这种方法获得的单层片材横向尺寸相对较小,且剥离过程所使用的有机溶剂和表面活性剂可能存在一定毒性^[79]。相比之下,湿化学合成法更容易控制材料的尺寸和形状,但制备过程易受反应温度、时间、前驱体浓度和溶剂的影响^[62]。另一种典型的自下而上工艺是化学气相沉积(CVD)法,该方法可制备具有高晶体质量、可扩展尺寸、可调厚度和优异导电性能的超薄二维材料,实际应用前景广阔,但其需要特定的衬底和高温、高真空条件。由此可见,目前使用较广泛的制备方法都有其各自的优缺点。因此,未来需要更多关注二维无机材料制备方法的优化。例如,采用气态或液态非金属前驱体代替传统固体前驱体或许可以提高材料的均匀性和可控性^[80];选择与材料晶格匹配的基材作为 CVD 衬底助力二维无机材料外延生长;开发类似于金(Au)这样具有低活性表面能的材料作为底物^[81],实现毫米级单层二维无机纳米片的高质量、高效率生产。

综上所述,二维无机材料由于其独特的结构,能够针对病损皮肤修复进程中的细菌、炎症、氧化应激等发挥有效的生物作用,应用前景尤其广阔。但在临床实际应用之前,二维无机材料的生物安全问题亟待解决。笔者认为,以 BP 为例的这类具有良好生物相容性、生物降解性且降解产物可被人体所利用的二维无机材料应该得到更多的关注和更大的投入。或许这类材料在未来很有可能被开发成为安全有效的医疗器械,并应用于病损皮肤修复的临床治疗中,从而使患者受益。

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