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基于大分子生物材料治疗多发性骨髓瘤

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摘要 多发性骨髓瘤(multiple myeloma, MM)是第二大最常见的血液系统恶性肿瘤, 其发病机制复杂, 临床表现多样, 现有的治疗策略不能精准有效地作用于肿瘤细胞, 而大分子生物材料具有可设计性强、生物相容性优良以及药物负载能力高等优点, 应用于MM的治疗能有效地解决该问题。该文系统综述了来源于肽、蛋白质、多糖、复合金属离子的大分子生物材料, 并将其构建成水凝胶、微球及多种纳米系统, 显著增强了药物的靶向性, 提高了药物在骨髓中的富集程度, 并延长了滞留时间; 讨论了大分子生物材料通过增强经典凋亡通路、激活免疫效应细胞、重塑骨髓微环境多层面协同抑制骨髓瘤进展, 为治疗MM提供了高效、低毒、个体化的方向, 也为MM的深入研究提供了新的思路。

关键词 大分子生物材料; 多发性骨髓瘤; 水凝胶; 微球

Treatment of Multiple Myeloma by Macromolecular Biomaterials

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Abstract MM (multiple myeloma) is the second most common hematologic malignancy, characterized by complex pathogenesis and diverse clinical manifestations. Existing therapeutic strategies fail to precisely and effectively target tumor cells. However, macromolecular biomaterials offer advantages such as high design flexibility, excellent biocompatibility, and superior drug loading capacity. Their application in MM treatment can effectively address this issue. This systematic review examines macromolecular biomaterials derived from peptides, proteins, polysaccharides, and metal ions. These materials are engineered into hydrogels, microspheres, and diverse nanoscale systems, which significantly enhance drug targeting, increase the degree of drug enrichment in the bone marrow, and prolong its retention time. The discussion highlights how macromolecular biomaterials synergistically inhibit myeloma progression through multiple pathways: enhancing classical apoptosis, activating immune effector cells, and remodeling the bone marrow microenvironment. This approach offers a highly effective, low-toxicity, and personalized therapeutic direction for MM and contributes novel perspectives for further exploration of the disease.

Keywords macromolecular biomaterials; multiple myeloma; hydrogels; microspheres

多发性骨髓瘤(multiple myeloma, MM)是一种以骨髓浆细胞异常增殖为特征的恶性肿瘤, 它占血液系统恶性肿瘤的10%, 占所有癌症的1%, 是仅次于淋巴瘤的第二大最常见的血液系统的恶性肿瘤[1-2]。据统计, 该病全球年发病率约50万例, 年死亡人数约10万例[3], 尽管近年来治疗该疾病的手段不断更新, 但

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患者的5年生存率仍仅有50%, 且复发率接近100%, 该疾病的形势已然十分严峻, 科学家们对该疾病的研究刻不容缓[4-5]。MM发生机制复杂, 临床表现多种多样, 这给治疗带来了极大的挑战。该疾病不仅会导致骨髓内肿瘤的发展, 还会伴随有骨质破坏、肾功能损害等一系列临床表现, 这些显著影响了患者的生活质量[6]。尽管近年来随着蛋白酶体抑制剂[如硼替佐米(bortezomib, BTZ)、卡非佐米]、免疫调节剂(如来那度胺、泊马度胺)、单克隆抗体(如达雷妥尤单抗、伊沙妥昔单抗)等新型药物的出现, 该疾病在治疗上取得了一定的进展, 患者的生存率也有明显的提高[7-8]。但是小分子药物不能在骨髓中停留足够长的时间, 并有效地与骨髓瘤细胞相互作用, 从而使这些药物不能精准、有效地作用于肿瘤细胞[9-10]。

近年来, 大分子生物材料因其自身的优越性能已逐渐成为了研究的热点, 相较于小分子药物而言, 大分子生物材料具有结构可设计性强、生物相容性优良、药物负载能力高并且在体内的行为可调控等优势[11-12]。大分子生物材料被设计成靶向肿瘤的载体, 可负载治疗肿瘤的药物, 显著提升了药物的稳定性和靶向递送效率以及药物的治疗安全性, 提高了复发性和难治性患者的安全性和缓解率, 这为MM的治疗提供了新的思路[13]。

本文从材料组成角度来看, 大分子生物材料包括肽、蛋白质类材料、多糖类材料以及复合金属离子材料等多种类型。其中, 基于蛋白质的大分子材料如单克隆抗体、抗体药物偶联物、双特异性抗体和融合蛋白拥有高度特异性的分子识别能力, 在MM免疫治疗中已取得了重要的进展[14-15]。多糖类材料具有良好的生物相容性和可修饰性, 主要应用于构建纳米递送系统, 它可以显著提升传统抗骨髓瘤药物的水溶性、体内稳定性及骨髓富集能力, 在一定程度上克服化疗耐药性[12]。复合金属离子大分子材料整合了金属离子的物理化学特性和生物大分子靶向能力, 实现了光热、光动力和肿瘤微环境响应性治疗, 为MM的治疗提供了新的可能。

大分子生物材料在MM治疗中的作用不仅限于药物递送层面, 还能调控骨髓微环境。骨髓瘤细胞对骨髓微环境高度依赖, 而大分子材料可通过调控血管生成、抑制破骨细胞活性及重塑免疫微环境等多种途径, 破坏肿瘤细胞赖以生存的生态位, 从而间接诱导肿瘤细胞死亡[16-17]。特别是抗血管生成策略与免疫治疗及纳米材料的结合, 被认为是未来提高治疗持久性和降低复发风险的重要方向[17]。因此, 系统地总结基于大分子生物材料治疗MM的策略十分有必要, 本文深入解析了大分子生物材料在药物递送、免疫调控及肿瘤微环境重塑中的作用机制, 这对于推动该领域的基础研究和临床转化具有重要意义。

1 材料的来源

1.1 基于肽、蛋白质的大分子生物材料

蛋白质、多肽具有强大的识别与结合能力且其靶向性强、毒性低、免疫原性弱、生产成本低, 利用它们制造出作用于肿瘤的药物不仅能够发挥其本身的性能, 还能直接杀伤肿瘤细胞[18], 这类材料(表1)在肿瘤方面具有很大的发展潜力。近期, 研究人员在利用单克隆抗体治疗MM方面取得了重大进展。例如在抗体药物偶联物(antibody-drug conjugate, ADC)疗法中, 单克隆抗体作为呈递药物的载体, 具有精准的靶向性, 能特异性地识别并结合肿瘤细胞表面的特定抗原[19]。在此基础上, 多臂连接子偶联多个药物分子, 形成药物束TE-1146, 该药物束与来那度胺联合使用相较于传统的达拉图单抗与来那度胺联合, 能在小鼠异种移植肿瘤模型中根除多发性骨髓瘤肿瘤[20]。在运用免疫检查点抑制剂治疗MM中, 单克隆抗体能完美地与T细胞上的蛋白结合, 阻止肿瘤细胞的免疫逃逸[21]。这种具有特定靶向功能的蛋白质载体, 能与细胞特异性识别并结合, 从而提高药物的治疗效果并降低对正常细胞的毒性。除此之外, 蛋白质纳米颗粒载体通过靶向递送、药物保护和增强疗效三重作用为MM治疗提供了新型解决方案, 基于超分子异二聚体肽的靶向脂质体, 在小鼠皮下异种移植多发性骨髓瘤模型注射24 h和48 h后, 靶向脂质体的有效存留在肿瘤中的药物显著高于非靶向脂质体(P=0.028)。蛋白质纳米颗粒可以提升传统化疗药、核酸药物的精准性与安全性, 也能与免疫治疗、放疗协同, 突破MM治疗的现有瓶颈[22-23]。细胞因子免疫复合物与融合蛋白是将具有靶向功能的蛋白片段和具备细胞杀伤或免疫激活能力的蛋白结构域结合, 形成兼具定位功能与治疗效果的生物大分子材料, 在小鼠急性骨髓性白血病模型中, IL-2/S4B6显著增强了细胞疫苗方法的有效性, 使得小鼠在120 d后生存率达到100%, 而单独使用

表1 大分子生物材料治疗MM

Table 1 Macromolecular biomaterials for the treatment of MM

大类 Major categories	材料类别 Material category	核心功能与机制 Core features and mechanisms	在MM中的关键疗效/应用 Key efficacy and applications in MM	参考文献 References
Protein/peptide-based materials	Antibodies and fusion proteins (BsAb, ADC, cytokine conjugates)	Precision targeting and immune regulation: through specific antigen recognition, these approaches enable direct cell killing, drug delivery, or activation of the immune system	Tumor eradication: the ADC drug TE-1146, in combination with lenalidomide, eradicated tumors in a mouse model Potent inhibition: BsAb significantly inhibits tumor growth in human xenograft models even at low doses 100% survival rate: the combination of the IL-2/S4B6 immune complex and the vaccine increased the 120 d survival rate in mice to 100%	[19-21,24-28]
	Protein/peptide nanocarriers (protein nanoparticles, peptide-targeted liposomes)	Targeted delivery and synergistic effects: utilizing biological targeting to deliver drugs, enhance tumor accumulation, protect the drug, and achieve synergistic therapeutic effects	Peptide-targeted liposomes exhibited significantly higher retention in tumors than non-targeted liposomes (P=0.028)	[22-23]
	Protein-based hydrogels/microspheres (HA hydrogels, protein microspheres)	Creating a biomimetic microenvironment: simulating the bone marrow niche for 3D culture, antibiotic susceptibility testing, and localized sustained-release drug delivery	Predicting therapeutic efficacy: the ADCC/CDC effects assessed using 3D models are significantly correlated with patient clinical outcomes Delayed progression: the sustained drug release from the pH-responsive hydrogel significantly delayed tumor progression in mice	[54-58,60-65]
Carbohydrate-based materials	Chitosan-derived nanosystems (targeted nanoparticles, prodrugs, nanomicelles)	Active targeting and controlled release: active targeting is achieved through modification (e.g. anti-CD38), and drug release is controlled in response to the microenvironment (pH/enzymes)	Significantly prolonged survival: delivery of BTZ via anti-CD38 chitosan nanoparticles increased survival rates in mice (32% survival rate at 35 d) Potent apoptosis: the selenium-chitosan composite significantly promotes apoptosis in MM cells Enhanced efficacy and reduced toxicity: CPT-TMC micelles are more effective than the free drug; the prodrug form of melphalan has lower toxicity	[29-30,32,34]
	Other functional polysaccharide materials (HA hydrogels, sugar polymers, dextran microspheres, chitosan/PLGA nanoparticles)	Microenvironment simulation, target inhibition, and nucleic acid delivery: simulating the bone marrow, inhibiting key enzymes (heparanase), and protecting and delivering nucleic acid drugs	Tumor suppression: sugar polymers mimicking HS can significantly reduce the survival rate of MM cells Effective treatment: chitosan/PLGA nanoparticles delivering miRNAs have a significant anticancer effect	[31,33,54,60,66]
Composite metal ion materials	Metal nanoparticles (ZnO, Ag, multifunctional composites)	Direct cytotoxic effects and synergistic effects: inducing apoptosis in target cells or enhancing the efficacy of radiotherapy and chemotherapy through synergistic effects, demonstrating potential for both therapeutic and diagnostic applications	Induction of apoptosis: ZnO nanoparticles can induce apoptosis in MM cells in a time- and dose-dependent manner Synergistic effects: the combination of silver nanoparticles with radiation therapy and various metal composites with chemotherapy has demonstrated strong synergistic effects	[51,89-91]
	MOFs (metal-organic frameworks)	Porous carriers and catalytic platforms: high drug-loading capacity, capable of integrating catalytic therapy, photodynamic therapy, and immunomodulation	This provides a highly versatile platform with great potential for the multimodal treatment of MM	[43-50]
	Other composites (calcium silicate, carbon nanotubes)	Drug sensitization and efficient delivery: enhancing the efficacy of chemotherapy, or serving as a scaffold to improve the delivery of poorly soluble drugs	Sensitizing chemotherapy: calcium silicate significantly enhances the antimyeloma activity of BTZ Long-term suppression: drug delivery via carbon nanotubes can achieve long-term tumor suppression	[52,93-94]

细胞疫苗时小鼠生存率约为12%, 单独使用IL-2/S4B6免疫复合物时小鼠生存率仅为0%。这为MM治疗提供了靶向性强、毒性可控的解决方案[24-25]。双特异性抗体(bispecific antibody, BsAb)是通过基因工程技术将两个不同的抗原结合域与抗体的恒定区融合, 形成能够同时识别两个靶点的新型抗体结构[26-27]。双特异性抗体teclistamab在0.5和1.0 μg剂量水平显著阻断多发性骨髓瘤H929预防模型肿瘤生长, 在每只动物服用10和50 μg剂量水平下显著抑制了多发性骨髓瘤RPMI 8226回归模型肿瘤生长。在MM的治疗中, BsAb通过精准靶向两种抗原和激活免疫效应细胞双重机制, 将分散的免疫细胞招募至MM细胞周围并激活其细胞毒性功能, 从而实现对MM的靶向治疗[26,28]。除此之外, 蛋白质类的大分子材料能在血液中长期循环, 且在体内表现出高稳定性, 这使得药物的有效浓度得以维持更长时间, 从而减少频繁给药。不仅如此, 天然蛋白质材料的降解产物通常无毒且可以被人体有效吸收利用, 避免长期残留积累可能引发的副作用。同时, 蛋白质的免疫相容性更保障了其临床安全性, 降低了免疫相关不良反应的发生风险, 这些均为治疗MM提供了良好的基础。

1.2 基于碳水化合物的大分子生物材料

基于碳水化合物的大分子生物材料通常是低毒的, 容易被修饰且具有强亲水性, 这让其在体内应用更安全。科学家们已经研发出多项此类材料作用于MM(表1)。硼替佐米是最有效的蛋白酶体抑制剂之一, 但其应用受剂量相关副作用限制。PUENTE等[29]提出了一种针对BTZ的靶向递送的材料。抗CD38壳聚糖纳米颗粒可在肿瘤微环境中促进药物释放, 并特异性结合MM细胞, 通过表面扩散与纳米颗粒胞吞作用促进BTZ摄取, 强化蛋白酶体抑制效果, 使用BTZ载荷的抗CD38壳聚糖纳米颗粒治疗MM模型小鼠, 可显著提高其总体生存率(35 d存活率为32%)(载体组第28天死亡、游离BTZ组第29天死亡和BTZ负荷非靶向NP组第31天死亡), 对骨髓瘤细胞产生强效细胞毒性。除抗CD38壳聚糖纳米颗粒外, ZHANG等[30]研究人员采用硒−壳聚糖−聚乙二醇−香芹酚纳米复合材料(SCP-Car-NCs)处理MM细胞, 显著降低了细胞活力并促进了细胞凋亡, 表明该复合材料在MM治疗中具有新的治疗潜力。微小RNA(microRNA, miRNA)的治疗方法需要合适的装置, 该装置需要保护包封化合物免受酶的快速降解, 实现高效的细胞摄取并保留其药理活性。壳聚糖/聚乳酸−羟基乙酸共聚物纳米颗粒在使用时能够免受降解同时使包裹的药物化合物选择性地向作用位点递送, 通过体外和体内测试证明, 该纳米药物通过miRNA的细胞内定位, 为MM提供了有效的抗癌作用[31]。美法仑(melphalan, Me)是一种用于治疗血液系统恶性肿瘤的抗癌药物, 但其临床应用受到水溶性差、消除快和缺乏靶向特异性的限制。研究发现, 采用聚合物缀合策略并使用甘氨酰甘氨酸(Gly-Gly)作为间隔基, 使得最终形成的O,N-羧甲基壳聚糖−肽−美法仑缀合物具有良好的组织蛋白酶敏感性, 其毒性更低, 且药物释放行为显著改善, 有望成为具有前景的抗癌前药[32]。肝素酶的异常表达是MM进展的关键因素之一, 而它可以降解肝素硫酸盐(heparan sulfate, HS), 促进肿瘤细胞增殖、迁移和对化疗的抵抗。科学家发现了模拟HS的糖聚合物能够作为强效肝素酶抑制剂, 显著降低骨髓瘤细胞的存活率[33]。LI等[34]研究人员开发了N,N,N-三甲基壳聚糖喜树碱(N,N,N-trimethyl chitosan camptothecin, CPT-TMC)纳米胶体, 用于高效安全的全身给药, 与单独使用喜树碱(camptothecin, CPT)相比, CPT-TMC更能有效抑制肿瘤生长并延长生存期, 解决CPT溶解度低及其活性内酯形式不稳定的问题。LI等[35]发现一种新型1-酰胺基-2-酮-4-硫代-脱氧吡喃糖, 它作为潜在药物靶点TRIP13抑制剂, 与先前报道的强效抑制剂不同, 该物质有助于开发基于碳水化合物的MM新型治疗药物。基于碳水化合物类的大分子生物材料本身的特性, 未来我们可以进一步利用它, 结合pH、酶等响应, 开发具有高靶向、高载药、低毒性的多功能生物材料, 拓展其在肿瘤治疗方面的应用。

1.3 复合金属离子的大分子生物材料

金属离子和生物大分子材料通过复合在一起形成复合金属离子大分子生物材料, 能够靶向递送药物、调节肿瘤微环境并且增强免疫治疗效果。这类材料的核心是将具有特定生物活性的金属离子与蛋白质、多肽、多糖等生物大分子结合, 利用大分子的靶向性、生物相容性及金属离子的特殊理化性能或者生物活性, 间接实现对肿瘤的治疗。

近年来, 纳米材料的兴起为癌症治疗带来了新的机遇。金属纳米颗粒(metal nanoparticles, MNPs)因其优异的物理、化学和生物学特性, 成为癌症诊疗研究的热点。金属纳米颗粒不仅能够作为药物载

体实现精准靶向递送，还能通过光热效应、光动力效应等多种机制直接杀伤肿瘤细胞，同时具备成像诊断能力，可实现治疗与诊断的整合[36-37](表1)。金属纳米颗粒由于拥有可控的尺寸、表面功能化的能力和优异的载药能力，可用于药物的载体[36,38]。DESAI等[36]总结了金属纳米颗粒通过被动靶向和主动靶向两种机制，能够有效增强药物在肿瘤部位的富集，减少对正常组织的毒副作用，并且金属纳米颗粒能够提升药物的水溶性和稳定性从而延长药物在体内的半衰期。例如，利用环糊精修饰的金属纳米颗粒可以有效包载疏水性药物，提升生物利用度，降低系统毒性，并且这种复合纳米载体通过外部刺激，如近红外光或磁场能够实现控制释放，进一步增强治疗效果[39]。肿瘤微环境(tumor microenvironment, TME)通常是酸性、缺氧、富含活性氧和高浓度谷胱甘肽的状态。因此，科学家们设计了多种响应性的金属纳米颗粒，它们能够精准识别和调控肿瘤微环境，并增强免疫治疗效果。YANG等[40]指出，响应肿瘤微环境的金属纳米颗粒能够调节肿瘤局部的氧化还原状态、释放药物并激活免疫细胞从而显著提升肿瘤免疫治疗的疗效。除此之外，纳米颗粒还可以和化疗、放疗及光动力疗法联合使用，多模式协同抗击肿瘤，增强抗肿瘤的效果。光热治疗(photothermal therapy, PTT)和光动力治疗(photodynamic therapy, PDT)是利用光能激活纳米颗粒产生热能或活性氧来杀伤肿瘤细胞的技术。金属纳米颗粒由于优异的光学性质和生物相容性，在PTT和PDT中发挥重要的作用[41-42]。CHERUKURI等[41]早期便报道了金属纳米颗粒在近红外光照射下产生局部高温进而实现肿瘤细胞的选择性杀伤。SHANG等[42]进一步总结了金属纳米颗粒作为光敏剂载体在乳腺癌光动力治疗中的应用，强调了其在提高光敏剂稳定性、靶向性及细胞穿透能力方面的优势，并探讨了金属纳米颗粒的表面可通过共价或非共价方式负载光敏剂实现更为精准的肿瘤定位和光响应释放。

在金属纳米颗粒探索的同时，金属有机框架(metal-organic frameworks, MOFs)也在逐步被科学家们所采用。MOFs是一种由金属离子或簇节点与有机配体通过配位键所构建的多孔晶体材料，它的结构各异，且具有易于功能化和良好的载药能力，成为了癌症诊疗领域的研究热点[43-45]。金属有机框架不仅能够像金属纳米颗粒一样实现对肿瘤的光动力治疗[46]，还因其结构的优势与模拟天然酶的纳米材料纳米酶结合，催化肿瘤微环境中的化学反应，增强了治疗效果[47-49]。纳米酶通过调控肿瘤微环境中的氧气供应、催化生成活性氧、耗竭谷胱甘肽等途径，来实现肿瘤细胞的选择性杀伤[47]。科学家们将能够选择性杀伤肿瘤细胞的纳米酶装载在具有优异结构的金属有机框架上，就如同具有眼睛的炮弹，能够给肿瘤细胞重大的打击。在如此具有靶向性和杀伤性的情况下，免疫佐剂功能化的金属有机框架提升了免疫激活能力，这进一步提升了肿瘤免疫治疗的精准化和安全性[50]。

上述复合金属离子的大分子生物材料在治疗各类肿瘤中大放异彩，但在MM中的应用探索尚浅，JANA等[51]将金属离子负载于大分子生物材料上形成3种纳米复合材料与化疗药物联合治疗MM，观察到3种纳米复合材料与来那度胺、波马度胺或美尔法兰联合使用具有强烈的协同效应，显著提高了其抗肿瘤活性，表明这些组合在未来临床研究中具有潜力。CAO等[52]将硅酸钙和硼替佐米联合治疗MM明显增强了硼替佐米抗骨髓瘤细胞的作用，并为未来利用纳米技术制备硅酸钙纳米材料作为硼替佐米载体奠定了基础。金属纳米颗粒能够提高治疗精准性，减少对正常组织的毒副作用，实现多模式协同治疗，并集治疗与诊断功能于一体。金属有机框架结构可调，功能化潜力大，并能结合纳米酶，实现高效的催化治疗，同时增强免疫治疗效果。这些均为未来整合靶向递药、光热、光动力、免疫治疗和催化调控等多机制治疗MM提供了有力的支撑。

1.4 其他大分子生物材料

还有一些其他的生物大分子在治疗MM中起着至关重要的作用，它们是一种来源于生物的功能性大分子材料。例如由病毒改造而来的病毒载体，这种载体可以携带一段已经人工编码好的嵌合抗原受体(chimeric antigen receptor, CAR)外源基因，导入到患者自身的T细胞基因组中，最终重编程T细胞，使患者体内具备靶向杀伤癌细胞的嵌合抗原受体T细胞(chimeric antigen receptor T-cell, CAR-T)[53]。

2 构建的方法

2.1 水凝胶构建3D生物模型

MM由于缺乏模拟肿瘤生物学特性的模型，其机制和治疗研究进展不大。而水凝胶可模拟骨髓

的物理化学特性, 支持MM细胞与基质细胞的共培养。例如, 透明质酸(hyaluronic acid, HA)水凝胶能支持MM细胞的存活, 并促进其迁移与克隆形成[54]。近年来研究发现, 3D培养中的间充质干细胞能形成细胞簇, 并保持其标准表面标记物和分化能力, 并且能表达关键的生态位相关分子, 如N-钙黏蛋白和CXCL12, 这对于骨髓瘤细胞的归巢和存活至关重要, 该模型的核心优势是能重现临床观察到的耐药性, 并针对不同的耐药类型依次进行研究, 对不同患者实现个体化医疗[55]。HE等[56]构建了患者来源的异种移植模型, 该模型的癌组织与临床的癌组织在形态特征和蛋白质表达上一致, 因此研究人员将该模型嵌入配对水凝胶, 用于组织培养药物敏感性测试, 从而筛选可以抑制肿瘤的药物。同轴生物打印技术构建的HA水凝胶模型包含矿物外层和软质核心, 成功模拟人骨髓结构, 可促进包裹MM细胞的生长和增殖, 为MM建模、药物开发和个性化治疗未来提供了新见解[57]。在建立多种多样的水凝胶模型的基础上, 利用水凝胶的特性能更准确地评估药物反应。在HA水凝胶中培养的原代MM细胞, 可用于测试达雷妥尤单抗的抗体依赖性细胞毒性(antibody-dependent cellular cytotoxicity, ADCC)和补体依赖性细胞毒性(complement dependent cytotoxicity, CDC), 其效果与患者临床反应及无进展生存期显著相关[58]。脂质体包裹的药物如硼替佐米、多柔比星在3D水凝胶模型中显示更强的MM细胞杀伤作用, 同时可降低对基质细胞的毒性[59]。除此之外, 这些水凝胶能够起到药物靶向递送作用从而达到局部治疗的效果。载有骨形态发生蛋白-6(bone morphogenetic protein-6, BMP-6)的HA-肝素水凝胶能诱导MM细胞凋亡并促进间充质干细胞成骨分化, 同时抑制BMP拮抗剂骨硬化蛋白的活性, 有望用于修复骨病变并清除残留MM细胞[60]。pH响应性水凝胶通过苯硼酸−儿茶酚键合释放硼替佐米, 在酸性微环境中持续释放药物, 在小鼠模型中可显著延缓肿瘤进展[61]。水凝胶通过模拟骨髓微环境、支持细胞培养、药敏试验以及促进MM细胞增殖与药物评估, 实现免疫调节与肿瘤抑制, 为MM的基础研究与临床治疗提供了仿生、精准、协同治疗的体外3D生物模型(表1), 这种体外三维生物模型让科学家们可以更好地研究疾病。

2.2 微球构建3D细胞培养模型

微球具有可功能化、生物相容性好及易于操控的特性, 被用于构建仿生微环境, 模拟骨髓瘤细胞与骨髓微环境的相互作用。例如, 蛋白质功能化的微球可与MM细胞共培养, 形成动态悬浮的微凝胶系统, 该系统可支持MM细胞的增殖, 并可用于其耐药机制的研究[62-63]。此类模型能更真实地反映肿瘤细胞在体内的行为, 尤其是对地塞米松、硼替佐米等药物的耐药性[64]。这种模型还可以作为载体递送药物, 如蛋白质微球可通过声化学方法封装抗癌药物, 并保持药物活性。这些微球在体外对MM细胞系显示出抗癌活性[65]。此外, 葡聚糖微球可用于栓塞治疗, 临床病例表明, 葡聚糖微球控制MM相关的出血或肿瘤供血既安全又有效[66]。此外, 荧光微球或与抗体结合的微球可用于同时检测细胞表面抗原, 从而辅助MM的免疫表型分析[67]。流式微球技术可定量检测患者血浆中细胞因子(如IL-6)水平, 为疾病诊断和治疗监测提供依据[68]。这些例子(表1)均表明微球在MM研究中能够良好地用于体外3D模型构建、药物递送、临床栓塞治疗及实验室检测, 为治疗MM奠定基础。

2.3 纳米系统

在过去几十年中, 纳米医学解决了一些和传统医学技术相关的问题, 引起了人们极大的关注[69]。传统药物对癌症的治疗非常重要, 但它的缺点也显而易见, 药物溶解度低、耐药性高且难以靶向肿瘤细胞, 这些问题都为临床治疗增加了难度[70]。纳米药物使治疗药物更加稳定且易于溶解, 还可以精确靶向肿瘤细胞, 并实现治疗药物的缓慢释放, 以此提高药物的有效性, 减少药物的副作用, 纳米药物(表1)成为了医学研究的一个十分有前途的领域[71-72]。

2.3.1 脂质体 现如今, 脂质体类纳米材料是最成熟、研究最广泛的。它是脂质双分子层构成的球形囊泡, 具有良好的生物相容性和高载药效率[73]。负载了美法兰或硼替佐米的脂质体纳米药物能够在骨髓中增强渗透性并产生滞留效应, 显著延长了药物的半衰期, 经过验证显示出比游离药物更强的抗肿瘤活性和更低的药物毒性[74-75]。除此之外, 经CD38或CD138配体修饰的脂质体, 能够主动靶向骨髓瘤细胞, 从而将药物更精准地递送至骨髓瘤细胞, 提升药物治疗效果[76-77]。

2.3.2 聚合物胶束 聚合物胶束是由两亲性嵌段共聚物自组装形成, 疏水核心能够包裹难溶性药物[78]。负载了卡非佐米、塞利尼索等药物的胶束能够提升

药物的溶解度和稳定性[79-80], 并通过连接达拉妥尤单抗、A6实现主动靶向, 在动物模型中表现出优异的抗肿瘤效果并延长了小鼠的生存期[81-82]。

2.3.3 纳米颗粒 聚合纳米颗粒是由可生物降解材料构成的颗粒, 在药物递送和免疫治疗方面表现突出[83]。它的优势在于能够实现药物的可控释放、降低细胞毒性, 并延长药物在肿瘤部位的滞留时间[84]。YU等[85]报道了一种具有强大的小尺寸纳米系统, 它能稳定负载药物并能控制抗体偶联, 这种免疫纳米药物将硫酸长春新碱载于达拉单抗免疫聚合体上, 在体内实现CD38靶向化疗和原位MM清除。将免疫原性BCMA72-80肽包裹于PLGA纳米颗粒中, 能够成功诱导抗原特异性细胞毒性T淋巴细胞反应, 表面功能化的聚合纳米颗粒能够主动靶向骨髓瘤细胞, 显著提高药物在骨髓瘤细胞中的内化效率, 并且协同诱导免疫原性细胞死亡和自噬[86-87]。无机纳米颗粒不仅仅可以作为药物载体, 其自身更有抗肿瘤活性[88]。平均尺寸约30 nm的氧化锌纳米颗粒能以时间和剂量依赖的方式诱导MM细胞凋亡[89-90]。而将放射性核素碘-131标记的单克隆抗体艾莎妥昔单抗与银纳米颗粒结合, 可以发现这两种物质在抑制细胞增殖和诱导凋亡方面起到了协同增效的作用[91]。除此之外, 利用植物提取物制备的无机纳米颗粒也显示出良好的应用前景, 它能够通过上调*P53*基因表达等机制有效杀伤癌细胞[92]。碳基纳米颗粒拥有极高的比表面积和独特的针状结构, 成为了装载药物的理想支架[93]。将口服蛋白酶体抑制剂通过修饰连接到多壁碳纳米管上, 能有效递送药物, 且在一定程度上降低了游离药物的细胞毒性, 还可以对肿瘤实现长期抑制[94]。

3 作用于MM的机制

3.1 作为载体, 增强传统诱导凋亡途径

为实现MM的精准治疗并降低传统化疗的系统性毒性, 在生物大分子药物表面修饰相应抗体、肽链或配体等靶向分子, 利用MM细胞表面特异性高表达的抗原, 可实现药物的主动靶向输送。研究证实, 在MM患者中, B细胞成熟抗原(B-cell maturation antigen, BCMA)的表达水平显著升高, 其可溶性BCMA的血清浓度均显著高于正常值上限[95]。这使其成为一个极具潜力的治疗靶点也同时是目前最成功且研究最广泛的靶点[96-97]。针对BCMA的CAR-T疗法已在早期及后续临床试验中显示出良好的疗效[98-99], 客观缓解率(objective response rate, ORR)在高剂量组中可达80%~100%, 其中完全缓解(complete response, CR)率也表现出显著提升[100-101]。CAR-T细胞通过其CAR结构识别肿瘤细胞表面抗原, 活化的CAR-T细胞释放穿孔素在靶细胞膜上形成孔道, 使颗粒酶B进入细胞内部, 激活caspase级联反应, 导致细胞凋亡[99]。除此之外, 部分MM细胞表面Fas表达水平较低, 但可通过地塞米松、蛋白酶体抑制剂等药物或细胞因子刺激增强Fas敏感性, 活化T细胞表面的FasL与MM细胞表面的Fas受体结合, 导致Fas受体三聚化, 其内部死亡结构域吸引衔接蛋白FADD, FADD的另一个死亡效应结构域继而募集procaspase-8。最终形成了死亡诱导信号复合物(death inducing signaling complex, DISC)。在DISC中, procaspase-8通过自身剪切被激活, 转化为有活性的caspase-8, 进而激活下游的效应caspase-3和caspase-7[102]。这两种凋亡形式共同诱导MM细胞凋亡(图1)[103]。有文章指出, FAS-FASL受体−配体信号通路在调控凋亡中起关键作用, 已被认为参与决定CAR-T细胞的存续性[104-105]。LIN等[106]在预印本中讲到增强Fas/FasL信号会促进CAR-T杀伤, 抑制异质肿瘤中的抗原逃逸。基于此CAR-T细胞被改造为持续高表达FasL后, CAR-T细胞通过其CAR识别MM细胞表面的抗原(如BCMA)并形成免疫突触, 除了释放穿孔素、颗粒酶外, 还能大量提供FasL信号, FasL通路和穿孔素、颗粒酶通路协同作用MM细胞, 形成更强大的杀伤作用。然而, CAR-T疗法在MM中面临耐药和复发挑战, 其机制包括抗原逃逸、T细胞耗竭以及免疫抑制性肿瘤微环境[96,107-108]。例如, 在临床试验中, 部分患者因抗原逃逸或T细胞清除而导致治疗失败[109]。为了克服这些限制, 研究正探索双特异性CAR-T细胞同时靶向BCMA和CD19或多靶点策略, 以降低抗原逃逸风险[110], CAR-T细胞同时靶向BCMA和CD19的早期临床研究显示出显著疗效。一项I/II期研究显示, 其ORR达到92%, 中位无进展生存期(progression-free survival, PFS)与中位总生存期(overall survival, OS)均为19.7个月, 1年OS率达85%[111]; 另一项联合输注研究同样报道了92%的ORR及18.3个月的中位PFS[112], 证实了该策略在克服抗原逃逸及延长生存方面的潜力。此外, 加入共刺激分子优化CAR设计或与免疫检查点抑制剂联

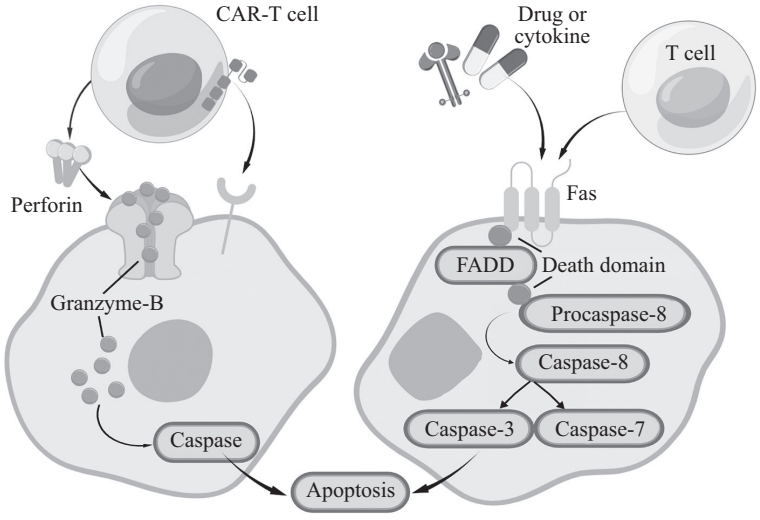
用的组合疗法可增强疗效并减少毒性[96,108]。总之, CAR-T疗法通过特异性抗原识别和T细胞激活机制发挥抗肿瘤作用, 但其受限于多种耐药因素, 未来需进一步研究以优化治疗策略[107,113]。

3.2 基于免疫调控的杀伤机制

现如今常用单克隆抗体和双特异性抗体方法治疗MM, 单克隆抗体方法通过特异性结合肿瘤细胞表面的抗原, 引发ADCC、CDC和抗体依赖性细胞吞噬作用(antibody-dependent cellular phagocytosis, ADCP), 从而直接杀死肿瘤细胞或标记它们以供免疫系统清除(图2)[2,114]。ADCC通过抗CD38抗体与MM细胞表面的CD38结合, 其Fc段与自然杀伤细胞、巨噬细胞等效应免疫细胞表面的Fc受体结合, 激活这些细胞并释放细胞毒性物质, 导致肿瘤细胞裂解[114-115]。ADCP通过巨噬细胞识别抗CD38抗体包被的MM细胞, 将其吞噬并清除[114,116]。CDC通过抗体与CD38结合可激活补体系统, 形成膜攻击复合物, 直接在肿瘤细胞膜上穿孔, 引起细胞溶解[114]。这些免疫效应机制已在临床应用中被证实可显著改善患者预后。关键性III期研究显示, 基于达雷妥尤单抗的方案在中位随访28.0个月时, 达雷妥尤单抗组疾病进展或死亡风险降低44%(HR=0.56, P<0.001), 30个月PFS率达70.6%, 显著优于对照组的55.6%, 且其CR比例提升至47.6%(对照组24.9%)[117]。双特异性抗体则是一种新的、更直接的方式, 它直接连接免疫细胞与癌细胞, 强制激活杀伤癌细胞。BsAbs通过一端结合MM细胞上的抗原, 另一端结合T细胞的CD3ε链, 促使T细胞与肿瘤细胞直接接触, 形成免疫突触。这导致T细胞活化、细胞因子IFN-γ和IL-2等释放以及细胞毒性颗粒的分泌, 最终裂解肿瘤细胞[118-121]。总之, 单克隆抗体主要通过募集和激活患者自身免疫系统来间接杀伤肿瘤细胞, 而双特异性抗体则构建了一座桥梁, 直接连接并强力激活T细胞, 对肿瘤进行精准杀伤。两者共同构成了当前MM靶向免疫治疗的重要支柱。

3.3 调控肿瘤微环境, 间接促进癌细胞死亡

3.3.1 *抑制破骨细胞活性, 破坏恶性循环* MM的特征性骨病源于骨重塑过程的严重失衡, 其核心是破骨细胞活性异常增高而骨形成受抑, 导致溶骨性病变[122]。MM细胞通过分泌多种细胞因子(如RANKL、CCL3、MIP-1β、IL-3等), 强烈促进破骨细胞生成。同时, MM细胞分泌多种Wnt信号通路拮抗剂(如Dkk-1、

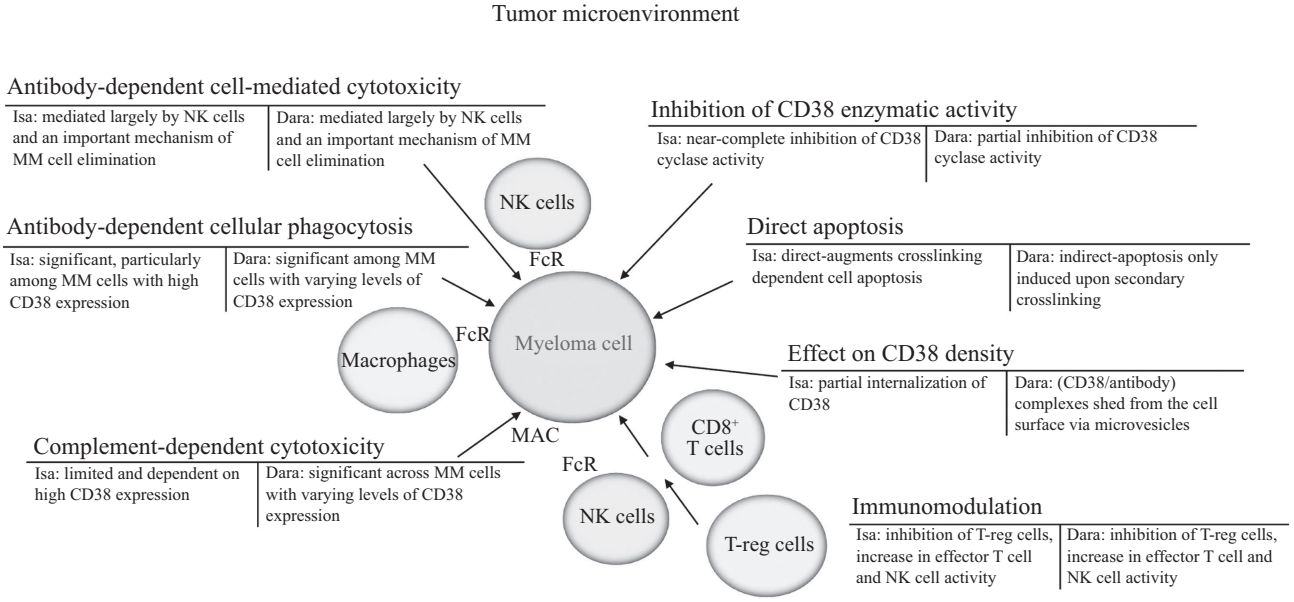


活化的CAR-T细胞释放穿孔素在靶细胞膜上形成孔道, 颗粒酶B进入细胞内部, 激活caspase级联反应, 导致细胞凋亡。药物或细胞因子刺激增强Fas敏感性, 活化的T细胞与Fas受体结合, Fas受体三聚化, 其内部死亡结构域吸引衔接蛋白FADD, FADD的另一个死亡效应结构域募集procaspase-8, 并自身剪切激活转化为有活性的caspase-8, 进而激活下游的caspase-3和caspase-7, 导致细胞凋亡。

Activated CAR-T cells release perforin, which forms pores in the target cell membrane; granzyme B enters the cell interior, activates the caspase cascade, and leads to apoptosis. Stimulation by drugs or cytokines enhances Fas sensitivity. Activated T cells bind to the Fas receptor, causing it to trimerize. The internal death domain of the Fas receptor attracts the adaptor protein FADD. Another death-effect domain of FADD recruits procaspase-8, which undergoes self-cleavage to convert into active caspase-8, thereby activating the downstream caspase-3 and caspase-7. This leads to apoptosis.

图1 多发性骨髓瘤细胞凋亡示意图

Fig.1 Schematic diagram of apoptosis in multiple myeloma cells



抗CD38单克隆抗体伊沙妥西单抗和达雷妥尤单抗的作用机制。Dara: 达雷妥尤单抗; FcR: Fc受体; Isa: 伊沙妥西单抗; MAC: 膜攻击复合物; MM: 多发性骨髓瘤; NK: 自然杀伤细胞; T-reg: 调节性T细胞。

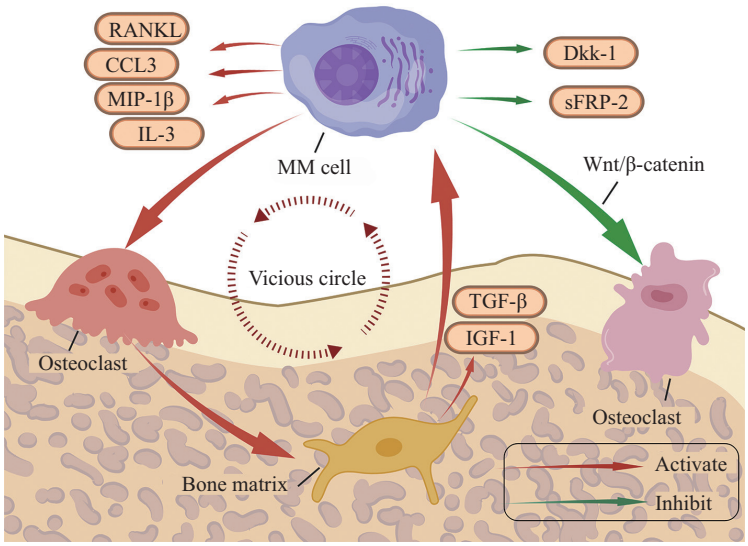
Mechanisms of action of the anti-CD38 monoclonal antibodies. Dara: daratumumab; FcR: Fc receptor; Isa: isatuximab; MAC: membrane attack complex; MM: multiple myeloma; NK: natural killer cell; T-reg: regulatory T cell.

图2 抗CD38单克隆抗体伊沙妥西单抗和达雷妥尤单抗的作用机制(本图引用自参考文献[114])

Fig.2 Mechanisms of action of the anti-CD38 monoclonal antibodies isatuximab and daratumumab (adapted from reference [114])

sFRP-2等), 这些分子阻断了Wnt/β-catenin经典通路, 而该通路是成骨细胞分化、成熟的关键[122-124]。这使得破骨细胞过度活化而成骨细胞分化被抑制。但这一过程并非孤立存在的, MM细胞与破骨细胞之间形成了一个相互促进的恶性循环, MM细胞在刺激破骨细胞的形成与活化时[124], 反过来, 破骨细胞介导的骨吸收会释放储存在骨基质中的生长因子, 为骨髓瘤细胞的增殖和存活提供支持信号, 从而形成一种前馈循环, 加快疾病进展(图3)[103,122]。因此, 抑制破骨细胞活性被视为打破这一恶性循环、治疗骨髓瘤骨病的关键策略。双膦酸盐类药物是经典的破骨细胞功能抑制剂, 能有效降低包括高钙血症、病理性骨折在内的骨骼相关事件发生率[125]。此外, 可针对破骨细胞分化与活化的关键通路RANK/RANKL/OPG进行干预, 例如Denosumab是一种较新开发的治疗转移性骨病的药物, 它直接靶向并抑制RANKL, 从而阻断破骨细胞的分化生成, 并抑制骨吸收活性, 且临床证实其在预防骨骼相关事件方面不劣于甚至优于双膦酸盐, 且无肾毒性风险[123]。这为将骨靶向治疗整合到MM的整体治疗框架中提供了重要的理论依据。值得注意的是, 蛋白酶体抑制剂硼替佐米在发挥抗骨髓瘤作用的同时, 也能够抑制破骨细胞功能, 成为骨保护剂[126]。硅胶原酸凝胶和硼替佐米释放的硅胶凝胶, 可用于局部治疗骨溶解性骨病和MRD(minimal residual disease)。这两种材料都能降低破骨细胞活性, 且不会干扰成骨细胞的分化和功能, 从而能够修复骨缺损, 并局部控制恶性浆细胞生长[127]。通过抑制破骨细胞活性、减少骨吸收, 可以剥夺骨髓瘤细胞赖以生存的微环境生长信号, 可能使其更易走向凋亡, 从而间接发挥抗肿瘤效应[122,128]。硫酸乙酰肝素模拟糖聚合物靶向肿瘤微环境, 通过抑制乙酰肝素酶, 阻止其对细胞外基质的降解, 从而可能延缓骨破坏的进程并抑制肿瘤生长[33]。MM骨病的核心是破骨细胞激活与成骨细胞抑制之间的严重失衡, 二者与骨髓瘤细胞构成一个相互促进的恶性循环。因此, 靶向干预此恶性循环的骨靶向治疗是阻断MM骨病进展的关键策略。现有的策略包括直接抑制破骨细胞(如双膦酸盐、硼替佐米), 局部修复骨缺损(如硅胶原酸凝胶)或调节肿瘤微环境(如硫酸乙酰肝素模拟物)。这些治疗能有效防治骨骼并发症、改善生活质量, 更重要的是, 它能够打破恶性循环从而剥夺肿瘤细胞的生存支持, 间接发挥抗骨髓瘤效应。

3.3.2 抗血管生成 在MM的进展中, 血管生成是



MM细胞分泌RANKL、CCL3、MIP-1β、IL-3等细胞因子刺激破骨细胞的形成和分化。同时, MM细胞分泌Dkk-1、sFRP-2等Wnt信号通路拮抗剂, 阻断了Wnt/β-catenin经典通路, 使得成骨细胞分化被抑制。除此之外, 更重要的是MM细胞与破骨细胞之间形成了一个相互促进的恶性循环, MM细胞在刺激破骨细胞的形成与活化时, 反过来, 破骨细胞介导的骨吸收会释放储存在骨基质中的生长因子, 为骨髓瘤细胞的增殖和存活提供支持信号, 加快疾病进展。

MM cells secrete cytokines such as RANKL, CCL3, MIP-1β, and IL-3, which stimulate the formation and differentiation of osteoclasts. At the same time, MM cells secrete Wnt signaling pathway antagonists such as Dkk-1 and sFRP-2, blocking the canonical Wnt/β-catenin pathway and thereby inhibiting osteoblast differentiation. Furthermore, and more importantly, a mutually reinforcing vicious cycle develops between MM cells and osteoclasts. While MM cells stimulate the formation and activation of osteoclasts, the bone resorption mediated by osteoclasts releases growth factors stored in the bone matrix, providing supportive signals for the proliferation and survival of myeloma cells and accelerating disease progression.

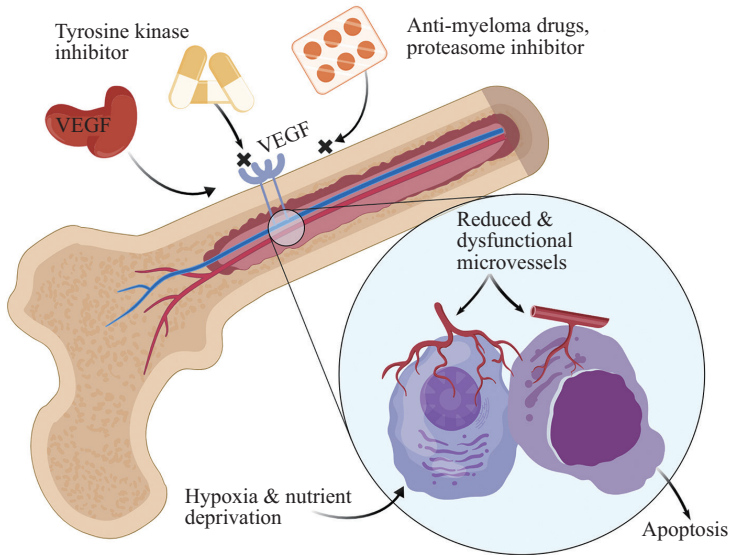
图3 多发性骨髓瘤中骨病变机制

Fig.3 Mechanisms of bone disease in multiple myeloma

一个关键的病理特征, 其活跃程度与患者预后及疾病活动状态密切相关[129]。针对这一机制, 抗血管生成治疗已成为一种重要的治疗策略。这主要通过直接递送靶向血管生成细胞因子VEGF或其受体的药物单克隆抗体、酪氨酸激酶抑制剂来抑制肿瘤新生血管的形成[130-131]。此外, 许多临床常用的标准抗骨髓瘤药物如免疫调节剂、蛋白酶体抑制剂也被证实具有抗血管生成效应[130]。抗血管生成药物所诱导的血管抑制, 会导致肿瘤微环境发生明显的变化, 包括功能性微血管网络的减少与结构异常[132]。这种微血管结构的改变直接导致肿瘤组织内缺氧和营养匮乏。恶化的微环境所诱发的代谢应激间接促进骨髓瘤细胞凋亡(图4)[103]。通过破坏肿瘤依赖血管的微环境间接诱导癌细胞死亡, 是MM治疗领域极具吸引力的研究方向[129]。将高分子生物材料作为抗血管生成药物的载体, 将在未来惠及更多的患者。

3.4 基于微量金属元素的作用机制

金属元素与MM的发生发展密切相关, 科学家们发现金属离子能够通过各自独特的机制在MM的发生与发展中发挥调节作用。有文献表明锌作为超氧化物歧化酶(superoxide dismutase, SOD)的辅因子, 它可以通过激活NRF2通路并抑制NOX2和KEAP1表达, 进而降低化疗后的氧化应激和炎症因子(如TNF-α)表达水平, 高剂量锌也可以通过线粒体途径诱导MM细胞凋亡, 这些均能起到抑癌作用[133]。临床研究证实, 在为接受自体干细胞移植的MM患者补锌后, 患者体内初始$CD4^+$ T细胞和T细胞受体切除环(T cell receptor excision circle, TREC)水平可显著增加, 促进免疫重建[134]。硒蛋白如谷胱甘肽过氧化物酶(glutathione peroxidase, GPX)和硫氧还蛋白还原酶(thioredoxin reductase, TrxR)能通过清除脂质过氧化物来减轻肿瘤氧化损伤[135]。而特定有机硒化合物(如Ebselen)可通过诱导氧化应激选择性抑制MM细胞增殖[136]。铁的作用关键在于平衡促癌与促死亡, 它作为DNA合成必需的辅因子[137], 过高会促进MM增殖, 但MM细胞对铁积累导致的脂质过氧化高度敏感, 易发生以Xc/GSH/GPX4通路为核心调控机制的铁死亡(ferroptosis)[135,138](图5), 这为克服硼替佐米耐药提供了新策略。铜通过特异性信号轴驱动疾病进展, 研究发现COMMD3蛋白高表达与MM不良预后相关,



抗血管生成治疗通过递送靶向血管生成细胞因子VEGF、酪氨酸激酶抑制剂、蛋白酶体抑制剂或其他抗骨髓瘤药物，导致功能性微血管网络的减少与结构异常。造成肿瘤组织内部的缺氧和营养供应缺乏，使骨髓瘤细胞走向凋亡。

Anti-angiogenic therapy reduces the size and causes structural abnormalities in the functional microvascular network by delivering targeted anti-angiogenic cytokines such as VEGF, tyrosine kinase inhibitors, proteasome inhibitors, or other anti-myeloma drugs. This leads to hypoxia and a lack of nutrient supply within the tumor tissue, causing myeloma cells to undergo apoptosis.

图4 抗血管生成治疗示意图

Fig.4 Schematic diagram of anti-angiogenic therapy

其通过ATOX1-ATP7A-LOX轴调节铜水平，进而促进MM细胞增殖和髓外迁移[139]。多种金属元素在MM的发生发展和治疗中扮演着复杂的角色。它们是维持正常生理功能的必需元素，但也能通过调节氧化应激影响细胞死亡。深入探究这些金属元素，利用铁死亡克服耐药、通过补锌促进免疫重建、靶向铜信号轴抑制转移均为开发新型治疗策略提供了重要的理论依据和潜在靶点。

4 总结与展望

大分子生物材料在医疗领域前景广阔，为治疗MM提供了有力地支撑。科学家们以肽、蛋白质、多糖和金属离子为原料形成了各种各样的大分子生物材料。蛋白质类的大分子生物材料具有高度特异性，能够精准识别肿瘤细胞，解决靶向性不足的问题，而以多糖为原料所形成的大分子材料具有低毒性和可修饰性，这使其在体内的代谢清除过程更为安全可控，也同时为耐药问题提供了可能得解决方法，在引入金属离子后实现肿瘤微环境响应释放。这些大分子生物材料的出现为目前我们所遇到的问题提供了新的解决思路。本文系统综述了来源于肽、蛋白质、多糖、复合金属离子的大分子生物材料在MM治疗中的研究进展，重点总结了其在精准药物递送、免疫重定向、肿瘤微环境调控中的优势。通过构建水凝胶、微球及多种纳米系统显著促进了药物在骨髓中的富集与滞留，还为模拟骨髓生态位、筛选个体化治疗方案提供了重要平台。从作用机制层面看，大分子生物材料通过增强经典凋亡通路、激活免疫效应细胞、重塑骨髓微环境多层面协同抑制骨髓瘤进展。大分子生物材料正处于快速发展的阶段，随着对材料、肿瘤和微环境之间的深入探索，可开展更多的临床转化，这为利用大分子生物材料治疗MM提供了高效、低毒、个体化的方向，还为其他疾病打下了坚实基础。

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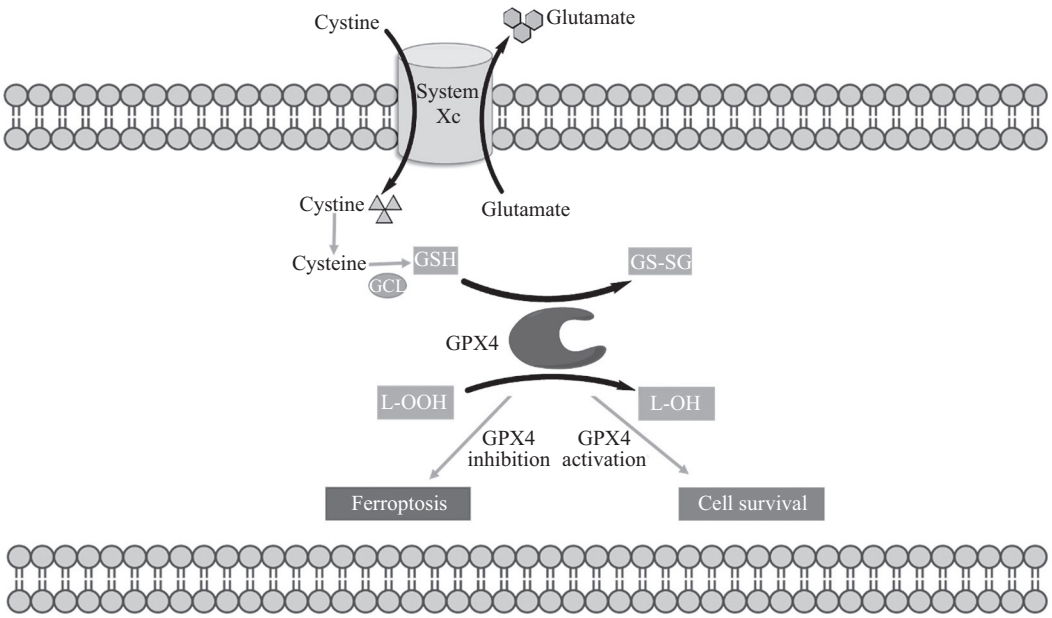

铁死亡诱导的磷脂过氧化过程由半胱氨酸/谷胱甘肽/GPX4调控通路介导。Xc系统反向转运蛋白介导细胞外半胱氨酸与细胞内谷氨酸的交换。当胱氨酸被内化后, 会被还原为半胱氨酸, 后者是谷胱甘肽生物合成的前体之一。GPX4利用GSH作为辅因子, 将有毒的脂质过氧化物还原为相应的醇类。GSH或GPX4的耗竭都会导致脂质过氧化物水平升高, 从而损伤细胞膜, 并引发铁死亡——这是一种与多种人类疾病相关的细胞死亡形式。

The ferroptotic induced peroxidation of phospholipids is mediated by the cysteine/GSH/GPX4 regulatory pathway. The system Xc antiporter mediates the exchange of extracellular cystine with intracellular glutamate. When cystine is internalized, it gets reduced to cysteine which is one of the precursors for the biosynthesis of GSH. GPX4 utilizes GSH as a cofactor for the reduction of toxic lipid peroxides into the respective alcohols. Depletion of either GSH or GPX4 will cause an increase in lipid peroxides that will damage the cell membrane, and lead to ferroptotic cell death—a form of cell death implicated in a wide variety of human diseases.

图5 由半胱氨酸/谷胱甘肽/GPX4调节通路介导的铁死亡诱导的磷脂过氧化作用(本图引用自参考文献[135])

Fig.5 The ferroptotic induced peroxidation of phospholipids is mediated by the cysteine/GSH/GPX4 regulatory pathway (adapted from reference [135])

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