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镁及光热治疗在口腔颌面头颈部肿瘤中的研究进展

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摘　要

癌症是全世界人类生命的主要威胁。位于牙龈、舌和口底的晚期恶性肿瘤还会造成颌骨破坏，即使截骨也不可避免地存在肿瘤细胞残留，疾病复发患者的预后和生活质量有很大影响。传统的癌症治疗方法，有很大的局限性，手术难以确保彻底性，放疗和化疗在杀死肿瘤细胞的同时会对正常组织造成不可逆的损伤以及较严重的并发症。光热治疗(photothermal therapy, PTT)是一种非侵入性新型肿瘤治疗方式，在近红外光(near-infrared, NIR)照射下，将光能转变为热能发挥作用，也是目前比较前沿的癌症治疗策略。镁基生物可降解金属具有优异的成骨、血管生成性能，同时强大的力学强度，是一种已经应用于临床的新型的生物医用材料。其中金属镁颗粒具有作为光热剂(photothermal agent, PTA)的潜力，具有很高的光热转换效率，可以在局部范围内迅速产热，从而在肿瘤的光热治疗中具有明显的优越性。本文综述了镁的光热效应在抗肿瘤方面的应用。镁的抗肿瘤作用主要来自其降解产物。更重要的是，在肿瘤组织切除后，镁同时具有抗肿瘤和组织再生的双重功能，在肿瘤治疗中显示出巨大的潜力。

关键词

镁，光热治疗，光热剂，口腔颌面头颈部肿瘤，近红外光，镁基生物可降解金属，口腔鳞状细胞癌，光动力疗法

Research Progress of Magnesium and Photothermal Effect in Oral, Maxillofacial, Head and Neck Tumors

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Abstract

Cancer is the main threat to human life worldwide. Late-stage malignant tumors located in the gums, tongue, and floor of the mouth can also cause damage to the jawbone, and even with osteotomy, residual tumor cells are inevitable. This has a significant impact on the prognosis and quality of life of patients with disease recurrence. Traditional cancer treatment methods have significant limitations, with surgery being difficult to ensure thoroughness, and radiation therapy and chemotherapy causing irreversible damage to normal tissues and more serious complications while killing tumor cells. Photothermal therapy (PTT) is a non-invasive new type of cancer treatment that converts light energy into heat energy under near-infrared (NIR) irradiation, and it is currently a cutting-edge cancer treatment strategy. Magnesium-based biodegradable metals have excellent osteogenic and angiogenic properties, as well as strong mechanical strength, making them a new type of biomedical material that has been applied in clinical practice. Among them, magnesium metal particles have the potential to serve as photothermal agents (PTA), with high photothermal conversion efficiency and the ability to rapidly generate heat locally, thus demonstrating significant superiority in photothermal therapy for tumors. This article reviews the application of magnesium's photothermal effect in anti-tumor treatment. The anti-tumor effect of magnesium mainly comes from its degradation products. More importantly, after tumor tissue resection, magnesium has dual functions of anti-tumor and tissue regeneration, showing great potential in tumor treatment.

Keywords

Magnesium, Photothermal Therapy, Photothermal Agent, Oral, Maxillofacial, Head and Neck Tumors, Near Infrared, Magnesium-Based Biodegradable Metals, Oral Squamous Cell Carcinoma, Photodynamic Therapy

1. 背景介绍

癌症是困扰全世界的一种严重疾病，传统治疗是通过手术切除，然后进行化疗/放疗以杀死剩余的肿瘤细胞。来源于牙龈、舌和口底的晚期恶性肿瘤还会造成邻近颌骨破坏，需要同期截骨，即使截骨也不可避免地存在肿瘤细胞残留，手术引起的广泛骨组织丢失和不可避免的肿瘤细胞残留对患者的预后和生活质量有很大影响[1]。同时黏膜愈合不良，失去保护屏障，术后感染机率增加，细菌感染引发炎症反应，阻碍软硬组织修复过程，对患者的容貌和生活质量产生较大影响。

因此，迫切需要开发具有双重功能的新型生物材料，包括有效消除残留癌细胞以防止肿瘤复发和促进组织再生以修复手术缺损的能力，并且对健康组织危害较小的新疗法。本文介绍了镁及光热治疗在口腔颌面头颈部肿瘤中研究现状进行综述。

2. 癌症的新兴治疗法

随着科学的发展，科学家们在癌症治疗方面发挥巨大作用，不断出现新的治疗方法，这些新兴疗法包括免疫疗法，基因疗法[2]，光动力疗法(photodynamic therapy, PDT) [3]和光热治疗[4]。

2.1. 光热治疗

光热治疗是在“光”的照射下，利用光热转换剂产生的光热效应，从光中收集能量并将能量转化

为热量，来提高周围环境的温度并引发癌细胞的死亡[5]。这种非辐射转换已经被认识到巨大的作用，1900 年 Niels Ryberg Finsen 使用过红光治疗天花，使用蓝光治疗皮肤狼疮，获得了 1903 年的诺贝尔医学和生理学奖。近些年，激光被逐渐用于肿瘤消融，利用其高能量诱导周围温度增高，从而损伤破坏细胞活性。目前随着深入研究，逐渐用于无创性的癌症治疗、诊断，很有希望成为下一代非侵入性癌症治疗诊断新兴技术。PTT [4] [6]具有某些优势：① 可调节剂量的外部激光作为诱导光热效应的触发器，808 nm 近红外(NIR)光已广泛应用于医学领域。② 精确地瞄准肿瘤，对周围健康组织的损害降至最低，对皮肤几乎没有热损伤的特性。③ 一种高效非侵入性治疗方法，已应用于伤口愈合、癌症治疗、代谢调节等领域[7]。温和的热刺激(40℃~45℃)可以促进细胞的生存能力，导致皮肤、血管和骨骼的自愈或再生；适度的热刺激(45℃~50℃)可以通过诱导细胞膜崩溃和蛋白质失活来有效杀灭肿瘤和细菌，而不影响正常细胞；而过度的热暴露(>55℃)会导致组织灼伤[8]。当超过人体预警温度 40℃，并达到 41℃时，热休克反应出现，会诱导基因、蛋白表达模式的一系列迅速变化，其中一点就是热休克蛋白(heat shock proteins，别名热激蛋白，HSP)的产生，目的是以减轻初始热损伤对机体的影响。当温度达到 42℃时，组织会发生不可逆的损伤，将组织加热至 42℃~46℃持续 10 分钟就会导致细胞坏死[9]。当达到 46℃~52℃时，会因为微血管形成血栓，造成局部缺血，细胞会在很短时间内迅速死亡[9]。当组织温度 > 60℃，达到这一温度需要在光热效应 PTT 作用下实现，在此温度下，由于蛋白质变性和细胞膜破坏，细胞可瞬时死亡[9]。

2.2. 光热转换剂 PTA

理想的 PTA 应具有更高的光热转换效率(PCE)，吸收不与肿瘤背景重叠，并且在肿瘤中具有良好蓄积[10]。同时良好的生物相容性、可吸收性以及低毒性也是必要的特性，所以外源性 PTA 会增强 PTT 效果[11]。

2.2.1. PTA 及 PTT 存在的缺点

由于 PTT 对癌症治疗的有效性的某些缺点或生物屏障，如果是深部组织，光穿透深度有限，会导致照射范围外以及边缘的肿瘤消融不完全。除此之外，不同的 PTA 在肿瘤中的递送效率不同，如果在肿瘤区域过热，会对周围正常组织造成不必要的损伤，以及本文前述内容提到的热休克蛋白(HSP)，由于在某些癌症中过度表达而产生对 PTT 的对抗性[12]，从而失去光热效应功能。

2.2.2. 克服 PTT 缺点的方法

已经取得了许多进展来克服这些缺点，例如采用适当的激光剂量[13]，确定施用 PTA 后的最佳治疗时间[14]，改善 PTA 的 PCE [15]，开发在第二 NIR 窗口中具有吸收的 PTA [16]，以及通过调节纳米颗粒(NP)的形状、尺寸、和表面化学或肿瘤微环境(TME) [17]。此外，还可通过与其他疗法的组合也可以改善治疗结果以及刺激药物释放、提高药物递送效率、调节肿瘤微环境(TME)，引发肿瘤特异性抗原释放，或者影响其他生物学相关反应来直接致死癌细胞，还可以通过增强其他疗法来达到这一目的[18]。

2.2.3. 光热转换剂 PTA 分类

一般分为有机材料和无机材料。无论哪种材料，预期 PTA 仅局部升高温度，以减少对健康组织的损伤，为了实现这一目标，PTA 的选择通常被调整到 750 和 1350 nm 之间的组织透明窗口，包括第一(750~1000 nm) (NIR-I)和第二(1000~1350 nm) (NIR-II) NIR 窗口。无机材料包括贵金属材料[19]、金属硫化物材料[20]、碳基纳米材料(石墨烯和碳纳米管等)和其它二维(2D)材料(黑磷、纳米片、氮化硼和石墨碳氮化物、MXenes 等) [21]。无机 PTA 比有机 PTA 具有更高的光热转换率，以及更优异的光热稳定性，能充分将热能转化为热效应。但有机 PTA 可能在生物降解性和生物相容性方面表现更佳。

3. 镁基生物可降解金属

3.1. 新型有效的光热转换剂

镁基生物可降解金属是否克服上述这些缺点，成为新型有效的光热转换剂 PTA，同时符合理想的抗肿瘤材料的特性，也是我们研究的重点。

目前要想成为理想的 PTA，还要具有：(1) 合理的光热转换剂药物载体，可在治疗肿瘤的同时降低毒副作用。(2) 能够同时抑制肿瘤细胞，而不损伤健康组织的新型生物材料[22]。(3) 具有临床潜力的下一代生物可降解材料。(4) 其中一种方法是将镁合金用于癌症治疗，有潜力成为理想的 PTA。目前发现镁在能量代谢、大分子合成、遗传信息表达等方面具有多种生物学功能，可用于癌症治疗，不损伤健康组织[23]。目前研究发现镁合金结合光热治疗 PTT 是骨肉瘤(OS)应用的潜在生物材料，该材料采用低温沉积 3D 打印技术，是一种含镁可降解高分子多功能多孔仿生支架，具有光热效应抑制肿瘤复发，并序贯释放镁离子，还可有效促进骨缺损修复[24] [25]。

3.2. 镁能够抑制肿瘤发生发展

近些年来研究发现，镁能够通过中和肿瘤微环境中弱酸性、抑制低氧水平、降低高活性氧水平以及提高免疫水平来抑制肿瘤发生发展的。肿瘤微环境由各种细胞组成，细胞包括：免疫细胞、炎性细胞、肿瘤相关成纤维细胞，还包括一些细胞因子和趋化因子，还有促进生长的微血管，与肿瘤的发生、生长、转移和复发关系密切。增强的有氧糖酵解(Warburg)有利于肿瘤细胞的存活和侵袭[26]，乳酸的大量积累为肿瘤细胞的迁移和免疫逃逸提供了有利条件[27]。

镁是一种较活泼金属，在组织中发生化学反应，是因为能够降解生成抗肿瘤产物氢气、镁离子和氢氧化镁，在实体瘤中才具有治疗性能。镁腐蚀产物具有巨大的抗肿瘤潜力：(1) H_2 具有抗氧化和抗炎特性，能够有效抑制氧化应激、增强常规抗肿瘤药物的敏感性，机制需探索[28]。(2) $Mg(OH)_2$ 持续碱化肿瘤微环境，抑制肿瘤进展，抑制增殖、激活抗肿瘤免疫[29]。(3) 肿瘤患者多合并低镁血症，会加速恶性进程。(4) 局部肿瘤微环境中 Mg^{2+}浓度的上调具有抗肿瘤效应，同时 Mg^{2+}也有抗炎作用[30]。(5) 肿瘤患者多合并低镁血症，影响组织细胞的酶促反应和代谢功能，进而加速肿瘤的恶性进程，还能够改善患者的整体状况、进而实现综合抗癌疗效，因此可认为肿瘤介入治疗中维持抗肿瘤微环境，可在实体瘤治疗中具有抑制肿瘤进展的潜在用途。镁降解产物与 PI3K/AKT 通路相关研究：Mg^{2+}通过 AKT/mTOR 和 Bax 信号通路促进肿瘤凋亡[31]；H_2 通过 PI3K/AKT 信号通路抑制肿瘤细胞增殖[32]；$Mg(OH)_2$ 可能通过抑制 PI3K/AKT 信号通路抑制肿瘤细胞的永生化[33]。PI3K/AKT 在癌症研究中一经典通路，在癌症发生发展中发挥作用。

3.3. 镁的临床研究

镁基生物可降解金属(BM)是用于生物医学应用的有前途的生物材料，由于其高生物降解性和良好的机械和生物相容性[34]。镁在能量代谢、大分子合成、遗传信息表达等方面具有多种生物学功能[35]。研究证实了镁基可吸收金属支架在不同冠状动脉、肺动脉和下肢血管中的手术成功率和耐受性[36]。此外，镁及其合金被认为是骨修复应用的潜在材料，因为其弹性模量与人骨接近，具有必需的营养元素、高机械性能和良好的生物相容性[34] [37]。Mg^{2+}可以促进成骨分化也在体外和体内实验中得到了很好的证明[38]。

3.4. 镁的抗肿瘤研究

3.4.1. 抗软组织肿瘤

在抗肿瘤方面表现突出。同时在骨肉瘤(OS) [39] [40]、乳腺癌[41]、卵巢癌[42]、前列腺癌[43]、结肠

癌[44]、胆囊癌[45]、肝癌[46]、直肠癌[44] [47] [48]、食管癌[49]和其他癌症，并证实了其抗肿瘤和抗复发作用。镁合金还能促进组织愈合，可以填补肿瘤切除后的组织缺损，促进健康组织再生，改善患者预后。

3.4.2. 抗骨肿瘤

在抗骨肿瘤方面镁合金不仅能抑制肿瘤细胞生长，还能促进肿瘤切除后骨缺损处新骨形成，显示出镁合金在抗骨肿瘤应用中多功能作用的巨大潜力[44]。1) Mg^{2+}抗肿瘤：纯镁丝通过释放 Mg^{2+}激活锌指蛋白 Snail1 从细胞质向细胞核的转运，从而诱导骨肉瘤(OS)细胞凋亡，抑制增殖。此外，镁丝产生的氢氧化物气体消除了过多的细胞内活性氧，抑制骨肿瘤细胞生长[50]。2) 镁钙合金抗肿瘤：利用 MgCa0.7 合金处理 OS 细胞，发现其可抑制 Saos-2 骨肉瘤细胞系[51]。3) 合金表面涂层抗肿瘤：a) 使用双膦酸盐(BP)负载的微弧氧化涂层镁锶合金颗粒来抑制 OS [52]。BP 涂层镁颗粒通过诱导细胞凋亡、坏死和镁降解的协同效应来破坏肿瘤并预防肿瘤复发；在镁合金表面制备了层状双氢氧化物，增强了其抗肿瘤作用[53]。4) 镁合金多孔结构抗肿瘤及生物活性支架促骨再生：镁合金的多孔结构允许细胞浸润并促进成骨细胞的附着和生长，同时降解时，它会释放出镁离子对 OS 细胞的抗肿瘤作用[53]；植入的生物活性支架可以通过 Mg^{2+}刺激骨髓基质细胞(BMSC)的成骨分化能力，从而促进骨缺损区域的新骨生成[54]；因其多孔结构，使 Mg^{2+}在降解过程中可在其中进行离子交换，具有双功能生物活性支架[55]。5) 镁合金已被用作光热剂(PTA)，在光热治疗中发挥作用[25]，由于 Mg 颗粒可以直接用作 PTA 而无需负载颗粒，并且可以同时实现良好的光热转换性能和对周围健康组织的积极影响，是潜在生物材料。

4. 光热治疗 PTT 在头颈部肿瘤中的相关研究

光热治疗 PTT 这一无创治疗方法已在伤口愈合[56]、癌症治疗、代谢调节[57]等方面得到应用，基于可靠的组织穿透性、高能量、对皮肤几乎无热损伤 808 nm 近红外(NIR)光作为光热效应的触发器已广泛应用于医学领域[58]。光热疗法利用将光转化为热的光敏纳米颗粒(NP)，非常适合对暴露的浅表肿瘤的治疗。一种用于口腔癌症的 pH 响应电荷逆转纳米药物系统，以聚多巴胺(PDA)改性的黑磷纳米片(BP-NSs)为基体材料，利用聚丙烯酰胺盐酸盐－二甲基马来酸(PAH-DMMA)电荷反转系统对其进行进一步的表面改性，有可能成为一种非常有前景的口腔癌症治疗新模式[59]。作为一种浅表性癌症，大大降低了因为深度而影响光的穿透[60]。特别是，纳米 PTA 可以通过增强的渗透性和保留(EPR)效应和主动靶向作用在肿瘤中积累[61]。手性钼(Cys-MoO3-x)纳米颗粒和手性钼(Cys-MoO)纳米粒子(NP)由于导电性和光吸收率的良好初始光热光谱分析而被选为通过半胱氨酸分子的修饰来治疗口腔鳞状细胞癌(OSCC)细胞的理想设计，具有良好的应用前景[62]。负载有盐酸阿霉素(DOX)的多功能透明质酸(HA)修饰的金纳米棒/介孔二氧化硅基纳米颗粒，即 DOX-AuNRs@mSiO-HA 纳米粒子，用于光声成像(PAI)引导的协同化疗光热治疗在口腔鳞癌治疗中具有更好的治疗效果[63]。一种癌症细胞膜涂层金纳米棒(GNR@MEM)在第二近红外窗口中具有优异的光热转移能力和在 X 射线照射下的放射增敏能力。光热疗法和放射疗法的结合有效抑制了口腔鳞癌生长，没有明显的全身毒性[64]。

颌骨肿瘤

颌骨因其复杂的结构以及与周围特殊解剖关系，口腔颌面部恶性肿瘤最常侵犯邻近骨组织器官，正常的骨生理功能就会被破坏[65]。肿瘤细胞募集并激活破骨细胞和成骨细胞，导致生长因子从骨基质中释放。这些生长因子可以反馈刺激肿瘤生长并促进进一步的骨损伤[65]。肿瘤细胞增殖和骨吸收之间的这种“恶性循环”加速了肿瘤病变。有研究使用一种双靶向纳米仿生药物递送载体 Asp8 [H40-TPZ/IR780@(RBC-H)]，作为靶向线粒体光敏剂，释放的 IR 780 在 808 nm 激光照射下不仅表现出高效的光热转换特性，而

且具有单线态氧(Singlet oxygen, $1O_2$)产生能力，并可进一步加剧肿瘤缺氧微环境，具有良好的骨靶向和癌症靶向以及免疫逃逸能力，实现精准抗癌治疗的有效多靶向药物递送载体[66]。

5. 光热治疗 PTT 走向临床的研究进展及挑战

光热治疗为癌症治疗提供了高度局部化的治疗策略。一些重要的临床研究逐步开展，头颈癌患者中进行了该 PTT 平台的初步研究(NCT00848042) [67]。吲哚菁绿色是 FDA 批准用于荧光血管造影的 NIR 染料，20 多年前在临床前肿瘤模型中使用 805 nm 激光显示为 PTT 的有效造影剂[68]。Li 等人[69]报告了用于激光免疫治疗的吲哚菁绿色 PTT 方法在治疗难治性晚期转移性乳腺癌患者中的局部肿瘤消融的临床转化。

使用镁合金结合近红外光对肿瘤治疗可取得一定的疗效。首先，正常组织可以耐受短时间的照射，如果不控制照射的持续时间和功率，则不能以精确的精度加热深部组织，使得热量可能对肿瘤周围的正常细胞和正常组织产生有害影响，精确的温度控制是必要的[70]。其次，植入材料的生物安全性是一个重要的考虑因素。应注意调节降解产物的释放，以达到更好的抗肿瘤效果。在临床应用和进一步临床转化前，应对其肝、肾清除率、清除周期和完全降解时间、降解产物的急性和慢性毒性进行评价，以确保其生物安全性。

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