•综述•

铂类配合物在恶性肿瘤化疗−免疫治疗策略中作用机制及其研究进展

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摘要: 铂类配合物, 尤其是二价铂 [platinum(II), Pt(II)] 化合物, 已经成为治疗恶性肿瘤的经典化疗方案。由于其稳定性不足、容易诱发获得性耐药和强烈的细胞毒性, 限制了其在临床中的广泛应用。尽管干扰程序性死亡蛋白 1 (programmed cell death protein 1, PD-1)/程序性死亡配体 1 (programmed cell death protein 1, PD-1) 相互作用的抗体与铂类配合物联合免疫疗法在抗癌治疗中取得了显著的临床进展, 但其高效性往往伴随显著的毒性和免疫相关不良反应, 限制了其长期应用。相比之下, 四价铂 [platinum(IV), Pt(IV)] 配合物凭借其独特的八面体几何结构, 展现出较好的抗癌潜力。通过修饰其轴向配体, Pt(IV) 配合物不仅具有更高的惰性和更好的肿瘤选择性, 还能够在靶向肿瘤微环境时以特定方式释放轴向配体。这一机制赋予其克服耐药性、减少毒性并增强免疫系统激活的能力, 使其成为当下抗癌领域的研究热点。更重要的是, Pt(IV) 配合物能够通过多种途径实现抗肿瘤效果, 包括通过触发 DNA 损伤诱导肿瘤细胞发生凋亡、自噬和铁死亡。该多重作用机制不仅增强了抗肿瘤效力, 还显著减少了传统铂类配合物的不良反应。本文总结了铂类配合物, 特别是 Pt(IV) 配合物在化疗−免疫联合治疗中的抗肿瘤作用机制, 探讨了其在抗肿瘤治疗中的潜力, 为开发高效、低毒、靶向性强的 Pt(IV) 配合物提供了理论支持。

关键词: 铂类配合物; 肿瘤化疗−免疫治疗; 抗肿瘤机制; 耐药性; 恶性肿瘤

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Advances of platinum-based complexes in chemo-immunotherapy strategies for malignant tumor

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Abstract: Platinum-based complexes, particularly divalent platinum [platinum(II), Pt(II)] compounds, have become classic chemotherapy agents for the treatment of malignant tumors. However, their widespread clinical use is limited due to issues such as insufficient stability, the induction of acquired resistance and strong cytotoxicity. Although antibodies that interfere with the interaction between programmed cell death protein 1 (PD-1) and programmed cell death ligand 1 (PD-L1), in combination with platinum-based compounds, have shown significant clinical progress in cancer treatment, their high efficacy is often accompanied by substantial toxicity and immune-related side effects, which limit their long-term use. In contrast, platinum(IV) [Pt(IV)] complexes, with their unique octahedral geometry, have demonstrated promising anticancer potential. By modifying the axial ligands, Pt(IV)-based complexes not only show higher inertness and improved tumor selectivity, but also enable the targeted release of active ligands in the tumor microenvironment. The mechanism allows Pt(IV)-based complexes to overcome drug resistance, reduce toxicity and enhance immune system activation, making them a research hotspot in the current cancer field. More importantly, Pt(IV)-based complexes can exert anticancer effects through multiple pathways including causing DNA damage to trigger apoptosis, autophagy and ferroptosis in tumor cells. This

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multifaceted action mechanism not only enhances antitumor efficacy but also significantly reduces side effects associated with traditional platinum-based compounds. This review summarizes whole anticancer mechanisms of platinum-based complexes, particularly Pt(IV) complexes in chemo-immunetherapy combination therapies, discussing their potential in cancer treatment and providing theoretical support for the development of efficient, low-toxicity and highly selective Pt(IV)-based complexes.

Key words: platinum-based complex; tumor chemotherapy-immunotherapy; anti-tumor mechanism; drug resistance; malignant tumor

恶性肿瘤的传统治疗方式包括手术、化疗和放疗[1]。尽管手术通常是治疗肿瘤的首选方法, 化疗和放疗依然是标准治疗手段, 特别适用于无法通过手术完全切除或已经扩散的恶性肿瘤[2]。许多化疗药物作用于高表达的特定靶标 (酶或基因), 因而其疗效会因肿瘤分型而有所不同[3]。相比之下, 铂类抗肿瘤药物作为细胞周期非特异性药物, 具有独特的抗癌活性和毒性谱, 交叉耐药性较低, 通过与 DNA 交联形成铂-DNA 加合物 (platinum-DNA adduct, Pt-DNA), 直接损伤 DNA, 表现出较强的细胞毒性作用, 常用于与其他抗肿瘤药物联合使用, 具有良好的抗癌效果[4]。然而, 铂类配合物在临床应用中仍然面临许多挑战, 如药物稳定性差、肿瘤选择性低、严重不良反应以及易产生获得性耐药, 限制了其广泛使用, 但也推动了铂类配合物的持续改进和新一代铂类配合物的开发和研究[5,6]。因此, 研究人员正在寻求更安全有效的二价铂 [platinum(II), Pt(II)] 化疗药物替代品, 其中四价铂 [platinum(IV), Pt(IV)] 前药被认为是具有较大潜力的新型铂类化疗药物。

如图 1 所示, 迄今为止, 除了已经在临床上使用的 Pt(II) 抗肿瘤药物, 有几类 Pt(IV) 抗肿瘤药物曾进入临床试验。其中沙曲铂 (satraplatin, 化学名称为 SP-1) 作为一种口服 Pt(IV) 药物, 曾在多个临床试验中评估其对前列腺癌的生存期[7]。奥马普拉丁 (ormaplatin, 化学名称为 LJ-901) 和伊普普拉丁 (iproplatin, 化学名称为 IPro) 也曾进入临床试验, 特别是在卵巢癌、肺癌和头颈部肿瘤等领域的研究, 为 Pt(IV) 抗肿瘤药物的细胞毒性、摄取机制及未来新型铂类配合物的设计提供理论基础。顺式、反式、反式-[铂(IV)二氯(氨基)(二甲基亚砜)$_2$][*cis*,*trans*,*trans*-[$PtCl_2(NH_3)(DMSO)_2$]], 简称 LA-12, 作为一种被广泛研究的 Pt(IV) 抗肿瘤药物, 在临床前模型中展现了较好抗癌潜力, 尤其是在逆转肿瘤耐药性方面[8]。

以往研究表明, 铂类配合物不仅直接作用于癌细胞, 还能影响肿瘤微环境 (tumor microenvironment, TME) 中的肿瘤血管内皮细胞、肿瘤相关成纤维细胞及参与免疫逃逸的免疫细胞。如铂类配合物通过靶向 TME 中的免疫细胞抑制肿瘤血管生成和转移[9,10]。1969 年, 巴内特·罗森伯格首次发现顺铂的抗癌活性, 并提出其疗效可能与免疫系统相关。研究显示, 顺铂可通过改变癌细胞表面的程序性死亡配体 1 (programmed death-ligand 1, PD-L1) 增强其免疫原性[11]。然而, 顺铂、卡铂和奥沙利铂这 3 种临床铂类抗肿瘤药物在不同免疫背景下的治疗效果存在显著差异。奥沙利铂在免疫功能正常的小鼠肿瘤模型中表现出较好的抗肿瘤活性, 但在免疫缺陷小鼠中无效。相反, 顺铂在免疫功能低下和正常背景下均显示出一定的活性。这一差异提示, 尽管 DNA 损伤是铂类抗肿瘤药物的主要作用机制, 免疫系统在其抗癌活性中同样发挥着重要作用[12]。尽管铂类抗肿瘤药物与免疫系统的潜在关联已被提出, 现有研究仍主要集中于体外实验或动物模型。因此, 在评估这些药物在人类患者中的临床应用时, 必须谨慎考虑相关差异。常用的免疫细胞模型, 如小鼠 RAW264.7 细胞及人源 THP-1 和 U937 细胞, 虽然是广泛使用的巨噬细胞模型, 但其信号传导途径已发生失调, 无法完全代表人体内的实际生理状态[13]。本综述回顾了新型 Pt(IV) 配合物的发展历程及其抗肿瘤机制的研究, 重点分析 Pt(IV) 配合物在化疗−免疫疗法系统中研究现状, 为基于铂类配合物的化疗−免疫疗法的研究提供理论依据。

1 铂类配合物轴向配体及其还原机制

研究表明, Pt(IV) 前药已成为克服耐药性和减轻毒副作用的新型铂类抗肿瘤药物[14]。Pt(IV) 前药的设计与合成, 尤其是含生物活性配体的前药, 主导了铂类抗癌药物的研发思路。相比 Pt(II) 药物, Pt(IV) 配合物因其八面体六配位结构, 展现出较高稳定性与较少不良反应。通过调整 Pt(IV) 前药中轴向配体的结构, 可微调其亲脂性、水解稳定性和细胞摄取量[15]。

Pt(IV) 前药的生物活性轴向配体通常为氧供体, 常通过过氧化氢氧化 Pt(II) 配合物合成。此过程中羟基配体被引入轴向位置, 随后通过亲核取代反应与包含羧酸、酸酐等功能团的生物活性分子偶联, 生成生物活性轴向配体。羧酸盐作为轴向配体因其与 Pt(IV) 羟基的共轭特性及还原后释放活性配体的能力被广泛应

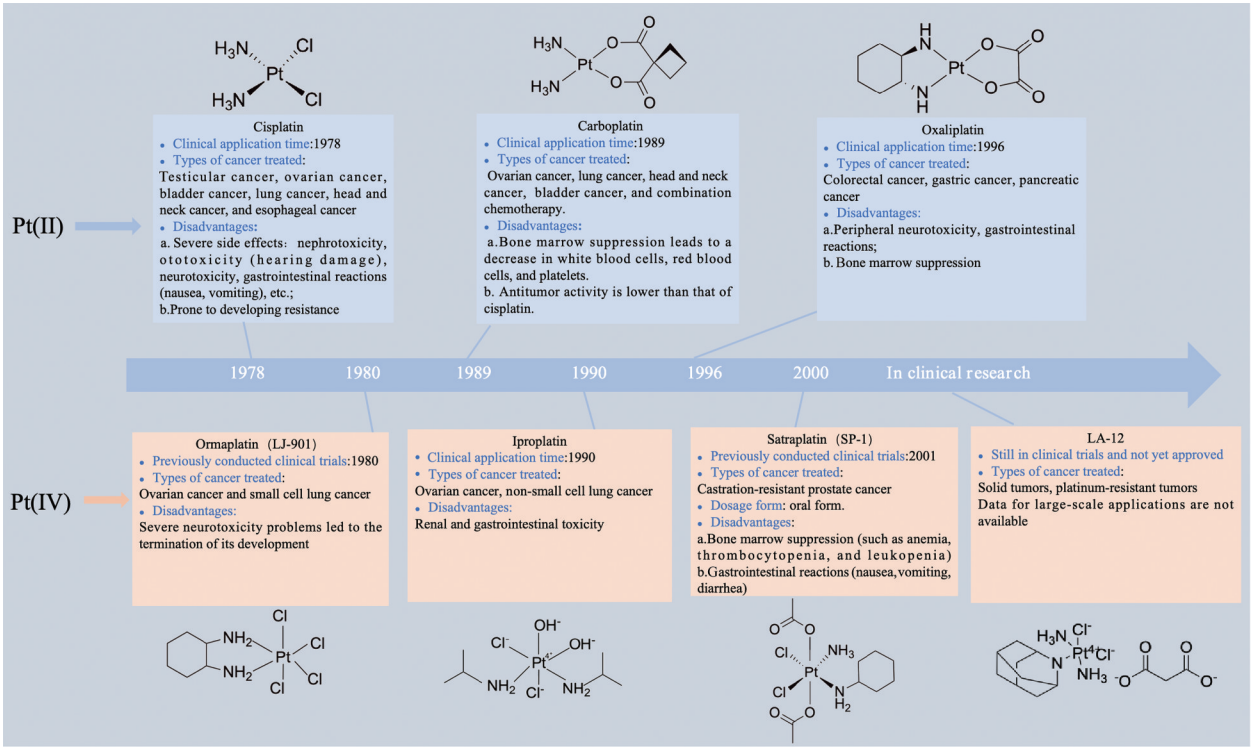

Figure 1　Currently clinically available platinum-based anticancer drugs. SP-1 is the chemical name for satraplatin, LJ-901 is the chemical name for ormaplatin, IPro is the chemical name for iproplatin, and LA-12 refers to *cis*,*trans*,*trans*-[$PtCl_2(NH_3)(DMSO)_2$]

用。对不含羧酸基团但具有羟基或胺基的分子, 自然接头连接羧酸基团被证明能有效促进活性分子的释放[16]。达沙替尼的羟基可通过碳酸二硫酯活化与氧铂反应形成碳酸盐键[16]。

轴向配体性质显著影响 Pt(IV) 配合物的还原速率。其中, 含氯的配合物还原速率快于含羧酸盐或羟基的化合物[17]。然而, 具有氨基甲酸酯轴向配体的 Pt(IV) 配合物的还原速度甚至超过其羧酸盐衍生物[15] (图 2)。研究表明, Pt(II) 药物形成与轴向配体丢失机制不同, 揭示还原反应复杂性。许多多靶点的 Pt(IV) 配合物在体内外显示出优异的抗肿瘤活性, 尤其是在肿瘤细胞选择性及毒性方面。开发提高抗肿瘤效率、降低毒性及逆转耐药性的 Pt(IV) 配合物, 将推动 Pt(IV) 配合物在临床上替代顺铂, 以克服传统铂类化疗的局限性。

2　铂类配合物治疗恶性肿瘤作用机制

近几十年来, 作为新一代铂类抗癌药物[18], 几种 Pt(IV) 前药已经进入临床试验。其主导了铂类抗肿瘤药物领域, 具有较高的亲脂性, 容易被癌细胞吸收, 激活通常基于电子转移触发的还原反应[14,16,19,20]。内源性 Pt(IV) 配合物在体内被维生素 C/细胞色素 c/抗坏血酸/谷胱甘肽/烟酰胺腺嘌呤二核苷酸等还原为生物活性配体和 Pt(II) 在体内发挥协同作用[21] (图 2)。其中, 顺铂等 Pt(II) 通过与 DNA 相互作用进而引发细胞凋亡[22], 奥沙利铂还通过诱导干扰核糖体生产或功能引起细胞凋亡[23]。如图 3 所示, Pt(IV) 配合物通过 p53-Bcl-2/Bax/Caspase-3 信号通路诱导线粒体介导的细胞凋亡, 通过抑制 MAPK/NF-κB 信号通路抑制恶性肿瘤细胞增殖, 通过作用于 PI3K/AKT 信号通路克服肺癌顺铂耐药[24]; Pt(IV) 配合物通过降低肿瘤细胞内谷胱甘肽过氧化物酶 4 (glutathione peroxidase 4, GPX4) 蛋白的表达水平, 调控核受体共激活因子 4 (nuclear receptor coactivator 4, NCOA4) 介导的铁蛋白自噬, 影响铁稳态和氧化应激, 激活 cGAS-STING 信号通路从而诱导肿瘤细胞铁死亡, 展现出抗肿瘤潜力[25-27]; Pt(IV) 配合物通过阻断免疫检查点 PD-L1 表达, 促进 M2 型巨噬细胞向 M1 型巨噬细胞的极化, 升高 $CD4^+$、$CD8^+$T 淋巴细胞水平等促进肿瘤免疫, 缓解免疫抑制[28,29]; Pt(IV) 配合物通过逆转 Wnt/β-catenin 信号通路逆转炎症肿瘤微环境; 抑制 HIF-1α 信号通路减少肿瘤细胞内上皮间质转化 (epithelial-mesenchymal transition, EMT) 从而抑制肿瘤细胞生成, 抑制肿瘤进展与转移[28,30]。

2.1　铂类配合物选择性作用于恶性肿瘤

转录因子 p53 被称为人类基因组的“守护者”, 在抑制肿瘤发展、修复受损 DNA 以及诱导细胞凋亡和衰老方面起着至

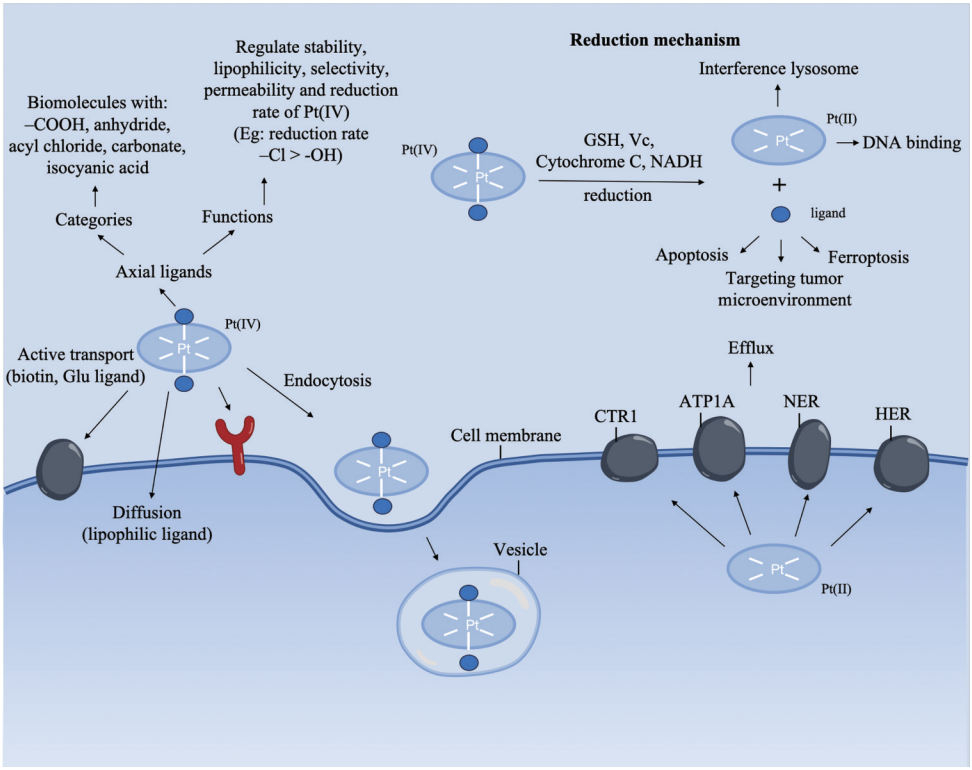

Figure 2 Axial ligands of Pt(IV) complexes and their reduction mechanism. CTR1: Copper transporter 1; ATP1A: Sodium-potassium ATPase alpha subunit; NER: Nucleotide excision repair; HER: Human epidermal growth factor receptor; GSH: Glutathione; Vc: Vitamin C; NADH: Nicotinamide adenine dinucleotide (reduced)

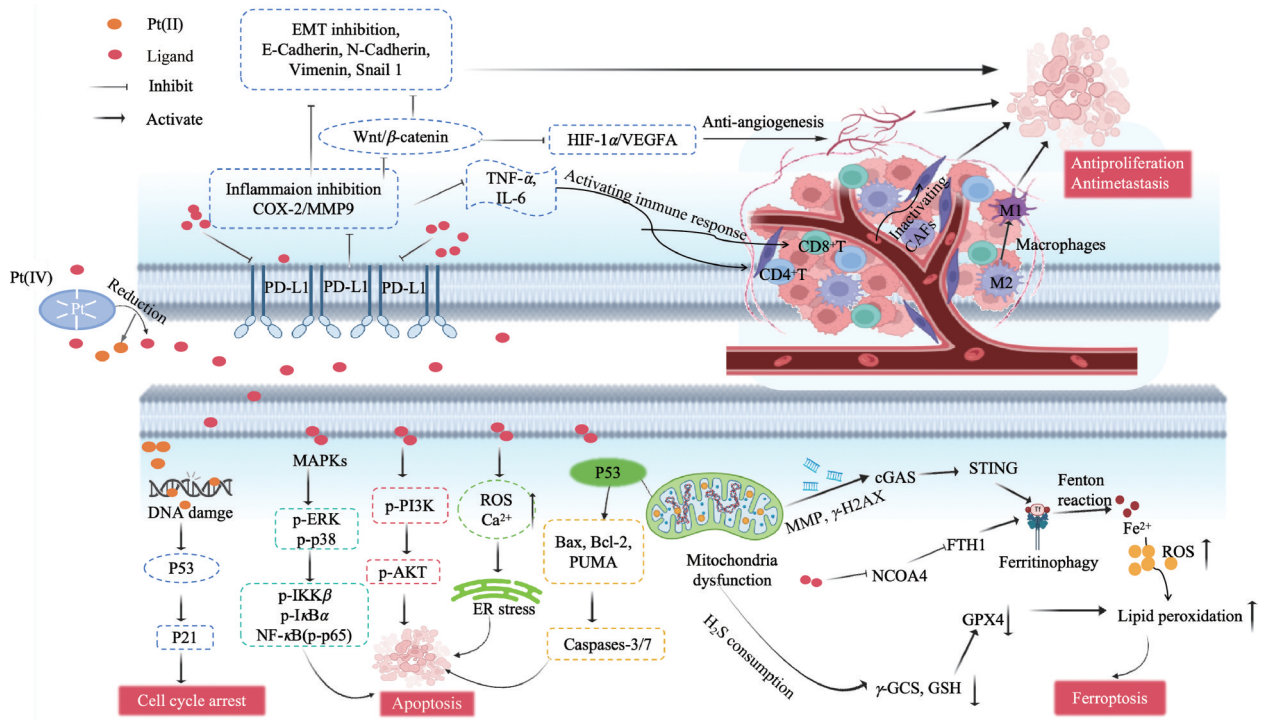

Figure 3 Mechanism of antitumor activity of Pt(IV) complexes. EMT: Epithelial-mesenchymal transition; TNF-*α*: Tumor necrosis factor-alpha; IL-6: Interleukin-6; VEGFA: Vascular endothelial growth factor A; ROS: Reactive oxygen species; ER: Endoplasmic reticulum; PUMA: p53 upregulated modulator of apoptosis; GPX4: Glutathione peroxidase 4; FTH1: Ferritin heavy chain 1; MAPKs: Mitogen-activated protein kinases; COX-2: Cyclooxygenase-2; MMP-9: Matrix metalloproteinase-9; AKT/PKB: Protein kinase B; ERK: Extracellular signal-regulated kinase

关重要的作用[31]。在应激条件下 (如DNA损伤、癌基因激活或缺氧), TP53基因被激活并表达p53蛋白, 该蛋白调节许多下游靶基因的转录, 包括Bax、p21、FAS和PUMA, 导致细胞通过凋亡途径死亡或启动细胞修复过程[32]。此外, p53还调节胱氨酸代谢和活性氧 (reactive oxygen species, ROS) 的反应, 促进癌细胞铁死亡[33]。然而, E3泛素连接酶MDM2蛋白过度表达会通过泛素化和蛋白酶体降解途径抑制p53的功能, 进而促进肿瘤的发生与进展[34-36]。为提高铂类化疗药物的肿瘤选择性, 研究者构建了新型Pt(IV)-RG7388 (一种选择性MDM2抑制剂) 铂类配合物, 恢复p53的肿瘤抑制功能。Pt(IV)-RG7388复合物在增强p53功能的同时, 能够提高对肿瘤的靶向性, 减少正常细胞的毒性反应, 表现出显著的治疗潜力[37]。

2.2　铂类配合物通过作用于肿瘤微环境抑制恶性肿瘤细胞增殖和转移　TME是一个复杂的环境, 涉及炎症、缺氧和免疫逃逸等过程, 促进肿瘤细胞的增殖和转移[38,39]。JAK/STAT通路在肿瘤发生和TME形成中发挥关键作用, 通过过度激活的JAK2/STAT3信号上调环氧化酶-2 (cyclooxygenase-2, COX-2) 和基质金属蛋白酶-9 (matrix metalloproteinase-9, MMP-9), 活化肿瘤相关巨噬细胞 (tumor-associated macrophages, TAMs) 分泌IL-6, 加剧炎症性TME, 促进肿瘤侵袭和转移[40,41]。缺氧TME通过JAK/STAT3/HIF-1α信号促进血管生成和免疫抑制, 加速肿瘤的增殖和转移[42,43]。因此, 靶向这些通路的抑制剂成为抗肿瘤药物的研究热点。

研究表明, 熊去氧胆酸 (ursodeoxycholic acid, UDCA) 可以抑制STAT3磷酸化, 逆转抗肿瘤免疫抑制并改善TME, 联合铂类配合物形成的UDCA-Pt(IV)复合物通过抑制JAK2/STAT3通路, 展示出良好的抗增殖与抗转移活性[44]。此外, 小檗碱Pt(IV)配合物通过DNA损伤诱导细胞凋亡, 并抑制Wnt/β-catenin和HIF-1α通路, 逆转炎症性TME, 抑制肿瘤转移和血管生成[30]。

髓系细胞触发受体2 (triggering receptor expressed on myeloid cells 2, TREM2) 抑制剂是肿瘤浸润巨噬细胞的关键促肿瘤标志物, 具有强大的免疫抑制活性。另一研究报道了Pt(IV)偶联物C55 (OPA), 由奥沙利铂和TREM2抑制剂青蒿琥酯组成。OPA通过重塑免疫抑制微环境, 降低免疫抑制性巨噬细胞数量, 促进树突状细胞和T细胞浸润, 从而抑制结直肠肿瘤的生长[45]。这些研究表明, 铂类配合物通过作用于TME, 可以有效抑制肿瘤细胞增殖和转移。

2.3　铂类配合物通过靶向肿瘤微环境抑制恶性肿瘤上皮间质转化　EMT是肿瘤进展和转移的关键过程, 抑制EMT被视为抗肿瘤转移的潜在策略[30]。免疫抑制在肿瘤进展中发挥重要作用, 尤其在EMT过程中, 肿瘤细胞分泌免疫抑制因子 (如TGF-β), 促进巨噬细胞向M2型极化, 帮助肿瘤逃逸免疫监视[46]。组胺−组胺受体H1 (histamine-histamine receptor H1, HRH1) 轴通过加剧TME中的免疫抑制, 推动EMT, 使肿瘤细胞获得更强的侵袭性、迁移能力和耐药性[47-49]。抗组胺药物能够通过激活免疫反应, 将“冷”TME转化为“热”TME[50]。地氯雷他定 (desloratadine, DLT) 作为HRH1拮抗剂, 已被证明能通过抑制EMT和调节β-catenin信号通路, 增强抗肿瘤活性, 并与免疫激活产生协同效应, 有效抑制肿瘤转移[51,52]。

Pt(II)药物因其诱导DNA损伤的抗肿瘤作用成为化疗基础, 但在转移性肿瘤中的应用受到耐药性和免疫抑制性TME的限制[18,53,54]。通过将多功能配体引入Pt(II)构成Pt(IV)配合物, 能够提高药物的化学稳定性和生物活性, 从而克服这些限制[55,56]。研究表明, 将DLT首次引入Pt(II)构成Pt(IV)配合物, 通过免疫激活和EMT逆转的协同效应, 能够有效抑制肿瘤增殖与转移。这种多功能Pt(IV)前药能够减少不良反应、增强药物选择性, 为抗转移铂类抗肿瘤药物的开发提供新思路[29]。

3　铂类配合物对恶性肿瘤耐药性的研究

3.1　Pt(IV)配合物克服Pt(II)对恶性肿瘤的耐药性　为了克服恶性肿瘤对Pt(II)的耐药性, 联合用药策略被提出, 尽管效果显著, 但伴随的毒性反应仍是一个问题。因此, 药物化学家设计并合成了新型Pt(II)衍生物, 尤其是Pt(IV)前药, 推动了铂类抗癌药物的创新发展[57,58]。如Wang课题组[59]研究了以奥沙利铂为基础的Pt(IV)前药复合物, 其中, 女萼曲嗪作为铁死亡诱导剂, 显著增强了奥沙利铂在HCT-116/奥沙利铂耐药细胞系中的疗效。也有研究报道了基于奥沙利铂的Pt(IV)前药, 结合谷氨酸−半胱氨酸连接酶抑制剂l-丁硫氨酸-*S*,*R*-亚砜胺, 显著增强了在奥沙利铂耐药小鼠异种移植瘤模型中的治疗效果[60]。Lippard和Hemman课题组的研究[61]发现, 奥沙利铂通过引发核糖体生物合成应激而有效杀死结直肠癌细胞 (colorectal cancer cells, CRC), 表明核糖体生成扰动在抗癌机制中起着关键作用, 而在顺铂中并不明显。

甘草次酸, 一种从甘草提取的天然五环三萜衍生物, 具有肝细胞靶向作用, 能有效克服肝癌的顺铂耐药性。甘草次酸功能化的Pt(IV)配合物通过诱导内质网应激 (endoplasmic reticulum stress, ERS)、生成ROS、引发DNA损伤、促进铁死亡和自噬、抑制细胞迁移与侵袭, 并激活线粒体依赖性细胞凋亡, 从而展现出克服多

药耐药性的潜力[26]。此外, 核因子κB (nuclear factor kappa B, NF-κB) 是重要的免疫和炎症反应调控因子, 其过度激活可促进癌细胞逃避凋亡, 并增强抗凋亡和耐药性。研究表明, 将NF-κB抑制剂与Pt(IV) 前药结合, 能够通过ROS/ERS和线粒体功能障碍等机制, 显著提高抗肿瘤活性, 克服多药耐药性[62]。这些策略不仅增强了铂类药物的抗肿瘤效力, 还提供了新途径来解决肿瘤治疗中的耐药性问题, 尤其是针对肿瘤微环境中的免疫逃逸、抗药性和转移的挑战。

3.2 铂类配合物重塑肿瘤微环境改善肿瘤免疫逃逸状态逆转化疗耐药作用研究 肿瘤耐药性可由吲哚胺2,3-双加氧酶 (indoleamine 2,3-dioxygenase, IDO) 和色氨酸双加氧酶2 (tryptophan 2,3-dioxygenase 2, TDO2) 过度表达引起, 导致犬尿氨酸 (kynurenine, Kyn) 积累, 激活芳香烃受体 (aryl hydrocarbon receptor, AhR), 抑制T细胞抗肿瘤活性, 促进免疫逃逸, 并与水通道蛋白4 (aquaporin 4, AQP4) 表达上调相关, 进一步增强肿瘤免疫逃逸能力[63]。AhR通过与人类DNA聚合酶κ (DNA polymerase kappa, hpolκ) 相互作用, 促进基因组不稳定性。人类DNA聚合酶κ与跨损伤合成 (translesion synthesis, TLS) 相关, TLS修复DNA损伤, 但错误修复可能导致基因突变, 使肿瘤细胞获得耐药突变, 进而增加化疗耐药性。这些免疫抑制和基因组不稳定性机制是肿瘤耐药性的主要原因[64]。为克服化疗和免疫疗法的耐药性, 研究者开发了与IDO和芳基肽受体1/2 (formyl peptide receptor 1/2, FPR1/2) 抑制剂偶联的Pt(IV) 前药。这些前药通过抑制TDO2-Kyn-AhR-AQP4代谢回路, 减少Kyn的免疫抑制效应, 同时也能够抑制TLS介导的基因组不稳定性, 从而逆转化疗免疫耐药, 增强抗肿瘤免疫反应[65,66]。这种Pt(IV) 前药的联合策略有望提高化疗和免疫治疗的效果, 克服肿瘤耐药性。

4 基于化疗−免疫疗法的铂类配合物抗恶性肿瘤研究现状

4.1 铂类配合物联合免疫疗法治疗恶性肿瘤的研究进展 免疫检查点抑制剂 (immune checkpoint inhibitors, ICIs) 为抗癌治疗带来了显著的进展, 2018年诺贝尔生理学或医学奖授予詹姆斯·艾利森 (James P. Allison) 和本庶佑 (Tasuku Honjo), 以表彰他们在免疫调节治疗肿瘤方面的开创性工作[67]。早期, 化疗因其引起的骨髓抑制和淋巴细胞减少症被认为主要导致免疫抑制[68], 然而, 近年来的研究发现, 在适当的联合治疗方案下, 细胞毒性化疗与免疫疗法之间可产生高度协同的抗癌效果[69]。化疗不仅可能逆转癌细胞的免疫逃逸机制, 还能通过影响免疫效应细胞的功能增强抗肿瘤作用[70,71]。

细胞毒性化疗与免疫疗法的相互作用复杂, 取决于治疗方案的具体特征, 包括所用药物、剂量、给药方案以及联合其他治疗方法的方式[72]。特别是ICIs与铂类化疗药物的联合使用, 在多个恶性肿瘤中表现出了显著的治疗潜力[71,73,74]。铂类配合物与免疫治疗的结合有助于增强免疫疗效、克服耐药性, 并已成为一种有效的治疗策略[75,76]。进一步研究其作用机制将有助于优化免疫治疗的临床应用, 进一步提高治疗效果。

4.2 铂类配合物与免疫疗法联合使用抗恶性肿瘤的临床研究 免疫治疗在肿瘤治疗中展现了显著前景, 但作为单一疗法, 尤其在复发和转移性肿瘤中, 其治疗应答率仍然较低[77,78]。因此, 将免疫治疗与化疗、放疗及靶向治疗等其他治疗手段结合使用, 已成为提升治疗效果和克服耐药性的重要策略[79,80]。根据美国临床肿瘤学会和国家综合肿瘤网络的治疗指南, 免疫治疗与其他治疗方法的整合已成为多种肿瘤一线治疗的关键组成部分。KEYNOTE-826研究显示, 帕博利珠单抗联合紫杉醇与顺铂 (或紫杉醇与卡铂) 方案, 且可选择性添加贝伐珠单抗, 显著提高晚期宫颈癌患者的总体生存期和无进展生存期, 并已获FDA批准作为晚期宫颈癌的一线标准治疗[81]。在非小细胞肺癌和晚期黑色素瘤的治疗中, 帕博利珠单抗或纳武利尤单抗与化疗的联合使用, 已成为推荐治疗方案[82]。此外, 帕博利珠单抗联合化疗在头颈部鳞状细胞癌中也显著提高了患者生存率, 而对于不适合免疫治疗的头颈部鳞状细胞癌患者, TPEx方案仍然是有效的替代方案[83]。在免疫联合化疗方案中, 白蛋白结合型紫杉醇替代传统5-氟尿嘧啶与铂类化疗, 能够显著提高疗效并减少毒副作用[84]。Pt(IV) 前药则通过靶向癌细胞核, 招募更多$CD4^+$和$CD8^+$ T细胞, 同时减少调节性T细胞 (regulatory T cells, Treg), 增强了化疗与免疫治疗的协同效应[85]。综合来看, 四价铂与免疫治疗联合使用, 不仅能够提升抗癌效果, 还为克服肿瘤耐药性提供新的治疗方向。

4.3 铂类配合物重塑肿瘤微环境改善免疫抑制状态 Lv等[86,87]研究表明, 化疗通过诱导补体信号传导, 能够增强B细胞的抗肿瘤特性, 从而促进有利的抗肿瘤免疫环境的建立。Pt(II) 类药物常因其严重不良反应、生物利用度低和免疫抑制作用而导致肿瘤复发。Pt(II) 药物通过磷脂酰丝氨酸 (phosphatidylserine, PS) 的暴露与免疫细胞受体结合, 诱发免疫抑制反应[88]。为解决这一问题, 研究者开发了一种新型化学免疫疗法, 通过脂质纳米颗粒 (liposome nanoparticles, LNPs) 递送Pt(IV) 前药和小干扰Xkr8 (small interfering

Xkr8, siXkr8), 通过减少PS暴露, 显著改善肿瘤免疫微环境, 有效抑制原发性肿瘤生长并防止复发[88]。此外, 铂类配合物还通过增加$CD8^+$ T细胞的浸润、减少Treg和TAM的数量, 进一步改善免疫抑制状态[83,89]。Pt(IV) 纳米前药通过双重激活机制释放药物并调节TAM极化, 从而增强免疫反应[90]。这些研究表明, 铂类配合物不仅能够重塑肿瘤微环境, 还能增强免疫治疗效果。

炎症微环境在肿瘤转移、EMT和免疫抑制中发挥重要作用[91,92]。为此, 转铁蛋白修饰的卡洛芬铂纳米颗粒 [carprofen platinum (IV) nanoparticles, Tf-NPs@CPF2-Pt(IV)] 被设计用于抑制炎症和EMT, 激活免疫反应, 增强抗增殖和抗转移能力[93,94]。该纳米颗粒通过转铁蛋白靶向肿瘤, 并持续释放活性成分CPF2-Pt(IV), 展现更优的药代动力学特性。通过上调γ-H2AX和p53引发DNA损伤, 抑制COX-2和MMP9, 同时降低炎性因子如TNF-α和IL-6水平, 逆转EMT并通过阻断PD-L1增强T细胞活性, 显著激发抗肿瘤免疫反应[28]。

4.4　铂类配合物增强免疫检查点抑制剂疗效作用　研究表明, 顺铂的免疫调节效应有助于提高ICIs联合治疗的效果。顺铂与阿替利珠单抗联合使用, 能够通过诱导循环免疫细胞的转录变化, 促进抗原呈递和T细胞活化相关程序的上调。在这一过程中, DNA损伤转导因子ATR (ataxia telangiectasia mutated and Rad3-related) 在顺铂的免疫调节作用中发挥关键作用, 而阿替利珠单抗则通过促进T细胞的启动与扩增或防止其衰竭, 从而进一步增强抗肿瘤免疫反应[95,96]。此外, 铂类配合物通过诱导DNA损伤, 增加肿瘤细胞表面新抗原的表达, 进而提高ICIs的疗效。它们还能够增加肿瘤细胞表面PD-L1的表达, 使肿瘤细胞更易于被ICIs识别和攻击。在头颈部鳞状细胞癌治疗中, 铂类配合物与放疗和免疫治疗联合使用表现出更好治疗效果[97,98]。

铂类配合物还能通过诱导细胞焦亡 (一种程序性细胞死亡) 激活抗肿瘤免疫反应。通过激活半胱天冬酶3 (cysteinyl aspartate specific protease 3, caspase 3) 来诱导细胞焦亡, 同时抑制COX-2表达, 有效提升免疫反应[99]。研究者开发了一种含有吲哚美辛 (In, COX-2抑制剂) 和Pt(IV)的两亲性聚合物 (表示为PHDT-Pt-In), 该聚合物对谷胱甘肽 (glutathione, GSH) 有响应, 能在谷胱甘肽作用下释放吲哚美辛抑制COX-2, 进一步增强顺铂诱导的焦亡。小鼠模型表明, Pt-In纳米颗粒显著抑制肿瘤生长, 并通过与α-PD-L1联合使用, 完全抑制转移性肿瘤, 将“冷肿瘤”转化为“热肿瘤”, 从而展现长期的抗肿瘤免疫效果[94]。在肿瘤免疫逃逸中, CD47通过抑制免疫细胞的作用帮助肿瘤细胞逃避免疫监视。因此, CD47被视为一个重要的免疫检查点。小檗碱Pt(IV)配合物通过阻断PD-L1和CD47免疫检查点, 增强$CD3^+$和$CD8^+$ T细胞的浸润, 促进巨噬细胞从M2型向M1型极化, 显著提升抗肿瘤免疫力[30]。

4.5　铂类配合物诱导免疫原性细胞死亡　铂类配合物能够诱导免疫原性细胞死亡 (immunogenic cell death, ICD), 激活抗肿瘤免疫反应。ICD通过释放损伤相关分子模式 (damage-associated molecular patterns, DAMPs), 如高迁移率族蛋白B1、热休克蛋白、钙网蛋白 (calsequestrin, CRT) 等, 激活树突状细胞、巨噬细胞和B细胞等抗原呈递细胞, 促进T细胞免疫反应[100]。铂类化疗药物通过诱导ICD释放肿瘤抗原, 促进免疫系统激活, 增强免疫疗法效果并改善TME[80]。奥沙利铂已被证明能有效诱导ICD。它通过引发DNA损伤、ERS及触发ICD标志物的表达, 促进DAMPs的释放, 从而激活抗肿瘤免疫[100,101]。此外, Pt(IV)前药与免疫调节剂 (如IDO抑制剂) 偶联, 可放大抗肿瘤免疫反应, 进一步增强ICD效果[102,103]。

焦亡作为ICD的一种形式, 通过气孔形成蛋白E (gasdermin E, GSDME) 介导的气孔形成来激活免疫反应[99]。研究已表明, 结合光热治疗 (photothermal therapy, PTT)、化疗和免疫治疗的铂类配合物, 如携带Pt(II)的ICG@HSA纳米颗粒 (indocyanine green-loaded human serum albumin nanoparticles) 可通过焦亡促进肿瘤细胞死亡并增强免疫反应[99,104-106]。化疗与ICIs联合使用, 能够显著提高治疗应答率, 改善生存预后, 并在新辅助治疗和术后治疗中增强疗效, 通过减少复发风险进一步延长患者的总生存期。

4.6　铂类配合物激活cGAS-STING信号通路　铂类配合物在激活cGAS-STING信号通路方面展现出显著潜力, 尤其在肿瘤治疗中, 通过诱导ICD来增强免疫反应。肿瘤细胞通常对细胞凋亡有抵抗性, 因此, 铁死亡和细胞焦亡等新的ICD形式可能对肿瘤治疗有所帮助[107]。铂类配合物通过增加癌细胞中的DNA损伤, 激活cGAS-STING通路, 促进I型干扰素和炎症因子的产生, 从而增强抗肿瘤的免疫反应[108]。Pt(IV)复合物OAP2 (由奥沙利铂与对乙酰氨基酚组成) 能通过下调线粒体外膜蛋白SAM50的表达, 促进线粒体膜重塑并释放线粒体DNA (mitochondrial DNA, mtDNA), 进一步激活cGAS-STING通路, 克服奥沙利铂在STING激活中的不足。此外, OAP2还能够促进树突状细胞 (dendritic cell, DC) 的成熟, 增强T细胞活性, 抑制肿瘤

细胞增殖和转移, 从而提供新的免疫治疗思路[109,110]。用于靶向递送Pt (IV) 前药还原响应型纳米颗粒[reduction-responsive nanoparticles, NP(3S)s] 通过诱导DNA损伤激活STING通路, 增强T细胞介导的免疫反应[108-110]。研究者还开发了结合顺铂和STING激动剂的二甲磺酰胺-2-铂(IV) 偶联物 (MSA-2-Pt), 该复合物能够上调与先天免疫相关的基因, 促进NK细胞浸润, 并激活T、NK和DC细胞, 从而显著增强抗肿瘤免疫反应[111,112]。这些研究表明, 铂类配合物能够激活STING有效改善免疫治疗效果。

5 小结与展望

铂类配合物, 特别是Pt(IV)配合物, 因其化学稳定性、肿瘤靶向性和多功能性, 在恶性肿瘤的化疗−免疫治疗中展现出重要价值。与传统Pt(II) 化合物相比, Pt(IV) 配合物通过轴向配体修饰提高了化学惰性和特异性, 能够在肿瘤微环境中通过还原反应释放活性Pt(II), 克服了传统铂类药物在稳定性、毒性和选择性方面的局限。其抗肿瘤机制包括DNA损伤、ICD、cGAS-STING通路激活及TME重塑, 为化疗与免疫治疗联合应用提供坚实基础。近年来, Pt(IV) 配合物在化疗与免疫联合治疗中取得了显著进展。通过轴向配体修饰, Pt(IV) 配合物不仅具有高肿瘤选择性, 还能释放生物活性配体, 增强抗肿瘤效应并克服耐药性。结合纳米载药系统等递送技术, Pt(IV) 配合物在治疗选择性、毒性降低及生物利用度提高方面表现出明显优势。然而, Pt(IV) 配合物在肿瘤治疗中的应用仍面临诸多挑战。尽管Pt(IV) 配合物提高了肿瘤特异性, 但仍可能在非靶向组织中过早释放活性Pt(II), 导致脱靶毒性。因此, 开发具有高选择性和可控释放能力的精准药物递送平台是提高治疗效果、减少不良反应的关键[113]。此外, 恶性肿瘤的分子特性和免疫微环境异质性为Pt(IV) 配合物的疗效带来挑战。针对不同肿瘤类型优化其结构设计及联合治疗方案, 是应对这一异质性的关键策略[114]。尽管Pt(IV) 配合物在一定程度上克服了Pt(II) 的耐药性, 肿瘤细胞依然可能通过代谢重编程、药物外排增强和免疫逃逸等机制限制治疗效果。因此, 深入探讨耐药机制并提出针对性解决方案, 有助于提升其临床前景[115]。Pt(IV) 配合物与ICIs或靶向药物联合应用, 虽增强了抗肿瘤协同效应, 但可能伴随免疫相关毒性和系统性不良反应, 如何平衡效能与安全性仍需进一步研究。尽管沙曲替铂等Pt(IV) 配合物已进入临床试验, 但其药代动力学、长期毒性及疗效仍需深入评估, 且在规模化生产和成本控制方面仍面临技术挑战[116-118]。

未来研究应聚焦构建肿瘤微环境响应的递送平台, 结合纳米材料或靶向配体, 实现Pt(IV) 配合物的高效递送与可控释放; 利用生物正交化学与点击化学技术, 提高药物的肿瘤选择性, 减少脱靶毒性[116-118]; 根据肿瘤分子分型和免疫特性, 设计个性化的联合治疗方案, 优化治疗效果; 进一步解析Pt(IV) 配合物在DNA损伤、自噬和铁死亡等多途径抗肿瘤效应中的机制, 为精准治疗提供理论支持[119-121]。

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