

铜和铜死亡在泌尿系统肿瘤中的研究进展

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摘要

铜死亡是一种新发现的细胞死亡形式, 由细胞内铜离子(Cu^{2+})异常蓄积触发。该机制在肿瘤研究领域引发广泛关注, 因其展现了作为癌症治疗新靶点的巨大潜力。在泌尿系统肿瘤中, 前列腺癌(PC)、膀胱癌(BC)和肾癌(RCC)是常见的恶性肿瘤, 临床治疗面临严峻挑战。最新研究表明, 铜稳态失衡与泌尿系统肿瘤恶性进展密切相关, 铜死亡机制的探讨为理解肿瘤细胞的生存与死亡提供了新的方向。本文就铜死亡在泌尿系统肿瘤中的最新研究进展作一综述, 包括铜与铜代谢的相互关系、铜死亡机制的阐述、铜在治疗中的应用以及未来的研究前景, 以期泌尿系统肿瘤治疗提供新的视角。

关键词

铜, 铜死亡, 泌尿系统肿瘤, 研究进展

Research Progress on Copper and Cuproptosis in Urological Tumors

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Abstract

Cuproptosis, a newly discovered regulated cell death mechanism, is induced by excessive intracellular copper accumulation. This mechanism has garnered significant attention in cancer research due to its potential as a novel therapeutic target. Among urological tumors, prostate cancer (PC), bladder cancer (BC), and renal cell carcinoma (RCC) are common malignancies that pose formidable challenges in clinical management. Emerging evidence highlights the critical role of copper homeostasis imbalance in the malignant progression of urological tumors, and the exploration of cuproptosis

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mechanisms provides novel insights into the survival and death of tumor cells. This review summarizes recent advances in cuproptosis research within urological tumors, including the interrelationship between copper and copper metabolism, elucidation of cuproptosis mechanisms, therapeutic applications of copper, and future research prospects. The aim is to offer new perspectives for advancing treatment strategies for urological tumors.

Keywords

Copper, Cuproptosis, Urological Tumors, Research Progress

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1. 引言

泌尿系统肿瘤包括前列腺癌(PC)、膀胱癌(BC)和肾癌(RCC)等,其全球发病率逐年上升[1]-[3]。当前临床管理面临双重挑战:晚期肿瘤治疗手段有限,以及早期筛查的高成本问题。由于此类肿瘤的高度异质性和转移倾向,多数患者在晚期确诊,术后生化复发常需依赖化疗和放疗,但传统疗法受限于全身毒性及耐药性,严重影响患者预后。因此,开发兼具高效性与安全性的新型治疗策略迫在眉睫[4]-[6]。

铜死亡(cuproptosis)是近期发现的一种新型调控性细胞死亡方式,其机制依赖于铜离子的异常蓄积。铜离子通过结合三羧酸循环(TCA)中脂酰化修饰的线粒体酶,导致蛋白毒性应激及铁-硫蛋白降解,最终引发细胞死亡[7]-[9]。铜作为必需微量元素,尽管在人体内需求量微小,却在信号转导、氧化还原平衡等关键生物过程中发挥重要作用[9]。在生物系统中,Cu主要以两种氧化态存在:二价铜离子(Cu^{2+})和一价铜离子(Cu^+)。 Cu^+ 是主要的氧化形式,在细胞内的生理和病理调节中起重要作用[1][10][11],其稳态通过精密调控的吸收、转运及排出机制维持,失衡可诱发多种疾病[12]。铜稳态的破坏可诱发疾病发作,如Wilson病[13]和Menkes病[14]等。

近年研究表明,铜代谢紊乱是多种肿瘤共性特征,如肺癌[15]、乳腺癌[16]、胆囊癌[17]、胃癌[18]和甲状腺癌[19]等。在泌尿系统肿瘤中,PC[20]、BC[21][22]和RCC[23]患者的血清和肿瘤组织中铜浓度均显著升高。研究表明铜稳态和铜死亡特征与肿瘤进展和预后密切相关,这与肿瘤细胞的增殖和转移能力密切相关。

由于泌尿系统肿瘤对新型疗法的迫切需求,铜死亡已成为一种有前景的方法。本综述系统分析了现有的关于铜和铜死亡的细胞和分子机制,并整合泌尿系统肿瘤领域的最新研究成果,重点探讨铜靶向治疗的转化潜力,旨在为精准医学时代的肿瘤管理提供依据。

2. 铜稳态

2.1. 全身铜稳态

铜作为必需微量元素,主要通过膳食摄入(如动物内脏、贝类),成人推荐日摄入量为0.8~2.4 mg以维持稳态[11]。其吸收始于小肠上皮细胞顶膜,由铜转运蛋白CTR1(*SLC31A1*编码)介导 Cu^+ 内流。进入胞质后,铜伴侣蛋白ATOX1将 Cu^+ 转运至基底侧膜,通过ATP7A依赖的ATP水解作用分泌至门静脉循环[24]。铜离子在血液中通过与蛋白质结合而不是以游离形式运输。血液中,约75%的铜与铜蓝蛋白不可逆结合,25%与人血清白蛋白可逆结合,余下0.2%以低分子复合物(如组氨酸-铜)形式存在[25][26]。铜离

子随后通过门静脉系统运输到肝脏[27], 肝脏是铜的主要储存器官, 也是体内铜排泄的主要器官。铜的储存功能是由金属硫蛋白 1/2 介导的, 这两种富含巯基的蛋白质通过其半胱氨酸残基以 pH 依赖的方式结合铜离子, 但它们结合和转运铜的具体能力尚不清楚。通过 ATP 酶铜转运 β 的作用, 过量的铜被排泄到胆汁中并排出体外[28]。

2.2. 细胞铜稳态

细胞内铜稳态的调节依赖于不同类型蛋白质的相互作用。第一类是与跨膜铜转运相关的蛋白质。与小肠上皮细胞一致, 肿瘤细胞摄取铜离子也需要 CTR1 的参与, *SLC31A1* 表达水平的升高和降低直接影响细胞内铜离子水平[29]。CTR1 对 Cu^+ 的亲和力大约是对 Cu^{2+} 的两倍, 主要介导 Cu^+ 的转运, Cu^+ 是铜死亡过程中的主要形式。在血液中运输到细胞表面后, Cu^{2+} 被前列腺六跨膜上皮抗原(STEAP)蛋白催化还原为一价铜离子, 并通过 CTR 氮末端的两个 His-Met-Asp 簇结合并维持在还原状态, 从而转运到细胞内[30][31]。铜通过跨膜转运蛋白溶质载体家族 25 成员 3 (SLC25A3) 从线粒体膜间隙跨过内膜进入线粒体基质。与细胞外排泄铜相关的 ATP 酶, 包括 ATP7A 和 ATP7B, 在 ATP 存在下将结合在金属结合位点的铜离子输出[31]。这些介导铜离子跨膜转运的蛋白质调节其细胞内分布。第二类是结合和储存铜离子的蛋白质。金属硫蛋白和谷胱甘肽作为天然的细胞内铜离子螯合剂, 结合铜离子从而防止其引起细胞损伤[32]。第三类是铜离子伴侣蛋白, 它们的相互作用确保了铜的正常细胞功能[33]。细胞质中的铜离子伴侣蛋白 ATOX1 通过两个半胱氨酸残基结合 Cu^+ 并将其转运到 ATP7B 的金属结合位点以进一步输出。超氧化物歧化酶铜伴侣蛋白直接与超氧化物歧化酶 1 相互作用并转运铜离子[34]。此外, 还有一系列线粒体内的铜离子伴侣蛋白在细胞色素 c 氧化酶(COX)的功能中起重要作用, COX 是氧化磷酸化的重要组成部分。这些伴侣蛋白通过储存或传递铜离子参与 COX 的组成和功能[35]。细胞内铜稳态的维持依赖于这些蛋白质的相互作用, 铜稳态的失调将导致细胞代谢紊乱甚至细胞死亡。

3. 铜死亡的机制

铜死亡是一种新近发现的细胞死亡形式, 主要是由于细胞内铜离子的过量积累而引起的, 其机制与传统的细胞死亡方式(如凋亡、坏死、铁死亡等)不同。过量的铜离子通过直接结合线粒体三羧酸循环的脂酰化成分, 导致脂酰化蛋白的寡聚化和铁硫蛋白的丢失, 从而增强蛋白质毒性应激, 最终诱导细胞死亡。脂酰化是一种特殊的翻译后修饰, 常见于二氢硫辛酰胺 S-琥珀酰转移酶(DLST)、二氢硫辛酰胺转乙酰酶(DLAT)等蛋白。这些酶需硫辛酰化以发挥功能: DLST 和 DLAT 分别是 α -酮戊二酸脱氢酶复合物与丙酮酸脱氢酶复合物(PDHC)的关键组分。前者催化 α -酮戊二酸氧化脱羧为琥珀酰辅酶 A, 后者催化丙酮酸转化为乙酰辅酶 A; 两者产物均为 TCA 循环中至关重要的代谢物[9]。

4. 铜和铜死亡机制在泌尿系统肿瘤中的作用

铜作为一种重要的微量元素, 在细胞生理和病理过程中扮演着多重角色。近年来, 研究表明铜的代谢异常与多种肿瘤的发生和发展密切相关。泌尿系统肿瘤, 包括膀胱癌、肾癌和前列腺癌等, 均显示出与铜代谢相关, 这为铜和铜死亡作为潜在的治疗靶点提供了新的视角。

4.1. 前列腺癌

前列腺癌(PC)是男性最常见的恶性肿瘤之一, 其发病率持续升高。对于局限性 PC 患者, 根治性前列腺切除术是标准的治疗方法[36]。然而, 大约 20%~30% 的患者在根治性治疗后会生化复发, 随后可能发展为临床复发和转移[37]。对于晚期 PC, 雄激素剥夺疗法(ADT)仍然是首选的治疗方法[38], 但长期 ADT 治疗经常导致耐药并进展为去势抵抗性前列腺癌(CRPC)[39][40]。因此, 开发针对 CRPC 的新型治

疗方式非常重要。

在 PC 中, 铜的代谢异常与肿瘤的发生和发展密切相关。先前的研究显示, PC 患者的血清和组织中铜离子浓度显著升高[41]。Feng 等人通过一项孟德尔随机化研究发现较高血铜浓度可能与较低的 PC 的发病率相关[42]。在前列腺癌的研究中, 铜不仅被认为是促进肿瘤生长的因素, 还可能通过影响细胞的生理和病理过程。Xie 等人通过合成的新型类固醇化合物抑制铜转运蛋白 1 (CTR1) 的表达, 结果显示这可以显著降低 PC 细胞的铜摄取, 从而抑制其增殖和肿瘤生长[43]。上述研究表明铜离子水平升高与 PC 细胞生物学功能相关, 而铜离子浓度的减低无法维持肿瘤细胞的生理功能, 导致细胞死亡。

在已经具有相对较高铜浓度的细胞内进一步增加铜离子水平, 可能有助于激活铜死亡。铜离子可以增强多种化疗药物的敏感性, 特别是对多西他赛(docetaxel)的敏感性。通过使用铜离子载体(如 elesclomol-CuCl₂), 研究者发现能够促进前列腺癌细胞的死亡, 并增强对多西他赛的化疗敏感性。这一机制涉及到铜离子诱导的自噬抑制和细胞周期的 G2/M 期滞留, 进而影响 mTOR 信号通路的活性[44]。此外, 铜的动态平衡在前列腺癌的免疫微环境中也扮演着重要角色。研究表明, 铜死亡与肿瘤微环境的异质性相关, 可能影响免疫细胞的浸润和肿瘤的免疫逃逸[45]。因此, 靶向铜死亡的治疗策略不仅能够直接杀死肿瘤细胞, 还可能通过调节肿瘤微环境, 提高免疫治疗的效果。

然而, 尽管铜死亡作为治疗新靶点的潜力巨大, 但在临床应用中仍面临诸多挑战。首先, 铜的生物学特性和其在体内的动态变化使得铜的靶向治疗需要精确控制, 以避免对正常细胞的毒性影响。此外, 铜的过量积累可能导致细胞毒性反应, 因此, 如何在治疗中平衡铜的浓度是一个重要的研究方向[46]。

4.2. 肾细胞癌

肾细胞癌(RCC)是常见的肾癌类型, 其中肾透明细胞癌(ccRCC)是最常见的亚型[47]。由于 RCC 对放疗不敏感, 根治性手术切除仍是目前主要的治疗手段。目前, 近 1/3 的 ccRCC 患者在诊断时已经出现远处转移, 药物治疗是大多数患者在此期间的主要治疗选择[48]。近十年来, 许多靶向药物和免疫检查点抑制剂在临床上得到应用, 并在一定程度上提高了患者的生存率。然而, 靶向治疗容易产生耐药性, 而免疫治疗仅对某些特定人群有效[48]-[50]。因此, 寻找新的治疗靶点对于治疗 ccRCC 和改善预后结果至关重要。

Panaiyadiyan 等人的研究显示 ccRCC 患者血液和尿液中的铜浓度升高显著高于正常人[23]。这项发现表明 ccRCC 患者中铜稳态的异常, 揭示了铜死亡可能在 RCC 发生发展中起到了重要作用。一项研究表明, *FDXI* 作为铜死亡的关键基因, 其表达水平与肾癌患者的预后密切相关, *FDXI* 的低表达常与不良的临床病理特征和不良预后有关[51]。另一项研究表明, *FDXI* 的过表达能够增强肾癌细胞的抗肿瘤免疫反应, 促进细胞凋亡, 从而抑制肿瘤的生长和转移[52]。Huang 等人通过多个数据库的生物信息学分析、qRT-PCR 和蛋白质杂交试验证实, ccRCC 患者中 *DLAT* 的表达低于癌旁组织, 且生存率较低, 临床预后较差[53]。

总之, 肾癌患者中观察到的铜死亡特征显示出作为有效预后指标的潜力。通过调节铜的代谢状态, 可能可以诱导肾癌细胞的死亡, 从而抑制肿瘤的生长。这种新颖的细胞死亡方式与传统的治疗手段, 如化疗和放疗, 形成了有机互补, 有望提高肾癌患者的治疗效果。然而, 铜死亡机制的具体作用方式仍需进一步探讨, 以便明确其在肾癌不同亚型中的作用差异。

4.3. 膀胱癌

膀胱癌(BC)现已成为全球男性第六大高发恶性肿瘤, 同时也是世界范围内最常见的十大癌症类型之一[54]。尽管近年来手术干预及化疗方案取得显著进步, 但该疾病较高的复发率及转移率仍是临床治疗面

临的重要挑战。有研究揭示了 BC 的肿瘤进展与细胞内铜离子稳态失衡存在密切关联, BC 患者血浆铜离子浓度较健康人群呈现显著性升高[55]。在膀胱癌细胞中, 铜死亡的机制尚不完全明确, 但已有研究表明, 铜死亡相关基因在膀胱癌的发生和发展中发挥了重要作用。磷酸二酯酶 3B (*PDE3B*) 作为一种与铜死亡相关的基因, 其表达水平在膀胱癌组织中显著下调, 且其低表达与患者的良好预后相关。*PDE3B* 的过表达能够显著抑制膀胱癌细胞的侵袭和迁移, 提示铜死亡可能通过调控肿瘤细胞的生物学行为来影响膀胱癌的进展[56]。

这些研究表明, 通过调控肿瘤细胞内的铜离子浓度可以诱导铜死亡, 从而最终实现治疗癌症。因此, 铜死亡机制在 BC 治疗中具有重要的潜在作用, 可能成为新的治疗靶点[57]。

5. 基于铜和铜死亡的治疗药物

5.1. 铜螯合剂

以前的研究表明, 铜通过促进血管生成在促进肿瘤生长方面起关键作用[58]。铜螯合剂种类繁多, 包括四硫钼酸盐(TM)、青霉胺和三氟氯化铵等。这些化合物通过与铜离子结合, 形成稳定的螯合物, 从而降低细胞内的游离铜浓度, 进而影响多种生物过程。TM 已被证明具有抗血管生成作用并抑制多种癌症的生长, 包括乳腺癌和卵巢癌[59][60]。一项针对晚期肾癌患者的 II 期临床试验研究表明, TM 可与其他抗血管生成药物联合治疗肾癌[61]。这些实验为未来药物开发提供了创新方向, 并展示了铜死亡与多种药理机制结合以增强抗肿瘤效果的潜力。

5.2. 铜离子载体

铜离子载体是一类能够结合铜离子并协助其跨生物膜运输的分子, 其中包括双硫仑(DSF)、elesclomol 和含铜纳米颗粒等。铜离子载体在癌症治疗中的应用已被广泛研究。在癌症治疗中, 研究者利用铜离子载体的原理是通过诱导癌细胞中过量的铜积累来选择性地靶向癌细胞, 从而诱导铜死亡。双硫仑(DSF)被发现能够促进金属硫蛋白的表达并阻碍 DNA 复制, 从而抑制肿瘤生长[62]。此外, DSF 能够螯合铜离子并将其转运到线粒体中, 从而诱导铜死亡。DSF 抑制 ccRCC 细胞增殖, 并与舒尼替尼产生协同抗增殖作用[63]。一项临床前研究表明, 单独 DSF 对前列腺癌肿瘤的生长影响极小。然而, 当 DSF 与铜联合给药时, 在激素敏感性和去势抵抗性疾病模型中观察到对肿瘤生长的非常显著的抑制[64]。在膀胱癌治疗中, DSF 作为铂类药物的增敏剂, 能与顺铂协同增强化疗效果[65]。此外, elesclomol-CuCl₂ 可以通过抑制前列腺癌临床前模型中的自噬和促进细胞周期停滞来增强多西他赛的化疗敏感性, 这说明铜离子载体可以改善药物的耐药性[44]。然而, 一项 Ib 期临床试验用铜与 DSF 治疗 9 名转移性去势抵抗性前列腺癌(mCRPC), 结果表明口服 DSF 不是 mCRPC 的有效治疗方法, 该试验已停止招募, 需要进一步工作来确定用于治疗 mCRPC 的稳定 DSF 制剂。由于该样本量较小, 并不能得到准确的试验结果[66]。

尽管小分子铜离子载体在肿瘤治疗中展现出潜力, 但其临床应用仍面临两大挑战: 一方面, 较短的血液半衰期限制了铜离子向肿瘤细胞的靶向递送效率; 另一方面, 长期使用可能导致体内金属稳态失衡, 进而加重患者的治疗相关不良反应。为克服这些局限性, 基于肿瘤微环境特性的精准铜治疗策略应运而生。其中, 含铜纳米颗粒因其独特的肿瘤靶向性能而备受关注。这类纳米颗粒能够有效利用肿瘤组织的特征性微环境(如酸性 pH 值、异常升高的谷胱甘肽和活性氧水平)以及肿瘤细胞特异性表面标志物, 实现药物的精准递送和可控释放。特别值得一提的是氧化亚铜纳米颗粒(Cu₂O NPs), 其由铜氧原子有序排列构成, 凭借显著的表面积-体积比优势, 能够与细胞和组织产生更高效的相互作用, 为肿瘤的精准治疗提供了新的可能[67]。一项使用 CRPC 细胞系作为模型的研究发现, 氧化亚铜纳米药物在体外和体内实验中均显示出显著的抗前列腺癌效果[68]。另一项临床前研究设计了一种活性氧化物(NOS)敏感聚合物, 用

于包封 elesclomol (ES)和铜以形成纳米颗粒(NP@ESCu), 结果表明不仅可以诱导铜死亡杀死癌细胞, 而且还可与 PD-L1 结合用于增强癌症治疗, 从而为未来的癌症治疗提供了新的策略[69]。从药代动力学角度, 铜螯合剂(如 TM)通过系统性降低铜生物利用度发挥广谱抗肿瘤作用, 但可能引起铜缺乏相关贫血; 而铜离子载体(如 DSF)需依赖肿瘤细胞的高铜需求实现选择性杀伤, 其神经毒性可能与铜透过血脑屏障有关。含铜纳米颗粒通过增强渗透和滞留效应(EPR)效应和 pH 响应释放实现靶向递送, 但粒径分布和长期生物安全性仍需优化。铜纳米医学为探索肿瘤治疗提供了广阔的前景。

6. 结论和展望

铜稳态在维持机体正常生理功能中发挥关键调控作用。值得注意的是, 三种主要泌尿系统肿瘤(前列腺癌、膀胱癌及肾细胞癌)中均存在铜稳态失衡现象, 而通过调节铜离子浓度诱导铜死亡可有效抑制肿瘤增殖。尤其在转移性前列腺癌和晚期膀胱癌的治疗中, 传统化疗方案因替代手段匮乏, 常导致药物耐药性频发及严重毒副作用。与之类似, 肾细胞癌因其显著异质性和对放化疗的天然抵抗性, 在临床干预中始终面临重大挑战。值得关注的是, 上述肿瘤中铜稳态的异常调控机制, 为开发基于铜死亡的新型治疗策略提供了重要理论依据。

现有研究表明, 铜在肿瘤发生发展中具有双重作用, 这为泌尿系统恶性肿瘤治疗提供了两种主要方向: 其一, 利用铜螯合剂降低铜的生物利用度以抑制肿瘤生长; 其二, 通过铜离子载体将铜递送至细胞内提升铜离子浓度, 从而诱导铜死亡。值得注意的是, 由于铜离子载体对肿瘤细胞的选择性较低, 采用基于纳米颗粒的递送系统实现铜离子的精准靶向输送, 可显著增强肿瘤组织的铜死亡效应, 同时降低对正常组织的损伤。这种兼具高效性、靶向性和低毒性的铜纳米药物已成为研究热点。铜纳米药物为肿瘤治疗开辟了新的途径, 也为突破现有治疗瓶颈提供了极具潜力的研究方向。

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