·综 述·

铜死亡与铜载体药物抗肿瘤机制的研究进展

蔡林峻，雷 靖，刘文斐，钱莹莹，马吉勇*
（南京医科大学附属南京医院呼吸与危重症医学科，江苏南京 210006）

摘要：铜参与诸多生命过程，铜稳态失衡会导致细胞死亡，该过程被称为铜死亡。肿瘤细胞为维持更高的细胞活性，铜负荷较高。利用铜载体及相关药物可以参与诱导肿瘤细胞的铜过载，引发肿瘤细胞铜死亡。现针对铜死亡与肿瘤的关系以及铜载体药物的抗肿瘤机制作一综述。

关键词：铜死亡；铜代谢；肿瘤；氧化激活反应；细胞死亡；铜纳米；铜配合物；铜螯合剂
中图分类号：R797.9；R73 **文献标志码：**A **文章编号：**1672-9188（2024）02-0181-06
DOI：10.13683/j.wph.2024.02.012

Research progress of cuprotosis and anticancer mechanism of copper carrier drugs

CAI Linjun, LEI Jing, LIU Wenfei, QIAN Yingying, MA Jiyong*
(*Department of Respiratory and Critical Care Medicine, Nanjing First Hospital, Nanjing Medical University, Nanjing 210006, Jiangsu Province, China*)

Abstract: Copper is involved in many life processes, and imbalance of copper homeostasis leads to cell death, a process known as copper death. Tumor cells maintained higher cellular activity and higher copper load. Copper carriers and related drugs can induce copper overload in tumor cells and lead to copper death of tumor cells. This article reviewed the relationship between copper death and cancer and the anticancer mechanism of copper carrier drugs.

Key words: cuprotosis; copper metabolism; tumor; oxidative stress; cell death; copper nanoparticles; copper complexes; copper chelating agents

铜是一种重要微量元素，参与多种细胞生化过程[1]。铜过载会产生大量活性氧（reactive oxygen species，ROS），导致氧化激活、DNA 损伤、自噬及细胞凋亡等细胞损伤[2]，即铜的细胞毒性作用[3—4]。近期学者通过研究发现一种新形式的细胞死亡，称为铜死亡。铜死亡主要参与线粒体的三羧酸循环（tricarboxylic acid cycle，TCA）[5]，诱发细胞死亡。

铜载体药物利用铜死亡形式，通过产生 ROS，诱发氧化应激反应，引起细胞死亡[6]。其机制包括：①抑制蛋白质的降解，激发热休克反应，引起内质网应激，诱导细胞死亡[7]。②直接损伤 DNA，引起细胞死亡[8]。③改变线粒体形态，抑制能量产生，导致细胞死亡[9—10]。④参与调节某些信号通路，抑制肿瘤细胞生长、转移，诱导肿瘤细胞死亡[7]。⑤通过光热疗法，引起细胞死亡[11]。越来越多的研究聚焦于铜载体药物的抗肿瘤机制。本文将从铜的代谢与氧化激活反应、细胞死亡、铜代谢与肿瘤及铜载体药物的抗肿瘤机制等方面来论述。

1 铜的生理功能与氧化激活反应

在细胞中，铜离子由铜转运 ATP 酶（ATP7A 和 ATP7B）进行转运[12]，如铜离子被转运至反式高尔基网络，形成铜原酶或参与各种酶的金属化[13]。

收稿日期：2023-02-22
作者简介：蔡林峻，硕士研究生，研究方向：肿瘤微环境与肺癌的免疫治疗。
通信作者：马吉勇，主任医师，研究方向：肿瘤微环境与肺癌的免疫治疗。

ATP7A 还可将铜传递给赖氨酸氧化酶（lysyl oxidase，LOX）家族，促进肿瘤的发生、转移，并在分泌途径中使赖氨酰氧化酶（recombinant lysyl oxidase，LOX）蛋白金属化，促进 LOX 介导的肿瘤转移 [14]。由于细胞内铜过载容易导致细胞铜死亡，而细胞内铜积累依赖于铜离子团的运输，故研究铜离子载体有利于研究其细胞毒性及抗肿瘤机制 [15]。铜还可由环氧酶传递至线粒体，参与氧化磷酸化 [16]。在细胞质中，铜离子能直接与大量的激酶结合，参与细胞生化过程 [17]。

铜不仅能直接诱导炎症细胞浸润 [18]，还可通过生成大量 ROS 诱导氧化应激、自噬及细胞凋亡；同时，ROS 介导的氧化应激又可引发多种炎症反应 [19]。尽管 ROS 适度增加有利于细胞增殖及存活，但 ROS 过载时，各种氧化大分子和代谢物则会引发细胞死亡 [20]。细胞内 ROS 的增加还会破坏单链或双链 DNA，激活相关蛋白激酶，导致细胞凋亡 [12]。故将化疗药物与铜离子联合应用，或能通过增加 ROS，促进肿瘤细胞凋亡，提高化疗药物的抗肿瘤能力 [21]。

2 细胞死亡与铜死亡

细胞死亡包括细胞凋亡、细胞自噬、细胞焦亡、坏死性凋亡及铁死亡等。其中，细胞凋亡及细胞自噬是受基因调控的程序性死亡；细胞焦亡和坏死性凋亡为病理性死亡；受离子调控的死亡则包括铁死亡及铜死亡。程序性死亡的细胞自噬需要应激反应启动，而细胞焦亡和坏死性凋亡则有半胱天冬酶家族蛋白参与，其中细胞焦亡受 gasdermin 家族蛋白调控，而坏死性凋亡受外来刺激诱导，如肿瘤坏死因子 -α。与铜死亡类似的铁死亡，则为铁过载引起细胞内脂质的过氧化，从而诱导细胞死亡 [22]；而铜死亡则是铜过载引起蛋白脂肪酰化，产生蛋白质毒性，诱导细胞死亡 [5]。

研究表明，铜死亡主要发生在线粒体的 TCA 循环中，TCA 循环促进铜与脂肪酰化成分结合，引起脂肪酰化蛋白聚集，诱发急性蛋白质毒性应激，导致细胞死亡 [5]。铜过载可导致细胞内 B 细胞淋巴瘤 -2 的信使 RNA（messenger RNA，mRNA）表达水平显著降低，改变线粒体膜通透性，并释放凋亡蛋白（如细胞色素 C）[23]。另一方面，铜复合物能调节细胞的氧化还原稳态，诱导细胞进入停滞期，甚至诱导细胞凋亡 [24]。此外，铜过载会诱导产生大量 ROS，过多的 ROS 生成伴随谷胱甘肽水平降低，导致细胞线粒体膜通透性升高，并诱导凋亡细胞死亡 [25]。ROS 也可诱导细胞凋亡，当 ROS 达到毒性水平阈值时，细胞即发生凋亡 [26]。铜死亡相关研究正如火如荼，其在抗肿瘤相关领域的应用也被热切关注。

3 铜代谢与肿瘤

肿瘤细胞中的铜离子一方面通过增加 ROS 的产生，提高细胞氧化还原状态，以维持肿瘤细胞的恶性表型 [27]；另一方面，其参与诱导肿瘤细胞的增殖 [28]。肿瘤细胞通常对铜离子有更高需求，故在肿瘤细胞中，铜蓝蛋白（ceruloplasmin，CP）mRNA 表达水平会升高。在临床检测上，肿瘤患者的血清及肿瘤组织中 CP 水平也相对较高 [29]。

铜可以激活相关蛋白和信号通路，从而促进恶性肿瘤的扩散。如通过激活 LOX/LOX 样蛋白与因子 MEMO1 促进肿瘤细胞转移 [30]。铜还可以通过磷酸二酯酶 3B 调节环磷酸腺苷 / 蛋白激酶 A 通路，促进细胞侵袭 [31]。

铜可促进血管生成、生长，从而促进肿瘤细胞的转移 [32]，故肿瘤细胞中含有更多的铜离子。鉴于此，将其与正常细胞进行区分，并实行相应的靶向治疗，选择性杀死肿瘤细胞 [33]。且当铜离子过载时，会引起肿瘤细胞死亡，故或能通过破坏铜转运，特异性增加肿瘤细胞中的铜含量，诱导肿瘤细胞死亡 [34]。

4 铜载体药物

4.1 铜纳米材料

纳米材料作为新兴抗肿瘤手段，有潜力被广泛应用。例如，纳米材料可利用光热效应杀伤肿瘤细胞 [35]，也能利用声动力学杀伤肿瘤细胞 [36]，还可诱导细胞死亡杀伤肿瘤细胞 [37]。铜纳米材料对肿瘤细胞具有良好的生物相容性、生物降解性及选择性细

胞毒性[38]。且铜纳米材料对正常细胞毒性小，不良反应少，更安全、可靠[39]。故铜基纳米材料可被用于抗肿瘤治疗[40]。

铜纳米颗粒能靶向肿瘤细胞，其对多种肿瘤细胞均有杀伤作用[41]。合成的氧化铜纳米颗粒对MCF-7、A549 肿瘤细胞系具有明显的细胞毒性[42]。氧化铜纳米颗粒被广泛用于杀伤肿瘤细胞，其释放的铜离子能阻滞细胞周期，诱导 DNA 损伤，发挥抗肿瘤作用[8]。由于纳米颗粒释放的铜离子也可将无毒的双硫仑（disulfiram，DSF）转化为高细胞毒性的 DSF/ 铜复合物，从而抑制肿瘤增殖。因此，加载 DSF 的硫化铜纳米颗粒对肿瘤细胞更具杀伤力[43]。

铜纳米材料还能促进 ROS 的生成，提升肿瘤细胞的死亡率[44]。氧化亚铜纳米颗粒会影响钙的运输，诱导钙离子在细胞内积聚，促进氧化应激、半胱天冬酶激活及细胞凋亡[45]。

铜纳米材料还可通过调节信号通路，诱导肿瘤细胞凋亡，发挥抗肿瘤作用[44]。氧化铜纳米颗粒释放的铜离子，激活参与诱导细胞凋亡的 p38 丝裂原活化蛋白激酶（mitogen-activated protein kinase，MAPK）信号通路[46—47]，参与诱导细胞的死亡[48]。

铜纳米材料可诱导细胞代谢方式的转变。以线粒体为靶点的耗铜纳米颗粒能通过抑制氧化磷酸化，增加糖酵解活性，诱导肿瘤细胞从呼吸到糖酵解的代谢转变，将有氧呼吸转变为糖酵解代谢，抑制能量产生，诱导细胞死亡[10]。

铜纳米材料也可在近红外光照下发挥抗肿瘤作用。在近红外照射下，铜纳米颗粒通过释放铜离子，让铜离子与肿瘤细胞 DNA 结合，造成 DNA 损伤，从而产生细胞毒作用，诱导细胞凋亡[49]。又如钯氧化铜纳米颗粒通过光热反应促进 ROS 生成、细胞核损伤，并调控蛋白表达，诱导肿瘤细胞光热解[50]。因此，铜纳米材料对肿瘤细胞具有杀伤作用。

4.2 铜配合物

铜（Ⅱ）配合物对肿瘤细胞在体外具有显著的细胞毒作用。铜（Ⅱ）配合物能够引起氧化激活反应，诱导细胞内生物分子破坏和细胞死亡[51]，并通过促进细胞内 ROS 生成，激活细胞凋亡和死亡机制[52]。DSF 可通过产生 ROS 引发氧化应激，抑制蛋白酶体活性，诱导细胞自噬，导致细胞凋亡[53]。DSF/ 铜复合物可以通过快速聚集蛋白、激活氧化应激及诱导热休克反应，促进细胞细胞死亡[7]。

铜（Ⅱ）配合物可通过调节信号通路发挥抗肿瘤作用，DSF/ 铜配合物通过转化生长因子 -β、核因子（nuclear factor，NF）-κB 信号通路和 ROS-p38MAPK 通路抑制转移，诱导细胞死亡[54]。DSF/ 铜配合物可以通过调节 Wnt/β- 连环蛋白 /NF-κB 信号通路抑制胃癌（gastric cancer）细胞生长[55—56]。铜（Ⅱ）异喹啉配合物 WN197 可激活 DNA 损伤反应通路，诱导细胞死亡[57]。铜（Ⅱ）配合物甚至能诱导氧化应激反应，抑制 P- 糖蛋活性，调节 NF-κB 信号通路介导，提高化疗药物的抗肿瘤能力[58]，如奥沙利铂（oxaliplatin）、顺铂（cisplatin）及伊马替尼（imatinib）[59]。

此外，铜（Ⅱ）配合物还可与 120 kV 或 6 MV 的 1 Gy 放疗相结合，抑制肺癌（lung cancer）细胞的生长、降低细胞活力，提升放疗效果[60]。

4.3 铜螯合剂

铜螯合剂最常见的作用机制是在细胞内螯合铜离子，随后排出金属。铜螯合剂通常在穿过细胞膜后形成铜络合物[61]，这使得细胞内铜离子水平升高。目前已知的铜离子螯合剂有四硫代钼酸盐、曲恩汀（trientine）以及 D- 青霉胺等[62—64]。

5 结语

铜过载时，ROS 大量生成，凋亡蛋白表达增加；错误蛋白大量累计，内质网产生应激；线粒体 TCA 被阻碍，从而诱导铜过载细胞产生凋亡，该过程被称为铜死亡。肿瘤组织中铜离子含量更高，以便维持其恶性表型，也因此可将其与正常细胞区分。临床上可利用高铜离子靶向肿瘤组织，使肿瘤组织中积累更多的铜纳米药物、铜配合物，进而产生铜过载，诱导铜死亡；同时也可配合放化疗，提高抗肿瘤能力。

综上，铜载体相关药物能靶向于肿瘤细胞，诱导铜死亡，在未来的抗肿瘤治疗中具有良好的应用前景。

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