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肿瘤多药耐药分子机制研究进展*

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摘要:化疗是治疗恶性肿瘤主要方法之一。然而不幸的是,先天或获得性耐药尤其是多药耐药的发生,最终导致化疗失败。因此,深入探讨多药耐药发生的分子机制,寻找可以有效预测肿瘤化疗敏感性的分子标志物以及逆转多药耐药的分子靶点,是提高化疗效果的有效途径。肿瘤多药耐药分子机制错综复杂,本文主要从 DNA 损伤修复、ABC 转运蛋白家族表达和功能异常、肿瘤干细胞、拓扑异构酶活性改变、上皮间质转分化、谷胱甘肽-S-转移酶表达改变、表观遗传学修饰以及缺氧等方面对肿瘤多药耐药分子机制进行阐述。

关键词:化疗;多药耐药;分子机制;研究进展

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The Research Progress in Molecular Mechanisms of Multidrug Resistance in Cancer*

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ABSTRACT: Chemotherapy is the first-line treatment for patients with advanced cancer. However, even though many novel chemotherapeutic drugs are used in clinical practice, chemotherapeutic approaches fail because of intrinsic or acquired drug resistance, particularly multidrug resistance (MDR). Thus, the exact mechanism of multidrug resistance remains to be further studied. Looking for molecular markers can effectively predict the sensitivity of cancer chemotherapy and searching for the molecular targets to reverse multidrug resistance is an effective way to improve the effect of chemotherapy. The molecular mechanism of multidrug resistance in cancer is complex. This article will focus on the mechanisms of multidrug resistance mainly from the following aspects: DNA damage repair, expression and functional abnormalities of the transporter family, cancer stem cells, the changes of the activity of topoisomerase, epithelial-mesenchymal transitions, changes in expression of glutathione-S-transferase, epigenetic modification and hypoxia.

Key words: Chemotherapy; Multidrug resistance; Molecular mechanism; Research progress

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前言

恶性肿瘤死亡率常年居高不下,严重影响国人健康。化疗是治疗恶性肿瘤的主要方法之一,随着科学的发展,不断有新的药物应用于临床。然而,由于耐药的发生尤其多药耐药的出现,即使临床上化疗药物再多或联合更多种化疗药物,最终也会导致化疗失败,甚至出现无药可医的局面。尽管当前肿瘤多药耐药分子机制研究相对较多,但截至目前,没有一种机制可以完全解释肿瘤多药耐药现象,即肿瘤多药耐药机制至今尚未完全阐明。因此,深入探讨肿瘤细胞多药耐药相关分子机制势在必行,只有阐明耐药机制,进而攻克恶性肿瘤的多药耐药性才是提高肿瘤患者疗效和预后最为有效的办法。通过阅读文献,本文将近年来已报道多药耐药分子机制进行综述,如 DNA 损伤修复、上皮间质转分化以及表观遗传学修饰等。期望经过

总结当前研究热点,使得大家对肿瘤多药耐药机制进一步加深理解,为将来攻克肿瘤多药耐药奠定一定理论基础。

1 DNA 损伤修复与肿瘤耐药

许多化疗药物以 DNA 作为最终靶点,通过直接或间接损伤肿瘤细胞 DNA 来发挥抗肿瘤作用。而 DNA 损伤修复则是在基因组内出现各种损伤时机体细胞的自我保护性反应。因此,DNA 损伤修复能力的增强与 MDR 密切相关^[1]。核苷酸切除修复(NER)是 DNA 最主要的损伤修复途径同时也是铂类药物损伤 DNA 后的主要修复途径。研究发现,作为 NER 途径中的关键分子,ERCC1 的表达水平与顺铂耐药密切相关,而且可以作为预测铂类药物化疗效果的有效指标^[2,3]。O6-甲基鸟嘌呤-DNA 甲基转移酶(MGMT)是烷化剂损伤后切除修复过程中的关键酶。因此,通过抑制 MGMT 功能进而逆转肿瘤耐药成为

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可能。有文献报道,通过 O6-BG 抑制 MGMT 功能后,结肠癌细胞对 5-氟脲嘧啶(5-Fu)敏感性显著增强^[4]。此外,胰腺癌细胞裸鼠移植瘤实验也证实,MGMT 功能失活后显著提高了裸鼠移植瘤细胞对烷化剂的敏感性^[5]。X-ray repair cross-complementing gene 1 (XRCC1)是碱基切除修复(BER)过程中的关键因子。有研究发现,XRCC1 mRNA 表达水平与非小细胞肺癌顺铂耐药密切相关。因此,XRCC1 可作为潜在的预测非小细胞肺癌顺铂耐药的分子标记物^[6]。

2 ABC 转运蛋白家族表达和功能异常与肿瘤耐药

药物外排增加是肿瘤细胞内药物蓄积减少的主要机制^[7],已经得到研究人员的广泛认同。而 ABC 转运蛋白家族是细胞由内向外排出化学药物的关键功能基因。ABC 转运子家族至少包含 48 个成员,根据其序列同源性及结构域组织方式分为 7 个亚家族(ABCA-G)^[8]。越来越多的报道证实该家族中至少有 12 个成员在药物转运过程中发挥重要作用,包括 P-glycoprotein(P-gp/ABCB1)、MRP1(ABCC1)、BCRP(ABCG2)等^[9,10],其中 P-gp 在肿瘤耐药中报道最多。目前已研究证实,P-gp 在肺癌^[11]、多发性骨髓瘤^[12]、视网膜母细胞瘤^[13]、白血病^[14]、卵巢癌^[15]、乳腺癌^[16]中表达显著升高并且导致上述肿瘤细胞对化疗药物产生耐药。

由于 P-gp 与人体多种肿瘤的多药耐药密切相关,因此,通过靶向 P-gp 逆转肿瘤耐药成为研究的热点。如 Gao L 等发现将抑制 P-gp 的表面活性材料包被紫杉醇后可显著逆转肺癌细胞耐药^[17]。c-Jun N 端激酶抑制剂 SP600125 通过抑制 P-gp 而显著增强肿瘤耐药细胞 KBV20C 对化疗药物的敏感性^[18]。尽管 ABC 转运蛋白家族在多种肿瘤耐药中的发挥重要作用,同时以其家族成员作为靶点也研发了多种特异性抑制剂,但由于毒副作用等多种原因,ABC 转运蛋白家族抑制剂在临床实践中并未取得理想的治疗效果^[19],有待于进一步改进。

3 肿瘤干细胞与肿瘤耐药

肿瘤干细胞(Cancer stem cell, CSC)是近年来肿瘤研究领域的热点。目前文献证实,CSC 是肿瘤细胞发生耐药的重要原因之一。例如,作为小细胞肺癌肿瘤干细胞标志,CD133 的表达与耐药和较强的致瘤性显著相关。进一步研究发现,经化疗药物作用后,CD133+ 的细胞在小细胞肺癌中比例显著增加^[20]。另外,最近的文献报道,在大规模急性髓性白血病(AML)病例中研究发现,当确诊时 AML 中的干细胞比例越高,化疗后病人的复发率越高、预后越差^[21]。此外,在人源性肿瘤模型研究中应用阿糖胞苷进行标准化治疗可显著降低末梢血白血病肿瘤负担,然而骨髓中 AML 干细胞展现出强大的耐药性从而导致肿瘤进展^[22]。而 Bertolini G 和 Lee TK 等发现,应用以顺铂为基础的标准化疗方案进行体内移植瘤实验,结果显示 CD133+ 和 CD24+ 干细胞分别在非小细胞肺癌^[23]和肝细胞瘤中富集^[24]。以上结果表明,肿瘤干细胞在人体多种恶性肿瘤耐药中发挥重要调节作用,是肿瘤高发病率和死亡率的罪魁祸首。

4 拓扑异构酶活性改变与肿瘤耐药

拓扑异构酶(Topoisomerase,Topo)是 DNA 复制解螺旋过

程中的关键酶,主要包括 Topo I 和 Topo II 两类。研究发现,通过外源性转染,上调乳腺癌耐药细胞系中 Topo II α 的表达水平后,耐药细胞对依托泊苷的敏感性显著增加^[25]。而另外一项研究发现,Topo II α 的表达水平与小细胞肺癌的耐药性呈负相关^[26]。与此同时,Topo II 在细胞中可被多种蛋白激酶磷酸化,而磷酸化水平与 Topo II 的催化活性呈负相关。Ganapathi R 等在白血病研究中发现,PKC 通过促进 Topo II 高磷酸化,下调其催化活性进而导致白血病细胞对 VP16 和 VM26 耐药性增强^[27]。此外,Ritke MK 也发现,白血病耐药细胞系中 Topo II 的催化活性下降是由磷酸化作用介导的^[28]。鉴于拓扑异构酶在肿瘤耐药中的重要性,Topo II 已作为抗肿瘤治疗的重要作用靶点,而且目前已有多个 Topo 相关抑制剂用于临床实践^[29]。

5 上皮间质转分化(Epithelial-mesenchymal transitions,EMT)与肿瘤耐药

既往研究证实 EMT 与恶性肿瘤的转移密切相关。而近期越来越多的研究发现,肿瘤细胞发生 EMT 后可产生多药耐药性。Huang S 等研究发现,抑制 MED12 的表达可在多种实体肿瘤包括结肠癌、肝癌和非小细胞肺癌中激活 TGF- β 通路,诱导 EMT 发生进而产生耐药性改变^[30]。Gupta PB 等在乳腺癌研究中发现,应用外源性 TGF- β 处理乳腺癌细胞后,乳腺癌细胞发生 EMT 改变的同时对阿霉素和顺铂的耐受性显著增强^[31]。同样,当诱导肿瘤细胞产生耐药时也往往伴随 EMT 发生。Voulgari A 等在研究结直肠癌、肝癌、胰腺癌及乳腺癌等多种肿瘤耐药时发现,对化疗药物耐受的肿瘤细胞均发生了 EMT 改变^[32]。以上结果证实,EMT 现象与肿瘤耐药密切相关。但 EMT 对肿瘤耐药的调控作用及其相关分子机制尚需进一步研究。

6 谷胱甘肽-S-转移酶与肿瘤耐药

谷胱甘肽(Glutathione,GSH)是细胞内关键的解毒系统。目前研究发现 GST 包括 α 、 μ 、 π 、 θ 四种同工酶。近年来文献报道,GST π 在细胞核内定位与妇科肿瘤的化疗耐药呈显著相关性^[33]。而 Ming G 等研究发现,GST- π 在胃癌细胞中表达增高与顺铂(CDDP)和 5-Fu 耐药相关^[34]。此外,Komiyama 等研究发现,GSH 的表达水平在顺铂耐药的骨肉瘤细胞中明显增高,当下调 GSH 表达后可显著提高耐药的骨肉瘤细胞对药物的敏感性^[35]。

7 表观遗传学修饰与肿瘤耐药

表观遗传学修饰如 DNA 甲基化和组蛋白去乙酰化参与调控肿瘤多个恶性表型,其中包括多药耐药。如联合应用褪黑激素和化疗药物可显著增强神经胶质瘤细胞 BTSCs 和 A172 对药物的敏感性。进一步研究发现,褪黑激素(Melatonin)与 DNA 甲基转移酶抑制剂相互作用,致使 ABCG2/BCRP 启动子甲基化水平增高从而提高了细胞对药物的敏感性^[36]。另一项胃癌耐药研究中,为了鉴定顺铂耐药相关基因,20 种胃癌细胞系被用于基因表达谱、DNA 甲基化表达谱及药物敏感性检测。结果发现,bone morphogenetic protein 4 (BMP4)在顺铂耐药细胞系中表达显著升高,而抑制 BMP4 可显著提高胃癌细胞对顺铂的敏感性^[37]。至于组蛋白去乙酰化酶与耐药的关系,Oehme 等研究发现,敲除或抑制组蛋白去乙酰化酶 10(HDAC10)的表达可显

著增强神经母细胞瘤对化疗药物的敏感性^[38]。

8 缺氧与肿瘤耐药

缺氧是众多实体肿瘤中普遍存在的现象。最近有文献证实,缺氧是肿瘤耐药发生和恶性进展的重要因素。Rice 等研究发现,与未处理的细胞相比,通过缺氧预处理的 CHO 细胞对氨甲喋呤和多柔比星耐药性显著增强^[39]。在黑色素瘤研究中发现,缺氧通过激活 HIF1(hypoxia inducible factor 1)活性,启动下游 MDR1 基因转录而上调 P-gp 表达,最终导致黑色素细胞耐药^[40]。此外,Yang SY 等证实缺氧后 HIF1 通过诱导 MDR1 的表达促进胰腺癌细胞系 Patu8988/5-Fu 多药耐药的发生^[41]。另一项研究发现,分子靶向药物索拉非尼在治疗肝细胞癌时,缺氧诱导 HIF-1 α 表达升高进而降低索拉非尼对肝癌细胞的杀伤作用。究其原因,缺氧致使肝癌细胞中 P-gp 表达升高、糖酵解增强以及 nuclear factor kappa B (NF- κ B) 的过度激活。然而,通过一个类似姜黄素结构的分子 EF24 可显著抑制 HIF-1 α ,进而增强索拉非尼的抗肿瘤作用^[42]。该结果提示我们在肝细胞癌中联合应用 EF24 和索拉非尼可能是一个潜在的、有希望的治疗肝细胞癌的策略。

9 小结

综上,多药耐药分子机制错综复杂。本文阐述了当前肿瘤多药耐药机制最新进展,为进一步深入理解肿瘤多药耐药奠定一定基础。尽管当前研究相对较多,但多数研究尚处于体外实验阶段,虽然取得了一定逆转耐药效果,但依然缺乏体内直接证据,同时,开展临床试验又面临众多制约。因此,攻克肿瘤多药耐药,寻找有效预测耐药标志物及逆转耐药靶点前景美好,但依然需要更多、更深入的工作来不断完善和发展。相信随着科学研究的深入,肿瘤多药耐药分子机制将不断完善,最终以此为靶点攻克多药耐药,造福全人类。

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