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肿瘤多药耐药机制及其应对策略的研究进展

Advances in research related to multidrug resistance mechanisms in tumors and their coping strategies

郑钰^{1,2} 综述;尹焕才^{1,2},殷建^{1,2} 审阅[1. 中国科学技术大学 生物医学工程学院(苏州),生命科学与医学部,江苏苏州 215613;2. 中国科学院 苏州生物医学工程技术研究所,江苏 苏州 215613]

[摘要] 多药耐药现象是当前临床肿瘤治疗的主要障碍,且尚无有效的逆转方案。经过长期探索发现,细胞内药物外排增加、代谢增强、吸收下降、DNA突变及修复功能增强、肿瘤微环境影响等多种机制均参与了多药耐药现象的发生,且这些机制受转录因子、miRNA及lncRNA等因素的调控。当前研究者已开发出多种应对策略,包括小分子、中药逆转剂、纳米载体及生物疗法等进行耐药肿瘤治疗,但其疗效和生物安全性仍有待于进一步提升,深入的机制探索和多模态的治疗方案开发将是未来多药耐药肿瘤治疗的重要发展方向。

[关键词] 化疗;肿瘤;多药耐药机制;逆转策略

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化疗是目前临床上应对肿瘤的主要治疗方案,但其疗效往往受耐药现象的限制。这一现象导致不仅化疗药物失效,还会进一步发展多药耐药(multidrug resistance, MDR),使肿瘤细胞对多种结构不同、作用靶点不同的药物产生耐药,进而导致化疗彻底失效,并成为肿瘤复发、转移以及90%以上化疗患者死亡的主要原因^[1-2]。经过长期探索,研究者发现多种因素参与了MDR的形成,包括细胞内药物外排增加、代谢增强、吸收下降、作用靶点突变以及损伤修复等^[3],这些因素往往同时发生,且肿瘤微环境进一步影响了肿瘤的耐药性发展。有鉴于此,本文将分别从降低药物蓄积、损伤修复以及肿瘤微环境等方面介绍MDR现象的发生机制,并探讨了MDR的主要调控因素以及当前应对策略的研究进展,为肿瘤MDR的基础研究与临床治疗提供较为全面的参考资料。

1 降低细胞内药物蓄积

肿瘤细胞应对化疗药物的直接反应往往是降低其在细胞中的蓄积,可能的途径包括增加外排、快速代谢及降低吸收,而这也是耐药现象发生的首要机制。

1.1 ABC结合盒(ATP-binding cassette, ABC)转运蛋白上调导致的细胞内药物外排增强

ABC转运蛋白介导的外排现象是研究较早的肿瘤MDR机制,并被认为是MDR逆转的重要靶标^[4]。ABC转运蛋白是最大的穿膜蛋白超家族,可分为ABCA~G等多个亚家族^[5]。其中P-糖蛋白(p-glycoprotein, P-gp)、MDR相关蛋白(multidrug resistance-associated protein, MRP)和乳腺癌耐药蛋

白(breast cancer resistance protein, BCRP)等参与了MDR的发生^[6]。这些转运蛋白利用ATP水解能量,介导了细胞内多种不同结构化合物的外排(表1),以实现机体自我保护^[7]。其中,P-gp研究最为充分^[8],并被证明参与了200多种药物的外排^[9-10]。其他蛋白与P-gp具有较大的底物重合性,但具有各自独特的底物特征。MRP主要外排药物是GSH结合产物^[11]。BCRP是一个半转运体,其主要运载硫酸盐产物^[12]。

表1 ABC转运蛋白及其部分外排对象

转运蛋白	底物	肿瘤类型	参考文献
P-gp	伊马替尼	慢性粒细胞白血病	[13]
MRP1	卡铂、吉西他滨、拓扑替康、多柔比星、紫杉醇	卵巢癌	[14]
MRP2	顺铂	非小细胞肺癌	[15]
MRP3	7-乙基-10-羟基喜树碱、拓扑替康	乳腺癌	[16]
MRP4	紫杉醇、顺铂	乳腺癌	[16]
MRP5	顺铂	非小细胞肺癌	[15]
MRP7	紫杉醇、多西他赛、长春瑞滨、维诺瑞滨	卵巢癌	[17]
BCRP	7-乙基-10-羟基喜树碱、拓扑替康	非小细胞肺癌、乳腺癌	[15] [18]

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[作者简介] 郑钰(2002—),女,硕士生,主要从事肿瘤多药耐药机制的研究,E-mail:zyyy0206@163.com

[通信作者] 殷建,E-mail:yinj@sibet.ac.cn

1.2 生物转化酶上调导致药物代谢增强

生物转化是药物进入细胞后,在酶催化下发生的化学变化过程。药物的生物转化主要分为两个阶段:其中I相代谢主要由细胞色素P450完成,通过对药物氧化、还原及水解,改变其结构;II相代谢酶则包括谷胱甘肽(glutathione, GSH)-S-转移酶、葡糖醛酸转移酶等,通过结合反应,增加药物亲水性。肿瘤细胞通过高表达生物转化酶,快速将抗肿瘤药物转化为亲水性产物,便于转运蛋白将其外排,进而发生耐药^[19]。例如,顺铂等药物的GSH结合物更易被MRP识别且泵出^[20]。另一方面,耐药肿瘤细胞的GSH水平往往显著高于常规肿瘤细胞,这些GSH在GSH-S-转移酶介导下可与过氧化产物结合,从而使化疗药物过氧化杀伤肿瘤细胞的机制失效^[21]。

1.3 囊泡辅助药物外排及耐药性传递

囊泡主要指分布于细胞内的囊状结构,由至少一层的脂质双层分子膜构成。研究^[22]表明,MDR肿瘤细胞内呈高度囊泡化,这些囊泡可在肺耐药蛋白(lung resistance protein, LRP,非ABC转运蛋白)等的协助下蓄积化疗药物,并通过胞吐作用排出实现耐药。排放至细胞外基质的囊泡参与了肿瘤细胞耐药性的产生及传递等过程。蔡志坚团队^[23]的研究结果表明,肿瘤细胞外囊泡可结合抗PD-L1抗体,使其更易被巨噬细胞清除,从而导致肿瘤治疗效果不佳。与此同时,化疗药物可促使耐药细胞释放包含ABC转运蛋白的细胞外囊泡,这些外囊泡可融入其他肿瘤细胞的细胞膜,提高后者药物耐受性^[24]。

1.4 抑制溶质载体超家族导致的药物吸收降低

溶质载体超家族蛋白为单羧酸转运体家族的一种,它们在细胞营养物质的运输、细胞代谢和pH调节中发挥重要作用^[25]。研究^[26]表明,甲氨蝶呤、5-氟尿嘧啶和顺铂等药物借助于溶质载体蛋白运载进入细胞内发挥药效。因此,肿瘤细胞通过抑制溶质载体蛋白的表达,有效减少药物分子摄取,从而实现耐药^[27]。

2 基因突变及其修复功能

2.1 基因突变导致靶点失效、耐药蛋白激活及肿瘤异质性产生

基因突变广泛存在于肿瘤细胞中,并被发现与靶点逃逸、耐药蛋白表达提升以及细胞异质性密切相关。例如,多个凋亡相关基因,p53、Bcl-2及c-Myc基因为常见的药物作用靶点,它们通过促进细胞凋亡杀死肿瘤细胞。当这些基因发生突变时,可导致化疗药物失效并导致耐药。同时p53突变还可激活P-gp等转运蛋白表达,提升药物耐药水平^[28]。另一方面,基因突变在同一肿瘤组织的各细胞中往往不

同,从而导致了肿瘤异质性。研究^[29]表明,肿瘤细胞群体在几乎所有可辨别的表型特征上都存在显著差异。具有较强耐药能力的细胞更易在化疗中存活,并通过增殖实现肿瘤复发^[30]。有鉴于此,FANG等^[31]将肿瘤异质性作为生物标志物来预测晚期非小细胞肺癌患者的治疗效果。

2.2 修复机制激动导致DNA损伤减轻

多种化疗药物的作用机制中包含了DNA损伤。例如,5-氟尿嘧啶通过抑制胸苷合成酶,干扰DNA及RNA合成,并导致细胞凋亡^[32]。同样,顺铂等铂类药物可通过形成DNA加合物,干扰癌细胞中DNA的复制,诱导细胞死亡。在此情况下,肿瘤细胞通过增强碱基切除修复和错配修复功能,修复DNA损伤,实现肿瘤耐药^[33]。

3 肿瘤细胞微环境与非细胞微环境介导的耐药机制

肿瘤微环境即肿瘤细胞存在的环境,包括巨噬细胞、成纤维细胞、脂肪细胞和胶原基质,以及它们释放的分子等^[34]。微环境对肿瘤耐药性的影响可分为细胞微环境与非细胞微环境两个部分,并具有较强的肿瘤异质性特征^[35]。

就细胞微环境而言,肿瘤相关巨噬细胞因其广泛分布于各种肿瘤的微环境中而最受关注^[36]。HALBROOK等^[37]发现,肿瘤相关巨噬细胞可分泌嘧啶类等代谢物,这些代谢物通过分子竞争在药物摄取和代谢水平上抑制吉西他滨,从而导致耐药。类似地,肿瘤相关巨噬细胞可分泌炎症细胞因子和趋化因子,促进形成炎症微环境,导致癌症干细胞生成并产生耐药性^[38]。来自癌症相关成纤维细胞的外泌体可刺激结肠癌干细胞的生成,并产生耐药性^[39]。脂肪细胞则被发现可通过激活Akt通路来增强卵巢癌细胞对化疗药物的耐受性^[40]。

非细胞微环境同样对耐药性有着重要的影响。首先,缺氧是肿瘤微环境的重要特征,即由于肿瘤生长迅速导致氧消耗增多及弥散距离增加,且由于血管破裂与供血不足,导致相对缺氧。这一缺氧环境可通过激活缺氧诱导因子-1家族启动P-gp蛋白的表达,使肿瘤细胞耐药性增强^[41]。除此之外,低血管密度也会导致血源性药物不能迅速进入肿瘤区域。其次,肿瘤细胞代谢旺盛可导致环境pH降低,而较低的pH值同样可诱导P-gp的表达,导致外排蛋白活性增加以实现耐药^[42]。

4 相关调控机制

4.1 转录因子调控ABC转运蛋白及生物转化酶

转录因子是一种具有特殊结构、行使调控基因

表达功能的蛋白质分子,其中孕烷X受体、组成型雄性激素受体、芳香族碳氢化物受体、过氧化物增殖酶体激活受体等可感受外源药物入侵,调控机体内ABC转运蛋白及生物转化酶,以尽快将外源物代谢排出,因此它们被称为外源物感受器^[43-45]。E2相关因子2则可被化疗药物引发的氧化自由基激活,并促进肿瘤细胞中ABC转运蛋白等耐药机制激活^[46]。此外,大鼠肝脏实验中发现过表达孕烷X受体可上调Bcl-2等凋亡抑制因子,抑制肿瘤细胞凋亡,进而导致耐药现象的发生^[47]。

4.2 miRNA 调控MDR 通路

miRNA是一种主要存在于非编码的内含子区域、长度为20~25 nt的RNA分子。它们的主要功能是在转录后水平上对基因表达进行调控。近年来,miRNA与肿瘤MDR机制的相关性被广泛报道^[48]。

miR-23a-3p在肝癌细胞中过量表达,通过直接靶向酰基-CoA合成酶长链家族成员4的3'-非编码区抑制索拉非尼诱导的铁死亡,导致索拉非尼耐药^[49]。YANG等^[50]发现,miR-1269b的表达在非小细胞肺癌细胞系中上调,其靶向PTEN以调节PI3K-Akt信号通路,促进了顺铂耐药。LI等^[51]发现,miR-185-3p在肺癌细胞中被下调,从而诱导肝型磷酸果糖激酶和间充质上皮转化癌蛋白的过度表达,并导致厄洛替尼耐受。尽管越来越多的研究表明,miRNA可成为癌症化疗预后的生物标志物,但由于miRNA具有多靶标调控功能,而同一个靶点也可被多个miRNA调节,使得其调控网络十分复杂,给相关研究和应用带来了困难^[52]。

4.3 lncRNA 调控ABC转运蛋白及其他耐药机制

lncRNA是一类长度约为200 nt的RNA分子,参与细胞内转录调节及转录后修饰等,并被证明与各种癌症的化疗耐药性密切相关^[53]。lncRNA MALAT1可通过激活转录因子STAT3来提高MRP1和MDR1的表达,进而降低体外和体内肿瘤细胞的顺铂敏感性^[54]。类似地,lncRNA H19通过激活PI3K-Akt-mTOR通路,刺激ABC转运蛋白的表达,从而增强绒毛膜癌细胞对甲氨蝶呤的抗性^[55]。TAN等^[56]研究发现,CAF-EV携带的lncRNA SNHG12进入非小细胞肺癌细胞后,通过与HuR结合促进了RNA的稳定性和XIAP的转录,因此增强了非小细胞肺癌细胞的顺铂耐药性。

5 主要应对策略

5.1 耐药靶点特异性抑制剂的研发

鉴于ABC转运蛋白研究开展较早,早期的MDR激活逆转剂的研发主要集中于其特异性抑制剂的筛

选。如P-gp药物外排抑制剂类黄酮与抗癌药物的联合给药被认为是克服MDR的一种可能治疗方式^[57]。此外,研究者也通过对ABC转运蛋白的调控信号通路进行探索,以期发现新的药物作用靶点^[12]。例如,一种基于萘酰亚胺衍生物的拓扑异构酶抑制剂LSS-11可通过DR5/PARP1途径,抑制STAT3与MDR1和MRP1启动子的结合,下调转运蛋白表达来克服紫杉醇耐药^[58]。此外,奥西梅替尼可通过抑制激活性突变和防止显性耐药克隆的增加,降低基因突变的影响,显著改善患者生存率^[59]。针对DNA损伤修复功能,有研究者提出采用多聚ADP-核糖聚合酶抑制剂抑制该功能,进而在临床治疗中克服耐药性^[60]。索拉非尼、雷戈拉非尼等激酶抑制剂则能够抑制尿苷二磷酸葡萄糖醛酸转移酶等生物转化酶的活性,实现MDR逆转^[61]。然而到目前为止,上述单靶点抑制剂的临床效果往往并不理想,这是因为MDR的多种机制往往同时发生,且可相互交叉补偿,单靶点抑制剂的使用反而导致了新的耐药现象发生^[57]。

5.2 基于中药的多靶点逆转剂研发

随着中药事业的发展,中药及中药单体逆转肿瘤MDR的作用逐渐被发现^[62]。例如,积雪草苷可通过抑制P-gp的表达,增加细胞内化疗药物的浓度,起到拮抗肿瘤MDR的作用^[63]。与西药相比,中药逆转剂有其独特优势^[64]。首先,中药成分具有多靶点作用机制,可避免耐药性的发生;其次,中药对人体损害较小,不良反应少;第三,中药可通过提高人体自身的免疫功能来抑制肿瘤的发生发展。然而由于中药成分较为复杂,其在MDR肿瘤治疗中的应用尚处于起步阶段,深入探索与临床应用仍有待开展。

5.3 纳米载体药物的研发

因其具有高稳定、便于修饰、载药量大、直径较大(10~100 nm)、可绕过耐药蛋白等优势,多种无机(如纳米金、二氧化钛等)及有机纳米载体(如脂质体、多糖类)被开发出来,用以对肿瘤细胞MDR现象的抑制^[65]。其中,纳米脂质体载体药物已经获得FDA批准用于临床治疗。研究者进一步将纳米载体与RNA干扰、热疗等其他治疗方法相结合,发现其可对MDR癌细胞表现出更强的杀伤作用^[66]。尽管如此,纳米载体潜在的生物毒性是限制其临床应用的主要障碍^[67]。

5.4 个体化生物疗法的研发

随着肿瘤发生及耐药机制研究的深入,多种生物治疗方法,包括体细胞、细胞因子、单克隆抗体及基因疗法等已被大力开发出来^[68]。这些治疗方法针对特异性靶点作用,可通过降低肿瘤抗药性或调节肿瘤生长、凋亡、转移等行为以实现耐药肿瘤的治疗。

疗。但这些方法的疗效易受肿瘤异质性(包括靶点表达水平、基因突变的差异)及不同微环境的影响,如针对P-gp的单克隆抗体的疗效易受肿瘤细胞中P-gp表达水平的影响^[69]。因此,完善的分子评估及在此基础上的个体化治疗方案选择是生物疗法临床使用的重要前提。

综上所述,肿瘤MDR是通过多种因素作用而形成的,且相互之间往往存在较强的补偿效应,导致单因素抑制往往无法获得预期的临床治疗效果。有鉴于此,深入探索MDR现象发生机制及其共同的调控机制,并在此基础上进行个性化、多模态的联合治疗,将是未来肿瘤治疗事业发展的重要方向。

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