中西医结合防治肿瘤耐药的研究进展

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摘要 化疗和靶向治疗是晚期恶性肿瘤的主要治疗方法之一, 而其耐药性是导致肿瘤治疗失败的重要原因. 引起肿瘤耐药的原因有肿瘤细胞的异质性、药物外排及代谢失活、肿瘤微环境变化、DNA损伤修复失调、表观遗传改变等多种因素. 当前, 临床上主要采取更换联合化疗用药或更换新的抗肿瘤药物的策略来克服肿瘤耐药, 但由于该方法作用靶点单一, 且治疗耐药过程中容易产生新的耐药甚至多药耐药, 导致肿瘤治疗的难度增大. 因此, 寻找高效、低毒、广谱的逆转肿瘤耐药方法或药物已成为当今肿瘤领域的研究热点及难点. 中医药由于成分复杂, 可以通过多组分、多靶点呈现多方面抗肿瘤作用, 因而在增强抗肿瘤药物敏感性或克服肿瘤耐药方面具有巨大潜能. 本文系统阐述了肿瘤耐药的发生机制, 分析了现代医学和传统中医学在克服肿瘤耐药方面的最新研究进展, 旨在为增强抗肿瘤药物的敏感性或克服肿瘤耐药提供一种新的思路和策略.

关键词 中医, 西医, 中西医结合, 化疗耐药, 化疗抵抗

肿瘤是当今严重威胁人类健康的重要疾病之一. 据统计, 2018年全球有1810万肿瘤新发病例, 960万患者因肿瘤死亡, 其中亚洲地区死亡人数占总死亡人数的57.3%^[1]. 以化疗和靶向治疗为主的综合治疗是目前晚期癌症患者的主要治疗手段, 然而这些药物在治疗肿瘤的同时亦会造成肿瘤细胞对药物的耐药, 导致治疗失败^[2,3].

肿瘤耐药包括原发性耐药和继发性耐药. 原发性耐药是指癌细胞在接触抗肿瘤药物之前已经具有的耐药性; 继发性耐药是指癌细胞在与抗肿瘤药物反复接

触后产生的对药物的抵抗性和耐受性^[4,5]. 此外, 癌细胞的耐药谱分为原药耐药谱和多药耐药(multidrug resistance, MDR)谱. 原药耐药谱指癌细胞只对开始接触的原药不敏感, 但对其他药物仍然敏感有效; 多药耐药谱是指癌细胞除了对开始接触药物不敏感外, 同时对其他未接触的、结构和作用机制不同的药物亦产生耐药^[6,7]. 此时, 若采用简单的更换化疗药物, 或者联合化疗用药效果均不理想, 同时还增加了抗肿瘤药物的不良反应. 因此, 寻找合适的耐药逆转剂已成为肿瘤领域研究的重大临床难题. 中草药以其多组分和多靶点效

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应的优势在我国肿瘤临床治疗方面获得了广泛的应用,且具有减轻抗肿瘤药物的毒副反应和提高癌症患者生活质量的鲜明特点^[8,9].近年来的研究表明,中药在增强抗肿瘤药物敏感性和克服肿瘤耐药方面显示出独特的优势^[10,11],为中西医结合防治肿瘤耐药提供了新的途径.本文以增强抗肿瘤药物敏感性和逆转肿瘤耐药为主线,系统地介绍具有代表性的化学药物逆转剂、中药(天然药物)逆转剂,并探讨其潜在的临床应用前景,为中西医结合逆转肿瘤耐药提供理论基础和新的策略.

1 肿瘤耐药机制

1.1 肿瘤耐药机制的现代医学研究

肿瘤耐药是一个多种因素、多基因、多信号通路参与的复杂过程.肿瘤耐药的现代医学机制涉及多方面,共性的耐药机制包括:基因组不稳定造成的肿瘤细胞异质性^[12],外加药物对其进行的淘汰“选择”,最终导致肿瘤耐药的发生^[13~15];肿瘤细胞膜转运体蛋白引起的药物外排增加,如依赖ATP的药物外排泵(P-gp、MRP1、BCRP等)可显著降低药物的摄取^[16,17];药物代谢酶的活性改变,如细胞色素P450的活性增强^[18]、谷胱甘肽S-转移酶(π GST π)的活化^[19]等;DNA损伤修复系统的激活^[20];肿瘤微环境的变化,如低氧、内质网应激、酸性微环境、炎症因子释放等^[21~23];基因突变或信号通路异常,如PTEN丢失、C-Met扩增、Notch、Ras、Mek、MAPK、PI3K等信号通路的异常活化均可造成细胞增殖失控,导致肿瘤耐药^[24~26].此外,细胞自噬和某些肿瘤相关基因的表达遗传学改变,如p53、PPP2R1B、Bcl-2等亦可引起肿瘤耐药^[27~29](图1).

1.2 肿瘤耐药机制的中医学研究

中医药是中华民族在几千年和疾病作斗争的过程中累积的瑰宝.中医对肿瘤最早的文献记载是公元前16世纪至公元前11世纪殷商甲骨文“瘤”字的出现.此外《内经》中的“肠覃”、“息贲”、“石瘕”,《难经》中的“积聚”,《诸病源候论》中的“石痈”、“石疽”,《伤寒杂病论》中的“癥瘕”等均有肿瘤的记载.中医认为肿瘤的发生是在正气亏虚的基础上,外感六淫或内伤七情等因素共同作用的结果.《内经》云:“邪气盛则实,精气夺则虚”,“正气存内,邪不可干”,“邪之所凑,其气必虚”.《灵枢·百病始生篇》曰:“虚邪之中人也,始于皮肤……稽留不去,息而成积”.《医宗必读》曰:

“积之成者,正气不足,而后邪气踞之”.《景岳全书》云:“脾肾不足及虚弱失调之人,多有积聚之病”.因此,肿瘤的发病是在正气亏虚的基础上,气滞、血瘀、湿聚、痰凝、热毒等内邪积聚,久而久之形成^[30~32].当代医家对于肿瘤的病机特点也做了深入研究与分析.国医大师周仲瑛教授和刘嘉湘教授根据长期的临床实践,提出脾气虚弱、湿毒瘀结为晚期肿瘤的基本病机^[33,34].上海中医药大学附属曙光医院李琦教授根据多年临床经验发现湿热是化疗耐药的病理因素^[35].湿性重浊、黏滞,而热性炎热,易伤津耗气,化燥伤阴,湿热相合则若油入面,湿遏热伏,胶着难愈.正如《湿热病篇》所云:“热得湿而热愈炽,湿得热则湿愈横.湿热两分,其病轻而缓,湿热交合,其病重而速”.因此,湿热证癌症患者多表现为炎热、升腾、缠绵难愈的特性,同时呈现对化疗药物和靶向药物的抵抗或耐药.

2 现代医学克服肿瘤耐药的药物

针对肿瘤耐药产生的机制,现代医学已经出现了一些应对的方法并将这些方法应用于肿瘤的临床治疗中.肿瘤的耐药性与传染病领域抗生素耐药很相似,对于单药化疗耐药的最初解决方案是将具有非重叠作用机制的化疗药物联合使用,这一思路也是从抗菌治疗法典中得到的启发.当前,现代医学克服肿瘤耐药的策略主要包括联合用药和更换新的抗癌药物等.

2.1 联合用药

经典逆转肿瘤耐药的药物是化学药物逆转剂.这类药物大多是针对细胞膜P-糖蛋白(permeability glycoprotein, P-gp)而设计相应的抑制剂,其作用机制复杂、种类繁多且发展较快,已从最初的第一代发展到第四代.但由于高毒性和对肿瘤药物药代动力学的影响,P-gp类抑制剂并未应用于临床^[36].当前,化学药物逆转剂的研究主要集中于联合应用高效、低毒、安全的“老药新用”方面(图2).Fong和To^[37]回顾并分析了非甾体类抗炎药、二甲双胍、氯喹等药物联合化疗、分子靶向治疗和免疫治疗的疗效.结果显示,联合应用上述药物具有逆转肿瘤耐药作用,可显著延长癌症患者生存期.但上述方案所致的不良事件不容忽视,因此需要大量样本的临床研究进一步评估.二甲双胍被证实具有逆转胰腺癌细胞对吉西他滨耐药和增强结直肠癌对氟尿嘧啶类药物敏感性的作用^[38,39].此外,3 β -乙酰基草酸、DUSP6(dual specificity phosphatase

图1 (网络版彩色) 肿瘤耐药的现代医学机制示意图

Figure 1 (Color online) Current understanding of drug resistance in cancer

6) 抑制剂、组蛋白去乙酰化酶抑制剂(histone deacetylase inhibitor, HDACI)等也被证实具有逆转肿瘤耐药的潜能^[40-43]。

2.2 更换新的抗肿瘤药物

除了联合用药, 更换新的抗癌药物也是克服肿瘤耐药的一种现代医学策略(图2)。例如, *T790M*突变是EGFR突变阳性晚期非小细胞肺癌(non-small cell lung cancer, NSCLC)患者对第一代EGFR-TKIs耐药的重要原因^[44], 第三代EGFR靶向药物奥希替尼可明显延长*T790M*突变的NSCLC耐药患者的生存期, 改善患者的预后^[45]。内分泌治疗耐药是影响激素受体阳性晚期乳腺癌患者治疗效果和预后的重要因素。近几年针对乳腺癌内分泌治疗耐药的机制研究取得较大进展, PI3K/Akt/mTOR信号通路活化被认为是乳腺癌内分泌治疗

耐药的重要机制之一^[46]。针对mTOR信号通路引发的乳腺癌耐药, mTOR抑制剂依维莫司呈现出逆转内分泌耐药的潜能^[47]。因此, 德国的AGO指南推荐依维莫司用于无病间期短、内分泌治疗不再敏感的乳腺癌患者, 突显了它的逆转耐药属性。

尽管现代医学在克服肿瘤耐药方面取得了显著进展, 一些新的联合用药方案或新的抗肿瘤药物亦展现出逆转耐药的潜能, 但这些药物往往作用靶点单一、毒副反应较大且治疗耐药过程中容易产生新的耐药甚至多药耐药, 导致肿瘤治疗的难度进一步增大。而中医药具有多组分、多靶点、多阶段性的作用特点, 因而在抗肿瘤耐药方面受到了广泛关注。

3 中医学克服肿瘤耐药的药物

辨证论治是中医学理论和临床治疗的核心, “扶正

图2 (网络版彩色)中西医抗肿瘤耐药的药物及其治疗靶点

Figure 2 (Color online) Drugs and therapeutic targets of Chinese medicine and Western medicine for reversing drug resistance

祛邪”是中医治疗肿瘤的基本原则。中西医结合肿瘤学既讲究辨证,也重视辨病,同时更注重辨证与辨病相结合。“气滞、血瘀、痰凝、正虚”是肿瘤形成的主要病因病机。基于此病机,中医形成了多种抗癌治则,包括理气行气、活血化瘀、化痰散结、扶正祛邪等^[48]。当前,中医药治疗已成为我国独具特色且安全有效的肿瘤辅助治疗方法。大量的临床证据表明,中医药在提高癌症患者生活质量、预防转移复发、抗肿瘤耐药、增效减毒和增强免疫力等方面发挥了重要作用^[49]。

近年来,不论是中药复方还是单体,中医药都显示了克服肿瘤耐药的独特作用.其克服肿瘤耐药的机制

主要与抑制细胞周期增殖、下调抗凋亡蛋白或多药耐药蛋白的表达、诱导非凋亡性细胞死亡、抑制某些生长信号通路等相关。相比现代医学耐药逆转剂, 中药具有安全、有效、多组分、多靶点、多阶段作用的特点, 这为克服肿瘤耐药提供了新思路和新途径(图2)。

3.1 榄香烯注射液

榄香烯(*elemene*), 包括榄香烯乳状注射液和榄香烯口服乳)是谢恬教授团队基于“消癥散结、扶正祛邪”治疗癌症的中医治则和创新提出的中西医结合“分子配伍理论”, 从天然姜科植物浙八味中药温郁金(温莪术)

中成功分离出的高效、低毒的小分子抗癌活性成分^[50]。榄香烯注射液的有效成分包括 β -榄香烯、 γ -榄香烯和 δ -榄香烯,其中85%为 β -榄香烯,是一种安全、有效的抗肿瘤药物,开创了中药倍半萜烯类化合物治疗癌症的先河。

榄香烯脂质体是具有中国自主知识产权的国家抗癌植物药,获得了中国、美国和欧盟的多项发明专利。目前,榄香烯脂质体注射液(批准文号: H10960114)和口服乳剂(批准文号: H10960114)已获得中国食品药品监督管理局(China Food and Drug Administration, CFDA)批准用于治疗多种癌症。循证医学证据表明,榄香烯脂质体对肺癌、肝癌、胃癌、食管癌、前列腺癌、中枢系统肿瘤和癌性腹水等安全有效,与放化疗联合具有增效减毒作用,尤其在延长患者生存期、抗肿瘤耐药、抗复发转移和改善生活质量方面独具优势。

榄香烯与化疗、内分泌治疗和分子靶向药物联用不仅具有协同增敏作用,而且可以发挥逆转耐药的独特功效。在肺癌中,榄香烯可通过抑制P-糖蛋白的表达逆转顺铂和厄洛替尼的耐药^[51,52];与吉非替尼联用可显著增强吉非替尼的疗效^[53]。在乳腺癌中,榄香烯通过重塑雌激素受体 α (ER α)的表达逆转乳腺癌细胞对他莫昔芬的耐药^[54];同时可通过外泌体降低耐药传递逆转乳腺癌的多药耐药^[55]。在大肠癌中,榄香烯可以通过诱导铁死亡和抑制上皮-间质转化(epithelial-mesenchymal transitions, EMT)增强KRAS突变型大肠癌对西妥昔单抗的敏感性,为KRAS突变型大肠癌患者的治疗提供一种新的策略^[56]。在神经系统肿瘤中,榄香烯通过抑制EGFR信号通路可增强吉非替尼对神经胶质瘤的敏感性^[57]。基于对中西医结合“分子配伍”理论的实践和肿瘤耐药的思考,结合榄香烯注射液逆转耐药的作用,谢恬教授带领团队通过以紫杉醇与榄香烯的质量比为1:20~1:2000进行配伍,研发了一种紫杉醇和榄香烯分子配伍的组合物。该组合物已用于治疗乳腺癌、肺腺癌、结肠癌、胃癌、前列腺癌在内的多种肿瘤,尤其对治疗紫杉烷类耐药乳腺癌、紫杉烷类耐药肺腺癌和紫杉烷类耐药结肠癌具有显著的抗紫杉醇耐药的作用^[58],开辟了中西医结合防治肿瘤耐药的新道路。

3.2 参芪扶正注射液

参芪扶正注射液(Shenqi Fuzheng Injection)是黄芪和党参按1:1比例提取制成的注射制剂。1999年参芪扶正注射液被CFDA正式批准用于抗肿瘤的辅助治疗^[59]。

研究显示,参芪扶正注射液与抗肿瘤药物联用可以起到增效减毒和改善患者生活质量的作用。在肺癌中,参芪扶正注射液可通过诱导细胞周期阻滞和促进细胞凋亡逆转肺癌细胞对耐顺铂的耐药^[60];同时对吉非替尼具有协同增敏作用,可逆转非小细胞肺癌对吉非替尼的耐药^[61]。在大肠癌中,参芪扶正注射液可显著改善大肠癌患者对化疗的敏感性,同时可增强患者的免疫力^[62]。上述研究表明,参芪扶正注射液初步显示了其逆转肿瘤耐药的潜力,但具体机制尚不清楚,未来有待进一步挖掘。

3.3 蟾毒灵

蟾毒灵(bufalin)为我国传统中药蟾酥的主要抗肿瘤活性成分,具有解毒、镇痛、开窍、强心以及抗肿瘤等功效。近几年的研究显示蟾毒灵具有逆转耐药作用。在肺癌中,蟾毒灵可通过抑制Met/PI3k/Akt信号通路和诱导细胞凋亡逆转肺癌细胞对吉非替尼的耐药,亦可通过抑制MCL-1的表达逆转肺癌细胞对奥西替尼的耐药^[63,64]。在肝癌中,蟾毒灵可通过抑制Akt信号通路逆转肝细胞性肝癌对索拉非尼的耐药,同时具有逆转多药耐药潜能^[65,66]。在大肠癌中,蟾毒灵与5-FU合用具有协同增敏的作用,且能够逆转大肠癌细胞对阿霉素和奥沙利铂的耐药^[67,68]。因此,蟾毒灵具有逆转耐药的潜在临床应用价值,值得进一步研究。然而,由于蟾毒灵的毒性作用,特别是心肌毒性的存在,使得蟾毒灵作为治疗药物应用于临床尚不可行。

3.4 厚朴酚与和厚朴酚

厚朴酚(magnolol)与和厚朴酚(honokiol)是我国传统中药厚朴的两个主要活性成分,具有抗癌、抗炎、抗菌、抗氧化、抗血栓、保肝等多种药理作用^[69]。与榄香烯相类似,厚朴酚与和厚朴酚是多靶点的天然化合物,可抑制癌细胞的增殖、侵袭和转移,同时具有逆转耐药作用^[70]。厚朴酚与和厚朴酚均可抑制P-糖蛋白的表达,逆转肿瘤多药耐药^[71]。和厚朴酚可通过促进Mcl-1的降解逆转肺癌细胞对奥希替尼的耐药^[72]。在头颈部鳞状细胞癌中,和厚朴酚具有抑制MAPK和Akt通路活化、逆转西妥昔单抗耐药的作用^[73]。和厚朴酚通过诱导caspase依赖性和非依赖性细胞凋亡可逆转多发性骨髓瘤对硼替佐米等的耐药^[74]。此外,厚朴酚还通过抑制跨膜蛋白Mucin 1和多药耐药蛋白1(MRP 1)的表达增强乳腺癌细胞对阿霉素的敏感性^[75]。因此,厚朴酚

与厚朴酚可能是两种有希望克服肿瘤耐药的中药活性成分。

3.5 姜黄素

姜黄素(curcumin)是来源于传统中药姜黄的有效成分。1815年,哈佛大学Vogel和Pelletier首次将其分离^[76]。姜黄素不仅在抗感染、抗氧化、抗炎和心脏保护方面具有强大的作用,而且对呼吸系统、消化系统、血液系统、泌尿系统、生殖系统等几乎所有类型的肿瘤具有显著抑制作用^[77]。近期的体内体外研究显示,姜黄素联合5-FU可提高结肠癌细胞对5-FU的敏感性^[78],说明姜黄素与5-FU合用具有协同增敏的作用。而且,姜黄素可通过诱导细胞凋亡增强前列腺癌细胞对多西他赛的敏感性^[79];通过下调COX-2和NF- κ B信号通路增强胃癌细胞对5-FU的敏感性^[80]。同时,姜黄素可下调EGFR和survivin的表达,逆转肺癌细胞对厄洛替尼的耐药^[81]。此外,姜黄素可通过抑制P-gp1和MRP1的表达逆转宫颈癌细胞对顺铂的耐药^[82]。因此,姜黄素是一种潜在的逆转肿瘤耐药的天然成分。

3.6 白藜芦醇

白藜芦醇(resveratrol)主要来源于虎杖、桑椹、花生和葡萄等植物,是一种多酚化合物。大量的体内和体外实验研究表明,白藜芦醇对肺癌、胃癌、前列腺癌、结肠癌、肝癌、乳腺癌等多种肿瘤具有抗癌作用^[83]。在结肠癌中,白藜芦醇可通过抑制P-gp1和MRP1的表达逆转结肠癌细胞的多药耐药^[84]。为进一步评估白藜芦醇的MDR逆转作用,Meng等人^[85]将白藜芦醇和紫杉醇包封制成脂质体复合制剂,通过体内外研究发现,复合脂质体可以有效逆转乳腺癌细胞对化疗药物的耐药。此外,尿激酶型纤溶酶原激活物受体(uPAR)是口腔鳞癌对西妥昔单抗耐药的重要原因。白藜芦醇可显著抑制uPAR的表达,克服西妥昔单抗的耐药^[86]。白藜芦醇还可通过PI3K/Akt通路抑制survivin的表达增加肾癌细胞对紫杉醇的敏感性^[87]。因此,白藜芦醇具有较好的逆转肿瘤耐药潜能,但鉴于尚无相关的临床研究,白藜芦醇抗肿瘤耐药作用还有待进一步证实。

3.7 槲皮素

槲皮素(quercetin)是一种具有多种生理活性和药理活性的天然小分子黄酮类化合物,广泛存在于洋葱、苹果、浆果及茶等植物中,对于多种癌症具有化

学预防及治疗作用。近年来的研究表明,它也是一种有效的多药耐药逆转剂。CYR61(cysteine-rich angiogenic inducer 61)是一个多药耐药相关蛋白。槲皮素能够抑制CYR61的表达,逆转胃癌细胞对多种化疗药物的耐药^[88]。在肝癌中,槲皮素可通过抑制FZD7/ β -catenin信号通路逆转肝癌细胞对5-FU的耐药^[89]。在乳腺癌中,一方面槲皮素可通过下调P-gp蛋白的表达逆转乳腺癌的多药耐药,另一方面其可上调雌激素受体的表达,克服乳腺癌对他莫昔芬的耐药^[90,91]。在胰腺癌中,槲皮素通过抑制P-gp蛋白的表达逆转了胰腺癌细胞对柔红霉素的耐药,同时通过调控RAGE/PI3K/AKT/mTOR信号轴增强了胰腺癌细胞对化疗的敏感性^[92,93]。此外,槲皮素还可下调deltaNp73的表达,逆转黑色素瘤对替莫唑胺的耐药^[94]。因此,槲皮素在逆转肿瘤MDR方面具有极好的临床应用前景。

3.8 其他中药复方和组分

除了上述中药复方和中药组分,一些来源于中药的其他药物也被证实具有逆转肿瘤耐药的作用。

PHY906是一种来源于中药黄芩汤(HQT)的植物药。此复方出自张仲景的《伤寒论》,由黄芩、甘草、芍药和大枣组成。近年来的研究发现,PHY906可以增强伊立替康(CPT-11)、5-FU、依托泊苷、紫杉醇、索拉非尼等多种药物的疗效并减轻其毒副反应^[95-97]。

丹酚酸(salvianolic acid)为传统中药丹参的水溶性活性成分。现代药理研究证实,丹酚酸A和丹酚酸B均具有逆转肿瘤耐药功效。在肺癌中,丹酚酸A可通过靶向c-met和Akt/mTOR信号通路逆转顺铂的耐药^[98]。在乳腺癌中,丹酚酸A能够下调transgelin 2的表达,逆转乳腺癌对紫杉醇的耐药^[99,100]。在结肠癌中,丹酚酸B能够抑制肿瘤干细胞的活性,逆转结肠癌的多药耐药^[101]。

藤黄酸(gambogic acid)是中药藤黄的主要活性成分。现代药理研究证实,藤黄酸具有显著抗肿瘤活性和逆转化疗耐药潜能。藤黄酸可通过抑制抗凋亡蛋白survivin和bcl-2的表达逆转胃癌细胞对多西他赛的耐药^[102]。在结直肠癌中,藤黄酸可通过激活JNK信号通路逆转结直肠癌细胞对5-FU的耐药^[103]。在乳腺癌中,藤黄酸可激活SHH(sonic hedgehog)信号通路,逆转三阴性乳腺癌对紫杉醇的耐药^[104]。

三氧化二砷(arsenic trioxide)是从中药砒霜中提取的主要活性成分,对急性早幼粒细胞白血病具有特效,而且亦具有增强抗肿瘤药物疗效和逆转肿瘤耐药的功

图3 (网络版彩色)“后羿射日”诠释中西医结合抗肿瘤耐药理念。诸多机制(太阳)促使肿瘤发生耐药(透明屏障),而中医药(草本弓箭)通过发挥高效、低毒、多靶点(数箭齐发)的独特作用,逆转了肿瘤耐药

Figure 3 (Color online) The ancient Chinese myth “Houyi Shoots the Suns” illustrates the drug-resistance therapy based on the combination of Traditional Chinese Medicine and Western medicine. Multiple mechanisms (sun) promote tumor resistance (a transparent barrier). Researches indicate that TCMs (grassy bow and arrow) can reverse drug resistance by exerting a unique function of high efficiency, low toxicity and multiple targets

效。在肝细胞性肝癌中,三氧化二砷可抑制14-3-3 η 在转录水平的表达,逆转肝癌细胞对化疗药物的多药耐药^[105]。在胰腺癌中,三氧化二砷可抑制Skp2的表达,增强胰腺癌细胞对吉西他滨的敏感性^[106]。低剂量三氧化二砷还可通过下调P-gp蛋白的表达抑制神经母细胞瘤的多药耐药^[107]。

4 总结与展望

耐药是肿瘤临床治疗的重大难题,增强治疗敏感性或克服耐药性是肿瘤领域亟须攻克的难题。现代医学在逆转肿瘤耐药方面取得了长足的进展,一些新的联合用药方案或新的抗肿瘤药物亦呈现出逆转耐药的潜能,但这些药物往往作用靶点单一、毒副反应较大且治疗耐药过程中容易产生继发耐药甚至多药耐药,导致肿瘤治疗的难度进一步增大。中药具有多组分、多靶点、多阶段性的作用特点,因而在逆转肿瘤耐药开发方面显示出巨大的优势(图3)。此外,长期的临床

实践也证实,多数中药与抗肿瘤药物合用具有毒副作用小、增效减毒作用显著,可从整体上提高肿瘤患者免疫力的优势。因此,我们相信中西医结合的策略会为克服肿瘤耐药和增强肿瘤治疗的敏感性带来新的希望。

尽管中医药的应用展现出光明的前景,但其自身也有一定的局限性。一方面,中医药由于成分复杂、靶点众多,加之复方辨证给药,很难理清其具体机制,未来有待进一步阐明。另一方面,中医药逆转肿瘤耐药的研究,目前尚缺乏强有力的随机对照试验,无论是复方还是单体都未成为临床一线用药。因此迫切需要对中医药复方或组分进行循证医学研究,评估其疗效和安全性,以加快向临床的转化。此外,当前的研究多数停留在探究单一成分和单一机制,未能体现中医辨证论治理论和君臣佐使配伍原则。随着科技的发展,尤其是中西医结合“分子配伍理论”理论的深入研究和实践,我们相信中西医结合在防治肿瘤耐药方面定会大放异彩,并能为将来的临床干预和新药研发奠定理论基础。

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Summary for “中西医结合防治肿瘤耐药的研究进展”

Combination of Chinese and western medicine to prevent and reverse resistance of cancer cells to anticancer drugs

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Cancer is a common and complex disease with various genetic and environmental risks. Chemotherapy and targeted therapy are one of the main therapeutic approaches for the treatment of advanced cancer patients. However, prolonged patient treatment often provokes drug resistance phenomena that render the therapeutic treatment highly ineffective. Therefore, the development of novel and effective treatment strategies to overcome drug resistance is urgent for cancer therapy. A variety of factors contribute to drug resistance, including tumor cell heterogeneity, drug efflux, drug inactivation, changes in tumor microenvironment, DNA damage repair disorders, epigenetic alterations in cancer cells and so on. However, how to circumvent drug resistance to improve anticancer efficacy remains to be determined. Currently, the most important approach for overcoming drug resistance is drug combination therapeutic regimen, however, it is easy to induce new drug resistance or even multi-drug resistance (MDR) which is defined as the resistance of cancer cells to multiple anticancer drugs with different structures and mechanisms of action. Whereas, the “multi-components and multi-targets” manifestations of Traditional Chinese Medicine (TCM) make them an attractive direction for developing new adjuvant therapeutics to reverse drug resistance. In recent years, several compounds derived from TCM have been reported to augment sensitivity or overcome resistance of anticancer therapeutic drugs, including elemene, bufalin, curcumin, magnolol, honokiol, resveratrol, quercetin, and so on. Thus, the combination of TCM and conventional anticancer drugs will hopefully provide a novel strategy for enhancing the effects of anticancer strategies and overcoming their resistance in the treatment of cancer patients. In the current paper, we review the molecular mechanisms of drug resistance and the therapeutic strategies. We also discuss the current basic research and clinical studies in overcoming drug resistance from Traditional Chinese Medicine. Finally, we focus the integrated traditional Chinese and Western medicine as a promising new therapeutic approach to enhance the effects of anticancer strategies or overcome their resistance in the treatment of cancer patients.

Traditional Chinese Medicine, western medicine, integrative traditional Chinese and western medicine, chemotherapeutic resistance, drug resistance

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