TRAIL耐药的研究进展

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摘要 肿瘤坏死因子相关凋亡诱导配体(tumor necrosis factor-related apoptosis-inducing ligand, TRAIL)能选择性地诱导肿瘤细胞凋亡, 因此作为抗肿瘤药物备受瞩目, 现已进入II期临床试验, 尽管有报道称部分肿瘤细胞对TRAIL耐药, 导致治疗效果不如预期, 但TRAIL用于肿瘤治疗的前景依旧被人们看好。通过对TRAIL耐药机理的研究将有助于寻找逆转肿瘤细胞耐药的靶点, 并通过联合用药来调节相关的信号分子以获得更好的抗肿瘤效应。该文将介绍TRAIL及其介导的细胞凋亡通路并总结近年来TRAIL耐药机理及逆转其耐药方面的研究进展。

关键词 TRAIL; TRAIL耐药; 肿瘤; 细胞凋亡

The Onward March of TRAIL Resistance

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Abstract The tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is a promising candidate for cancer therapy. Its property of being able to target cancer cells specifically while leaving normal cells unharmed has drawn the attention of researchers, and has entered phase II of clinical trials. Even though reports have indicated that resistance towards TRAIL has developed in a number of cancer cells, the prospect of using TRAIL to combat cancer remain positive. Understanding the mechanisms of TRAIL resistance will greatly aid in the search of targets to overcome TRAIL resistance, and through regulating related signaling molecules with the help of concomitant drugs, better anticancer results may be achieved. This review will cover TRAIL, its apoptotic pathway, and summarize the mechanisms of TRAIL resistance along with methods to reduce this resistance found in recent years.

Keywords TRAIL; TRAIL resistance; tumor; apoptosis

细胞凋亡是细胞遵循自身的程序结束其生命的过程, 在维持组织稳态和去除不需要的细胞中起重要作用。异常的细胞增殖和凋亡平衡将导致肿瘤发生, 因此, 化疗药物通过调节细胞凋亡可以避免肿瘤发生。但化疗药物常因为肿瘤耐药而导致治疗失效并引起肿瘤复发, 所以开发安全有效的抗肿瘤新药及探寻逆转耐药的方法是肿瘤治疗研究的新课题。肿瘤坏死因子相关凋亡诱导配体(tumor necrosis factor-related apoptosis-inducing ligand, TRAIL)广泛地表达于多种组织, 但因为正常细胞和肿瘤细胞对TRAIL的敏感性有差异, 使得TRAIL能选择性地诱导肿瘤细胞凋亡而对正常细胞没有杀伤作用, 因此具备了成为抗肿瘤药物的基本条件。虽然TRAIL仍面对肿瘤耐药的问题, 但是通过进一步研究其耐药机理及选择合适的药物配伍, 可以极大地提高TRAIL的临床应用价值。

1 TRAIL的发现与其结构特点

TRAIL是肿瘤坏死因子(tumor necrosis factor, TNF)超家族成员之一。1975年, TNF成为该家族首

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个被认为可用于肿瘤治疗的药物, 随后的研究却发现, TNF的主要功能是产生促炎因子, 全身应用TNF将引起严重的毒性[1-3]。TNF超家族的另一个成员CD95L(CD95 ligand, 又称FasL)也被证实能诱导各种肿瘤细胞凋亡, 但全身应用重组CD95L会引起暴发性和致死性肝毒性[4]。因此, TNF和CD95L用于临床治疗肿瘤面临瓶颈。由于TRAIL与TNF和CD95L序列具有同源性, 研究人员通过搜索DNA数据库发现了TRAIL[5], 随后发现, TRAIL也能诱导肿瘤凋亡, 并且不引起显著的不良反应, 因此成了肿瘤治疗的新希望。

*TRAIL*基因位于3号染色体, 长约20 Kb, 在多种人类组织中可检测到*TRAIL*的转录产物, 尤其是脾、肺和前列腺。人TRAIL包含281个氨基酸, 以II型跨膜蛋白的形式存在于细胞膜, 当TRAIL的细胞外段断裂后, TRAIL可以可溶性分子的形式从细胞膜上释放[6]。TRAIL单体的核心架构是由两个反平行式β折叠形成的一个β夹层结构, β折叠之间的其中一个环比其他的TNF家族成员额外插入了12~16个氨基酸, 使得这个突出的环能够进入相应的受体结合部位, 并在受体的特异性识别中起重要作用[7]。单体相互作用形成钟形的同三聚体, 较宽的一端称"底", 另一端称"顶", TRAIL以此形式发挥功能。在三聚体顶端的内面掩埋着锌结合位点, 锌离子参与维持TRAIL三聚体结构的稳定性和生物活性[8]。

2 TRAIL受体的种类

目前已知, TRAIL对应五种受体, 其中有两种可以诱导细胞凋亡, 它们是死亡受体4(death receptor 4, DR4)和死亡受体5(death receptor 5, DR5), 两者属于I型跨膜蛋白, 胞内段都含有死亡结构域(death domain, DD), 能触发胞内的凋亡信号。它们拥有58%的序列同源性, 尽管在它们与TRAIL结合时, 特定的结合位点有所不同, 但这并不影响两者整体结合构形上的相似性。此外, 虽然发现两者在与TRAIL结合时的热力学特性有所区别, 但这仍未能解释为何人类需要这两种不同的受体[7,9]。

另外, 三种受体是诱骗受体1(decoy receptor 1, DcR1)、诱骗受体2(decoy receptor 2, DcR2)和骨保护素。由于三者都缺乏功能的DD, 因此不能诱导细胞凋亡。DcR1是位于膜上的糖磷脂锚定蛋白, 缺乏胞内段; 而DcR2仅有截短且无功能的胞内死亡结构域[6]。当DcR1和DcR2过表达时会起到一定阻碍TRAIL诱导细胞凋亡的作用[10-11]。此外, DcR2还可能与DR5形成没有活性的异源复合体[10,12]或触发抗凋亡信号, 如核因子-κB(nuclear factor-κB, NF-κB)和Akt的活化[13-14], 从而减弱TRAIL诱导的细胞凋亡。而骨保护素的主要生理作用是通过抑制NF-κB受体活化因子配体(receptor activator for nuclear factor-κB ligand, RANKL)来调节破骨细胞的活性[15], 但也有报道称它能与TRAIL相互作用[16], 因此将其归为TRAIL受体的一员。

3 TRAIL诱导的凋亡通路

TRAIL以三聚体的形式与其受体DR4或DR5结合。DR4或DR5通过胞内区的DD募集了同样拥有DD的Fas相关死亡结构域蛋白(Fas-associated protein with death domain, FADD)。除了DD, FADD还有另一个DD样结构域, 称为死亡效应结构域(death effector domain, DED), 其可通过DED募集同样拥有DED的胱冬肽酶原-8或胱冬肽酶原-10, 由此形成死亡诱导信号复合体(death inducing signaling complex, DISC)。目前研究认为, 胱冬肽酶-10在凋亡诱导中是非必需的, 而胱冬肽酶-8是DISC的起始胱冬肽酶, 并且胱冬肽酶-10不能替代胱冬肽酶-8的作用[17]。无活性的胱冬肽酶原-8在DISC通过自身催化和形成同二聚体而被活化[18], 活化的胱冬肽酶-8同二聚体从DISC释放后裂解胱冬肽酶-3, 最终导致细胞凋亡, 此信号通路称为外源性细胞凋亡通路。此外, 胱冬肽酶-8还能裂解另一个关键底物Bid, 使其成为截短型Bid(truncated Bid, tBid)并从细胞质转移到线粒体, 活化促凋亡家族成员Bax(Bcl-2-associated X protein)和Bak(Bcl-2-antagonist/killer), 从而诱导线粒体外膜透化(mitochondrial outer membrane permeabilization, MOMP), 导致细胞色素c释放。细胞色素c、凋亡蛋白酶活化因子-1(apoptotic protease activating factor-1, Apaf-1)和胱冬肽酶原-9组成凋亡复合体。胱冬肽酶-9在凋亡复合体内活化后触发效应胱冬肽酶的裂解, 最终引起细胞凋亡, 此信号通路称为内源性细胞凋亡通路(图1)。

此外, 在TRAIL诱导的细胞凋亡通路中还有一些调节分子。譬如, 调节胱冬肽酶-8活性的细胞型FLICE抑制蛋白(cellular FLICE-like inhibitory protein, cFLIP), 有三种剪接变异体, 它们是$cFLIP_L$(cFLIP-

long)、cFLIP$_S$(cFLIP-short)和cFLIP$_R$(cFLIP-Raji)。这三种cFLIP变异体的N-端都有两个DEDs, 与胱冬肽酶-8和胱冬肽酶-10的两个DEDs高度同源。cFLIP$_S$和cFLIP$_R$的C-端结构域较短, 可以和胱冬肽酶-8或胱冬肽酶-10竞争结合FADD, 从而抑制DISC的促凋亡活性[19-20]。而cFLIP$_L$有较长的C-端结构域, 与胱冬肽酶-8高度相似, 但缺乏催化活性。cFLIP$_L$调节凋亡的作用比较复杂, cFLIP$_L$在表达水平高的时候有抗凋亡作用, 在表达水平低的时候, cFLIP$_L$却促进胱冬肽酶原-8募集到DISC, 从而有助于凋亡[21-22]。此外, 线粒体外模除了有促凋亡分子Bax和Bak外, 还有一组与之相抗衡的抗凋亡分子Bcl-2(B-cell lymphoma-2)、Bcl-xL(B-cell lymphoma-extra large)和Mcl-1(myeloid cell leukemia-1), 这两组Bcl-2家族成员之间的平衡将调节MOMP(major outer membrane protein), 从而影响内源性细胞凋亡通路。TRAIL诱导的细胞凋亡通路中还有一个关键的调节分子, 那就是X连锁凋亡抑制蛋白(X-linked inhibitor of apoptosis protein, XIAP), 它属于凋亡抑制蛋白(inhibitor of apoptosis proteins, IAPs)家族中八个人类类似物中最有效的一种[23], 它能直接结合胱冬肽酶-3、胱冬肽酶-7和胱冬肽酶-9并抑制它们的活化, 进而阻止细胞凋亡。然而在发生MOMP后所释放的第二线粒体衍生半胱天冬酶激活物(second mitochondria-derived activator of caspases, Smac)能直接结合并抑制XIAP, 随之释放胱冬肽酶, 最终引起细胞凋亡。

不同细胞根据凋亡通路的不同可分为两型。I型细胞的DISC活化胱冬肽酶-3后足以导致细胞凋亡; 而II型细胞的DISC活化胱冬肽酶-3后并不足以诱导细胞凋亡, 因此还需要内源性细胞凋亡通路的参与才能诱导细胞凋亡[24]。这可能是II型细胞表达高XIAP/胱冬肽酶-3比值导致外源性细胞凋亡通路活化的胱冬肽酶-3被XIAP阻滞, 因此需要线粒体释放的Smac来降低XIAP的阻滞作用以引起细胞凋亡。因此可以认为, XIAP是区别I型和II型细胞的关键因子。

4 TRAIL耐药及逆转其耐药的机理

目前对TRAIL耐药机理的解释众说纷纭, 这可能与细胞信号通路的复杂性和肿瘤类型的多样性有关。但从理论上来说, 肿瘤细胞凋亡通路中任一分子的改变或失衡, 譬如TRAIL及其受体活性不足和cFLIP、Mcl-1、IAPs过表达等, 都可能是造成肿瘤细胞对TRAIL耐药的原因。因此, 调节细胞凋亡通路各分子的表达或活性就成为了逆转TRAIL耐药的一种有效手段。此外, 调节细胞凋亡通路之外的其他分子, 如NF-κB、哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin, mTOR)、活化的信号转导转录活化因子3(signal transducer and activator of transcription 3, STAT3)、c-Jun氨基末端激酶(c-Jun

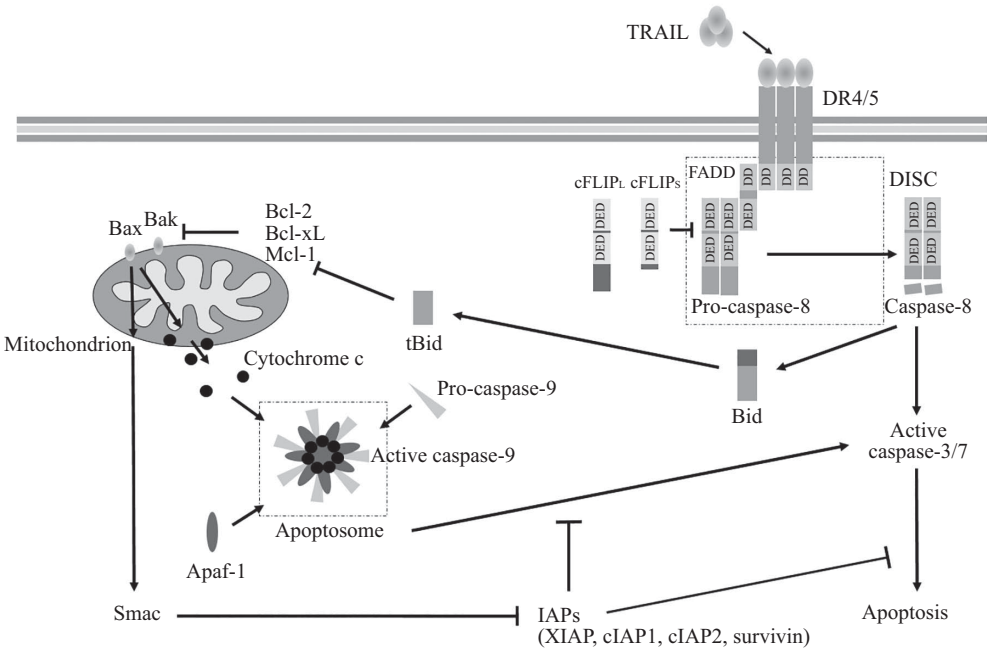

图1 TRAIL诱导的凋亡通路示意图

Fig.1 TRAIL induced apoptosis pathway

N-terminal kinases, JNKs)等, 也有助于改善TRAIL的耐药。

4.1 调节TRAIL逆转耐药

部分肿瘤患者对TRAIL治疗不起作用可能是TRAIL药理学特性的缺陷, 导致TRAIL短时间大量释放入组织并迅速被机体清除, 若将TRAIL以聚乳酸–羟基乙酸共聚物为载体制备成缓释微球制剂, 便可以减缓TRAIL在体内的释放, 同时还可缓解其潜在的毒性, 进一步提升TRAIL的安全性[25]。

此外, TRAIL作用于机体时靶向性不足也可能导致肿瘤治疗无效, 因此可利用条件复制型腺病毒作为肿瘤治疗载体, 让它选择性地在肿瘤细胞复制, 使肿瘤细胞自身表达TRAIL从而选择性杀伤肿瘤细胞[26]; 利用间充质干细胞对脑肿瘤的趋向性来运载*TRAIL*基因并表达及分泌TRAIL以靶向地诱导神经胶质瘤细胞凋亡[27]。此外, 构建重组CD19L-sTRAIL, 可以使sTRAIL(可溶性TRAIL)在CD19L的协助下靶向结合到$CD19^+$人白血病细胞上并诱导凋亡[28]。为了避免进入循环系统的肿瘤细胞形成转移灶, 可以将人重组E-选凝素(E-selectin)和TRAIL同时结合到纳米级的脂质体上, 这样TRAIL就能在E选凝素的帮助下更容易地与循环肿瘤细胞相接触并诱导其凋亡; 同时, TRAIL也在E选凝素的帮助下与白细胞结合, 并利用白细胞在循环系统中的靶向能力清除循环肿瘤细胞[29]。

然而, TRAIL的效能不足也是导致TRAIL对肿瘤患者不产生显著效应的原因。通过制备多价DR5激动剂来提高DR5的结合价, 这样便可以改善部分TRAIL耐药肿瘤细胞的凋亡效应[30]。此外, 制备高活性的重组TRAIL, 也是提高TRAIL诱导凋亡效能的方法。TRAIL和异亮氨酸拉链(isoleucine zipper, iz)标记融合后形成高活性的izTRAIL, 通过iz序列之间的疏水作用来稳定TRAIL三聚体, 从而提高izTRAIL的激动效应[31-32], 并且izTRAIL联合Smac类似物或蛋白酶抑制剂能协同诱导卵巢癌细胞凋亡[33]。

4.2 调节TRAIL受体逆转耐药

DR4或DR5表达量不足也是导致肿瘤细胞对TRAIL配体不敏感的因素之一。Tanaka等[34]发现, 二甲双胍与TRAIL的协同作用能诱导原本对TRAIL不敏感的胰腺癌细胞凋亡, 并证实其中部分机理与DR5表达提高有关。另外, 阿霉素也能上调肿瘤细胞DR5的表达, 从而增强高表达TRAIL的自然杀伤细胞和T细胞对肿瘤细胞的杀伤作用[35]。同样, 5-氟尿嘧啶协同TRAIL所诱导的含*KRAS*(Kirsten rat sarcoma viral oncogene homolog)突变基因非小细胞癌细胞的凋亡作用也是通过上调DR5而实现[36]。而α-hispanolol不仅上调DR5还同时上调了DR4, 从而提高TRAIL诱导肝癌细胞株的凋亡效应[37]。除了利用化学药物, 使用重组新城疫病毒作为载体特异性感染肿瘤细胞, 通过外源基因上调肿瘤细胞表面的DR5也能增强TRAIL所诱导的凋亡效应[38]。

但令人意外的是, 在某些研究中, TRAIL受体的表达反而有利于肿瘤细胞的生长甚至转移, 例如细胞核内的DR5能通过抑制miRNA let-7在胰腺癌细胞中的成熟来促进肿瘤细胞增殖。与之相反, 敲除*DR5*基因能抑制其增殖[39]。此外, 下调乳腺癌细胞的DR5能降低骨转移相关蛋白, 如HMGA2(high mobility group AT-hook 2)、p-Src(phosphorylated Src)和CXCR4(CXC chemokine receptor type 4)的水平以及提高钙黏蛋白E的表达, 从而抑制乳腺癌细胞的骨转移[40]。就此有人提出了TRAIL信号通路的双面性, 这可能与TRAIL受体下游信号通路的多样性有关[41-42], 这不仅提醒我们将TRAIL应用于临床治疗时需考虑其不良后果, 而且还提示了可能是部分肿瘤细胞对TRAIL耐药的原因, 将有待后续研究有效逆转的方法。

4.3 调节凋亡通路信号分子逆转耐药

细胞凋亡通路中的抗凋亡或促凋亡分子的表达或活性失衡都可以是引起TRAIL耐药的原因。HER2(human epidermal growth factor receptor 2)阳性的乳腺癌细胞对TRAIL耐药的原因被证实是因为$cFLIP_L$高表达, 并且降低$cFLIP_L$的表达水平能致敏相关肿瘤细胞[43]。此外, 三尖杉酯碱、Chal-24、R-roscovitine、雷公藤甲素、双香豆素和DZNep(3-Deazaneplanocin A)分别与TRAIL联合作用时能分别降低白血病细胞、肺腺癌细胞、恶性胶质瘤干细胞、胰腺癌细胞、肾细胞癌细胞和淋巴瘤细胞的抗凋亡蛋白cFLIP和(或)Mcl-1的水平, 随之引起胱冬肽酶-8及胱冬肽酶-3等下游促凋亡分子的活化, 最终提高了TRAIL对这些肿瘤细胞的促凋亡作用[44-49]。内源性细胞凋亡通路中, Bcl-2的高表达在脑癌干细胞中被证实与TRAIL耐药有关[50]。在II型细胞中, 由于依赖内源性细胞凋亡通路, Bax的缺失常常是造成TRAIL耐药的原因, 即便是Bak在细胞中仍有表达,

但由于其受控于Mcl-1, 所以无法引起细胞凋亡, 只有在敲除*Mcl-1*基因后, TRAIL耐药才得以解除[51], 因此降低Bcl-2和Mcl-1将会是逆转TRAIL耐药的靶点。但如果Bax和Bak同时缺失, 那么降低Mcl-1也将无法引起II型细胞凋亡, 这时抑制XIAP, 使外源性细胞凋亡通路足以诱导细胞凋亡成了逆转TRAIL耐药的一种方法[52]。在利用IAP抑制剂抑制IAP的实验中, 肿瘤细胞表现出对TRAIL的敏感性增强, 这也证实了这个方法的可行性[53]。用于治疗黑色素瘤的pan-RAF抑制剂(L-779450)联合TRAIL能上调促凋亡的Bim(Bcl-2 interacting mediator of cell death), 从而活化内源性细胞凋亡通路, 提高肿瘤细胞对TRAIL的敏感性[54]。

4.4 其他信号分子与TRAIL耐药

4.4.1 NF-κB与TRAIL耐药 NF-κB是一种转录因子, 普遍认为, NF-κB具有抗凋亡作用, 这可能与它能够诱导抗凋亡基因表达有关[55]。研究表明, DR4、DR5和DcR2都有活化NF-κB的能力, 但是相较于TNF和CD95L, TRAIL对NF-κB的活化作用较弱, TRAIL所活化的NF-κB在单独情况下并不足以抑制TRAIL所诱导的细胞凋亡[56-57], 这也是TRAIL比TNF和CD95更适合用于治疗肿瘤的原因之一。但是在细胞内多种信号通路的共同作用下, TRAIL活化的NF-κB仍有可能拮抗TRAIL所同时诱导的细胞凋亡通路, 由此便会造成肿瘤对TRAIL耐药, 因此利用蒽贝素或三氧化二砷来减弱NF-κB的表达, 能使TRAIL更有效地诱导细胞凋亡[58-59]。高良姜素通过抑制NF-κB能在转录水平下调Bcl-2蛋白, 从而提高肾癌细胞对TRAIL的敏感性[60]。此外, NF-κB所活化的Akt能抑制细胞凋亡, 利用反-2,4-双对羟苯基-2-丁烯醛[(E)-2,4-bis(p-hydroxyphenyl)-2-butenal]抑制NF-κB能避免Akt活化, 从而促进TRAIL诱导卵巢癌细胞凋亡[61]。TRAIL受体的DD除了能结合FADD外, 同样拥有DD的TNF受体相关死亡结构域(TNF-receptor-associated death domain, TRADD)也能与TRAIL受体的DD结合并导致NF-κB的活化, 因此以TRADD为靶点来抑制NF-κB的活化, 可以提高TRAIL的凋亡作用[62]。此外, 受体相互作用蛋白1(receptor interacting protein 1, RIP1)丝/苏氨酸蛋白激酶也具有DD, 并且同样能活化NF-κB。miR-21导致胱冬肽酶-8下调, 避免了RIP1被胱冬肽酶-8裂解, 也就避免了RIP1的消耗, 从而诱导NF-κB活化, 而NF-κB的活化又将在转录水平上活化miR-21、miR-30和miR-100, 这些miRNAs将干扰TRAIL的细胞凋亡通路, 由此便形成了正反馈的恶性循环, 从而引起TRAIL耐药, 以上所述的NF-κB和miRNAs都可以作为靶点来逆转TRAIL耐药[63]。

4.4.2 mTOR与TRAIL耐药 mTOR是一种丝/苏氨酸蛋白激酶, 属于磷脂酰肌醇3激酶(phosphatidylinositol 3-kinase, PI3K)相关蛋白激酶(PI3K-related protein kinase, PIKK)家族成员, 参与细胞生长、增殖、分化、蛋白质翻译和自噬的调节。PI3K/Akt/mTOR存活信号通路异常后可能会改变促凋亡和抗凋亡蛋白之间的平衡, 如Mcl-1、cFLIP等, 从而导致TRAIL耐药[64]。依维莫司是mTOR抑制剂, 它能使原本具有高度活化PI3K/Akt/mTOR信号通路的人类白血病Jurkat T细胞的DR5表达上调, 从而提高肿瘤细胞对TRAIL的敏感性, 但是对原本就缺乏PI3K/Akt/mTOR信号通路的肿瘤细胞没有显著效应[64], 至于依维莫司如何通过PI3K/Akt/mTOR信号通路引起DR5表达上调, 其机理并未阐明。mTOR调节蛋白质翻译的其中一个机理是直接磷酸化关键的翻译调节因子核糖体S6激酶1(ribosome protein subunit 6 kinase 1, S6K1)。吴茱萸碱通过抑制mTOR和S6K1磷酸化来下调抗凋亡蛋白Mcl-1的表达, 从而促进TRAIL诱导膀胱癌细胞凋亡[65]。此外, 在利用二甲双胍处理膀胱癌细胞的研究中, 通过抑制mTOR/S6K1通路, 还可以下调抗凋亡蛋白cFLIP, 从而致敏TRAIL, 诱导凋亡[66]。

4.4.3 STAT3与TRAIL耐药 STAT3会诱导一些与细胞分裂、存活和凋亡相关的基因表达, 并产生抗凋亡蛋白和血管内皮生长因子, 它们参与了细胞的浸润和转移[67], 因此高水平STAT3是肿瘤细胞对化疗药物耐药的原因之一, 并且已证实抑制STAT3可以逆转PI3K/Akt/mTOR信号通路所导致的肿瘤耐药[68-69]。*Akt*启动子有STAT3的结合位点, 因此, STAT3可以在转录水平调节*Akt*基因表达[70], 所以用反-2,4-双对羟苯基-2-丁烯醛[(E)-2,4-bis(p-hydroxyphenyl)-2-butenal]来降低STAT3的活性便可以抑制Akt的抗凋亡信号, 进而提高卵巢癌细胞株对TRAIL的敏感性[61]。此外, 木犀草素逆转肾细胞癌对TRAIL耐药的机理也与STAT3和Akt灭活有关[71]。热激蛋白90作为致癌蛋白的伴侣蛋白在面对应激的肿瘤细胞中常常高表达, 热激蛋白90的抑制剂NVP-AUY922能导致热激蛋白90丧失功能从而导致其客

户蛋白(client proteins)的降解, 其中包括STAT3和Mcl-1, 两者水平的降低是促进TRAIL诱导结直肠癌细胞凋亡的原因[72]。

4.4.4 JNKs与TRAIL耐药 JNKs由三个基因编码, 并且根据转录后不同的剪切形式可分为十种亚型, 有研究说明, JNK级联反应与诱导细胞死亡有关, 并且应激无法诱导缺乏JNKs的小鼠成纤维细胞凋亡; 而兴奋性神经素对敲除*JNK3*的神经细胞无凋亡作用[73]。因此JNKs的抑制也可能是部分肿瘤细胞对TRAIL耐药的因素, 槲皮素在显著提高细胞内活性氧水平后导致内质网应激, 内质网应激会导致肌醇依赖酶1α(inositol-requiring enzyme 1α, IRE1α)及JNK磷酸化, 随之引起CAAT区/增强子结合蛋白同源蛋白(CAAT/enhancer binding protein homologous protein, CHOP)表达。CHOP结合*DR5*启动子并上调DR5表达, 结果证实, 通过活化JNK槲皮素可提高卵巢癌细胞对TRAIL的敏感性[74]。丹参酮IIA也有相似的机理, 丹参酮IIA诱导活性氧导致JNK磷酸化, 随之上调CHOP进而诱导DR5表达, 从而逆转TRAIL耐药[75]。此外, 补骨脂酚和漆树酸也是通过JNK介导上调DR和下调存活蛋白来提高肿瘤细胞对TRAIL的敏感性[76-77]。

但是也有相反的研究结果说明, JNKs通过活化Akt来促进肿瘤细胞存活, 并参与了循环肿瘤细胞的内皮黏附(endothelial attachment)和渗出(extravasation)[78]。Azijli等[79]在应用非小细胞肺癌细胞的研究中表明, TRAIL活化的JNK能提高Mcl-1的表达从而引起抗凋亡效应。此外, TRAIL通过JNK抑制剂能上调DR4和DR5及下调DR1和DcR2, 从而逆转胰导管腺癌的TRAIL耐药, 并且在活体中, JNK抑制剂联合TRAIL能显著减少循环肿瘤细胞[80]。上述JNKs两种截然不同的结局可能与不同细胞中的JNKs有不同作用或是不同的信号背景影响JNK信号通路有关。因此JNKs在TRAIL信号通路中所起的作用仍需要更明确的机理来说明, 以使得JNKs能成为逆转TRAIL耐药的有效靶点。

5 结语

TRAIL的发现使肿瘤治疗多了一种途径, 并且有相关的I期及II期临床试验在进行着, 例如将TRAIL应用于骨髓瘤、非小细胞肺癌、软组织肉瘤等的治疗中[81-82]。但是由于TRAIL制剂的药理学特性仍不完善并且有部分肿瘤细胞对其产生耐药, 从而导致部分临床试验结果不令人满意, 所以TRAIL制剂在人体内的稳定性, 生物利用率和自身的活性等方面仍需改善; 而对肿瘤耐药机理的了解将有助于发现逆转耐药的分子靶点, 以便设计出相应的对策。目前认为, 比较有效的一种方式是联合用药, 即通过联合其他药物来调节TRAIL凋亡通路或其他与细胞存活有关的信号分子来提高该肿瘤细胞对TRAIL的敏感性。但我们也发现, 不同的研究之间对TRAIL耐药机理阐述存在着不小的差异, 这可能与各研究使用的细胞株不同以及不同细胞之间拥有不一样的基因背景有关[83], 因此对TRAIL耐药机理的确切定论仍需要更多的努力。虽然如此, 仍有不少联合用药的基础研究取得了明确的成果, 为今后的临床用药策略提供了理论依据, 一旦临床试验成功, 这将成为肿瘤治疗的重要手段。

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