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小分子石蒜碱抗肿瘤作用的研究进展

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摘 要:在治疗肿瘤中,小分子靶向药物与传统药物相比,因具有毒副作用更小、特异性更高和容易通过血脑屏障等特点,成为近年来抗肿瘤药物的研究热点。小分子石蒜碱是药用植物石蒜鳞茎的一种生物碱,具有抗炎、抗病毒等多种生物学活性,并且对多种肿瘤具有较好的抑制作用。综述了小分子石蒜碱在抗肿瘤方面的作用机制,石蒜碱主要通过诱导肿瘤细胞凋亡,抑制并阻断细胞周期,抑制肿瘤血管生成以及介导细胞自噬来抑制肿瘤的生长。与纳米技术相结合,石蒜碱药物研发将为新型抗癌药物的设计提供新的思路。

关键词:石蒜碱;肿瘤;信号通路

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Research Progress in Antitumor Effects of Small Molecule Lycorine

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Abstract: Small molecule drugs have been attracting attentions with their less side effects, higher specificity in tumour therapy, and more easily getting through blood-brain-barrier compared to the traditional medicines. lycorine is one kind of alkaloids originated and extracted from medicinal plant lycoris radiate bulbs, possesses biological activities of anti-inflammatory, anti-virus and anti-tumor. We summarized the anticancer mechanisms of small molecule lycorine, including inhibiting the growth of tumors by inducing tumor cell apoptosis, blocking cell cycle, prohibiting tumor angiogenesis and suppressing cell autophagy. Combined with nano-technology, the development of lycorine drugs will provide a new insight in the design of anticancer drug.

Keywords: lycorine; tumor; signaling pathway

肿瘤是在许多致癌因素的作用下,引起局部组织增生而形成的新生物,并可以通过血液、淋巴液进行远处转移至全身不同脏器,是目前威胁人类健康最重要的疾病之一。据统计世界上每年都有超过1 400万的人患上肿瘤^[1],并在2015年之后肿瘤在全球死亡病因中列居第二^[2]。饮食、慢性炎症、吸烟、辐射、大气环境污染等都可以促进肿瘤的发生。

小分子化合物一直被广泛应用于各种疾病的

治疗当中,尤其是植物中的成分运用甚为突出。与传统药物相比,小分子靶向药物治疗肿瘤具有副作用更小、特异性更高以及药效更高等优势,目前是肿瘤药物治疗的研究热点。传统肿瘤治疗采用的放化疗结合方法对正常细胞损伤较大,且患者到中后期会出现许多不良反应导致病情进一步加重。分子靶向治疗是通过生化等手段确定肿瘤的信号通路或者分子标记物为靶点来设计药物治疗肿瘤的方法。小分子药物的吸收不是由消化道

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上皮细胞介导的主动转运,而是通过浓度梯度提供动力的自由扩散方式进行吸收,并且因分子量较小的原因则更易通过血脑屏障作用于中枢系统。

石蒜碱属于吡咯苯三甲酸生物碱^[3](化学结构式如图 1 所示),由石蒜鳞茎提取而来,具有良好的抗病毒、抗炎、抗肿瘤活性^[4],作用机制多样。早在 1976 年,Jimenez 和他的同事首次发现了石蒜碱的抗肿瘤活性。科学家们陆续对石蒜碱进行了大量研究^[5]。目前有关石蒜碱对不同类型肿瘤的作用靶点研究已经陆续被报道。大量研究表明,石蒜碱可以通过调节大部分的肿瘤分子靶点和信号通路,产生诱导肿瘤细胞凋亡、调控肿瘤细胞周期、影响肿瘤细胞自噬,以及抑制肿瘤细胞侵袭和转移等多种作用^[6]。随着科学研究的不断深入,越来越多的靶点以及信号通路渐渐被阐明,本文就石蒜碱通过作用于肿瘤细胞的分子靶点以及信号通路等调控机制进行综述。

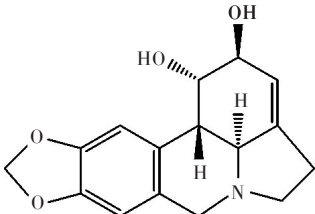


图 1 石蒜碱化学结构式
Fig. 1 Structure of lycorine

1 诱导细胞凋亡

细胞凋亡主要有两种途径:外部途径,主要通过细胞间的死亡配基(Fas 配基)来激活死亡受体,再通过促细胞凋亡信号通路使启动子半胱氨酸蛋白酶 8(Caspase8)和执行因子半胱氨酸蛋白酶 3(Caspase3)、半胱氨酸蛋白酶 7(Cspase7)被激活并启动凋亡程序;内部途径,是通过细胞内信号(例如 DNA 损伤、细胞应激、异常细胞信号等)引起凋亡蛋白 Bax、bcl 家族蛋白的活化从而激活线粒体释放细胞色素 C、启动 Caspase9 的活化或形成凋亡小体从而使细胞凋亡。线粒体介导细胞凋亡通路与促生存调节蛋白 Bcl-2、Bcl-xl、Mcl-1、以及促凋亡调节蛋白 Bax、Bid 家族成员有关,这些蛋白家族成员可以调控线粒体外膜的通透性从而促进细胞色素 C 的释放^[7],线粒体释放的细胞色素 C 促进支架蛋白凋亡蛋白酶激活因子 1(apoptosis protease-activating factor-1, APAF1)上 caspase9 的释放,线粒体同时释放出线粒体介导的 caspases 激活蛋白(second mitochondria-derived activator of caspas-

es, SMAC)阻断 caspase 抑制剂 X 连锁凋亡抑制蛋白(X-linked inhibitor of apoptosis protein, XIAP)激活 caspase-9,从而促进细胞的凋亡^[8-10],其调控机制如图 2 所示。

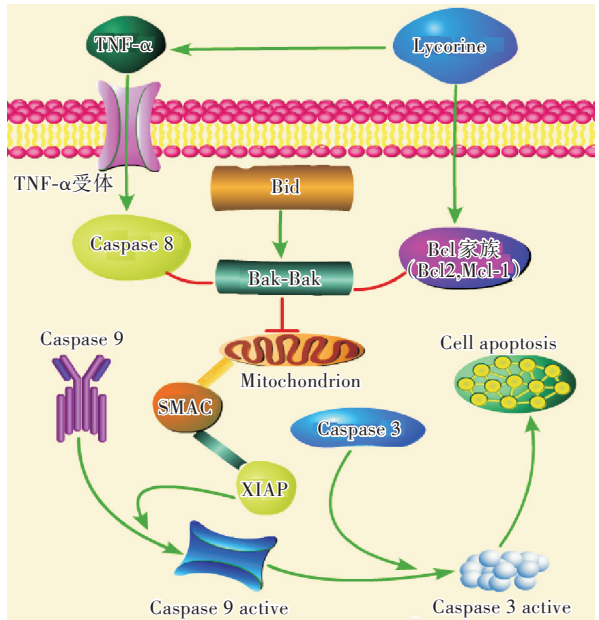


图 2 石蒜碱参与调控的细胞凋亡信号通路
Fig. 2 Pathway of lycorine involved in apoptotic signaling

有文献报道,石蒜碱通过失活 TCRP1/Akt/mTOR 通路从而促进人肝癌细胞的自噬和凋亡^[11]。石蒜碱还可以通过介导并影响 mTOR-S6K 信号通路诱导肺癌 A549 细胞凋亡^[12]。并且,石蒜碱还可以对肾癌、膀胱癌、乳腺癌、前列腺癌等都有促进肿瘤细胞凋亡的作用^[13-17],研究发现,它还可以作为线粒体和其他凋亡通路的诱导剂,介导并下调抗凋亡 Bcl-2 家族蛋白的表达,从而使下游的促凋亡蛋白 BAX 的表达量增加并导致肿瘤细胞凋亡^[18-23]。此外,石蒜碱可能参与调控另外一种 Bcl-2 家族蛋白 Mcl-1,因此 Mcl-1 被认为是诱导肿瘤细胞凋亡的另外一个重要的分子靶点。石蒜碱通过固有线粒体途径诱导 caspases 激活前蛋白进而下调 Mcl-1 并参与促进人白血病细胞凋亡^[24],这预示着石蒜碱具有成为白血病治疗药物的潜在可能。在膀胱癌中,石蒜碱抑制蛋白激酶 B(protein kinase B, PKB 或 Akt)的表达以及激活 caspase-3 和 Bax,激活固有的凋亡信号传导通路,导致膀胱癌细胞凋亡^[14]。由于 PI3K/Akt/mTOR 通路的表达改变与超过 40%的膀胱癌相关,因此,石蒜碱对膀胱癌具有良好的治疗潜力^[25]。

2 抑制细胞周期

根据肿瘤细胞的来源不同,石蒜碱可将其细

胞周期阻滞于G0 / G1或G2 / M期。在细胞周期中,特异性的周期蛋白、周期蛋白依赖性激酶(cyclin-dependent protein kinases, Cdk)和细胞周期蛋白依赖激酶抑制剂Cip/Kip或INK家族细胞周期蛋白依赖性激酶抑制因子(CDK inhibitor, CKI)共同协调并在细胞的整个G1、S、G2和M期发挥作用。

石蒜碱通过下调细胞周期蛋白-D(cyclin-D)和细胞周期素依赖性激酶4(CDK4),诱导多发性骨髓瘤细胞KM-3和慢性髓细胞白血病细胞系G1期细胞周期阻滞^[22, 26-27]。然而,在卵巢癌细胞HeyB1和急性早幼粒细胞白血病细胞HL-60中,石蒜碱可以分别通过在G2/M期下调cyclin-D3、CDK6和cyclin-E、CDK2诱导细胞周期阻滞^[28],具体作用机制如图3所示。p21是Cip/Kip周期蛋白依赖性激酶抑制剂家族的关键成员,能够结合并直接抑制cyclin E-Cdk2和cyclin B-Cdc2的活性^[17,29-31]。研究表明,无论肿瘤细胞是什么来源,石蒜碱都能上调p21的表达,因此,有人认为p21在G1期或G2期介导了石蒜碱诱导细胞周期阻滞。肿瘤抑制因子p53调控p21的表达和活性。虽然石蒜碱可以诱导p21表达抑制细胞周期进程,但上调p21的上游效应还不清楚。研究发现,石蒜碱可上调p53作为p21的上游诱导因子的表达,然而它也可以上调p53缺失的白血病细胞系中p21的表达^[27, 32]。因此,这提示p21的上调可能是由p53独立通路介导的,而p21可能是石蒜碱发挥细胞周期抑制活性的直接靶点。

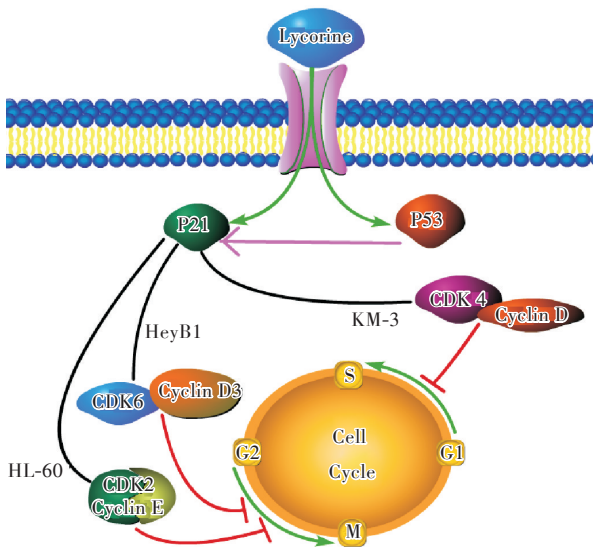


图3 石蒜碱抑制肿瘤细胞周期

Fig. 3 Cycle of lycorine inhibiting tumor cell

3 影响细胞自噬

细胞自噬是一种通过细胞内信号传导所引起的,将细胞内受损失活的大分子物质、细胞器、以及代谢废物送至溶酶体中降解的过程,降解后的细胞供能物质可以继续留在细胞内并被进一步充分利用^[33]。尤其在进展期的肿瘤细胞中,细胞自噬作为一种肿瘤细胞常见的生存方式参与维持细胞能量稳定、影响化疗药物的活性、以及诱导细胞死亡等过程^[34-37]。目前,自噬是如何促进肿瘤生长的具体机制尚不清楚,其机制可能与DNA损伤后介导的凋亡以及同时激活高迁移率组box 1受体介导的晚期糖基化终产物RAGE信号轴(HMGB1-RAGE信号通路)有极大关系^[38-40]。

高迁移率族蛋白HMGB1(high mobility group box-1 protein), 1973年首次在牛胸腺中被提取和鉴定,因其在聚丙烯酰胺凝胶电泳中的高迁移能力而得名,它是一个拥有215个氨基酸残基的分子,并且已经证实其与包括肿瘤在内的多种疾病有关^[41],这种分子在细胞中发挥作用的关键因素主要取决于其自身的亚细胞定位。HMGB1的应激信号路径的传导以及自噬激活作用在细胞外、细胞质、细胞核中都分别发挥着不同的作用^[42-45]。有研究报道,HMGB1-RAGE信号通路不仅可以介导免疫调节还可以促进炎症因子的激活从而促进结肠癌的发生和发展,并成为了由炎症因素导致肿瘤形成的经典通路之一^[46-47]。同时,石蒜碱是一种有效的自噬抑制剂,它可以诱导HMGB1蛋白酶体降解抑制MEK-ERK信号通路的激活,从而降低Bcl-2磷酸化,最终抑制细胞自噬^[48]。还有文献指出石蒜碱可以通过降低耐药相关蛋白1(Tongue cancer resistance-related protein 1, TCRP1)的表达水平诱导肝癌细胞凋亡和自噬;进一步抑制TCRP1蛋白后可以降低Akt磷酸化水平,从而抑制Akt/mTOR信号通路^[11],石蒜碱参与的细胞自噬相关细胞信号调控机制如图4所示。

4 抑制肿瘤侵袭和转移

肿瘤侵袭是恶性肿瘤细胞从原发瘤或继发瘤向邻近的宿主组织侵犯或占领的过程。而肿瘤转移是指肿瘤细胞由血管、淋巴管、体腔等途径把肿瘤细胞由原发部位带到另一组织或器官继续生长并形成与原发瘤病理类型相同病灶的过程。恶性肿瘤通常都伴有侵袭与转移,两者相互依赖,相互促进。

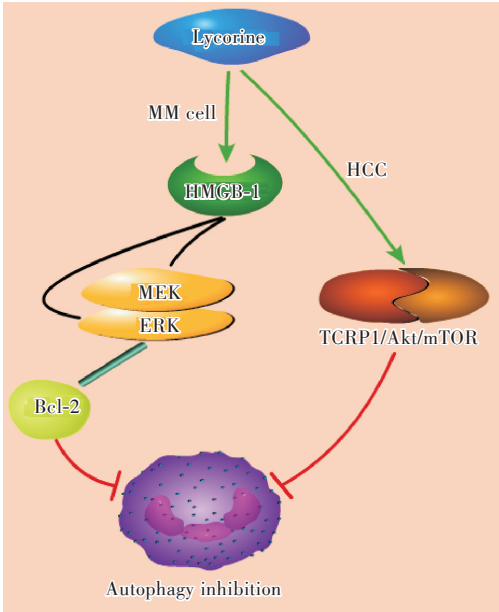


图 4 石蒜碱参与的细胞自噬调控机制
Fig. 4 Regulating mechanism of lycorine suppressing autophagy

局部粘着斑激酶(focal adhesion kinase, FAK)介导的信号转导系统是重要的细胞信号转导途径之一。在一项体内研究中,石蒜碱不仅抑制异种移植模型中乳腺肿瘤的生长,而且通过阻断 Src/FAK 途径抑制人乳腺癌细胞 MDA-MB-231 尾静脉模型中乳腺肿瘤的转移^[49]。

Ark 信号转导通路是信号通路中的一个重要分支,它在细胞生长、血管生成、肿瘤的侵袭和转移过程中起重要作用。已有研究证明石蒜碱通过抑制 Ark 的表达以及随后的体外激活 caspase3 和 Bax,最终诱导人膀胱癌 T24 细胞凋亡^[14]。在肝癌细胞中,石蒜碱通过 TCRP1/Akt/mTOR 通路促进细胞凋亡和自噬^[11]。石蒜碱还能抑制信号传导及转录激活因子(signal transducers and activators of transcription, STAT)的信号转导,降低转录因子 TWIST 的表达,促进肿瘤细胞上皮样变,逆转肿瘤细胞间质特征,使得 n-钙粘蛋白、波形蛋白、纤连蛋白的表达均减少,E-钙粘蛋白表达增加,从而维持细胞连接,阻断肿瘤细胞迁移和入侵的途径^[50-51]。

5 抑制肿瘤血管生成

血管是血液与血管周围的组织、器官进行物质交换的重要场所,尤其是毛细血管,它是仅由一层内皮细胞所构成的大小介于动脉和静脉末梢之间的管道,分布于全身的各个器官。毛细血管内血液流动极为缓慢,是机体物质交换的最重要场

所,丰富的物质交换同时也给机体正常组织或肿瘤组织的生长创造了有利条件。

肿瘤促进新生血管的形成是一个非常复杂的过程,通常包括血管内皮细胞移行、内皮基质降解、内皮细胞增殖、内皮细胞管道化以及血管环和基底膜的形成等步骤^[52-53]。肿瘤组织内的血管结构、功能、基质的异常导致肿瘤内部血管容易发生渗漏,更有利于肿瘤细胞的远处转移。因此抑制肿瘤血管生成在控制肿瘤生长和转移方面有着重要作用。

表皮生长因子受体(epidermal growth factor receptor, EGFR)是上皮生长因子细胞增殖和信号传导的受体,它与肿瘤细胞血管生成、肿瘤侵袭、转移及细胞凋亡的抑制有着密切关联。有文献报道石蒜碱可以调节 EGFR 的表达,使 EGFR 及磷酸化表皮生长因子受体(phosphorylation-epidermal growth factor receptor, p-EGFR)表达同时减少从而抑制神经胶质母细胞瘤的生长^[54]。血管内皮钙黏蛋白(VE-cadherin)是血管内皮细胞黏附连接的特异性蛋白,并在血管发生、形成、细胞内的信号转导等方面发挥重要作用^[55]。石蒜碱可以通过降低 VE-cadherin 基因表达和减少细胞表面对该蛋白的暴露来抑制黑色素瘤 C8161 细胞的血管生成^[56-57],详细分子机制如图 5 所示。

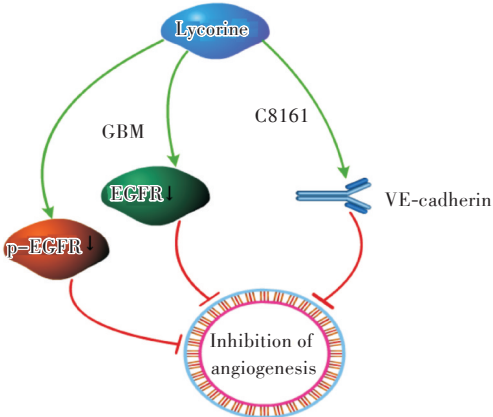


图 5 石蒜碱抑制肿瘤血管生成
Fig. 5 Lycorine inhibiting angiogenesis

6 结 语

石蒜碱在抗肿瘤药物中具有极大的开发潜力。抗肿瘤药物一般会产生耐药性,且靶向性较差、副作用较大。但石蒜碱作为一种植物生物碱,其结构简单,来源广泛,有着较好的开发优势。石蒜碱在低浓度下就可以产生强效抗肿瘤作用。但由于石蒜碱水溶性差,在很多方面限制了其在抗癌药物方面的开发研究。随着纳米技术的不断发

展,纳米药物具有增加药物可溶性,靶向性高的特点,纳米药物越来越得到大家的认可^[58-59]。石蒜碱与纳米技术相结合,会促进石蒜碱抗肿瘤药物的发展。相信通过科研工作者的深入研究,石蒜碱有望上市成为一种新型的小分子靶向性抗肿瘤药物。

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