·综述·

葫芦素B抗肿瘤机制和临床转化对策研究进展Δ

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摘　要　葫芦素B在多种肿瘤中均展现出显著的抗肿瘤活性，可通过调控Janus激酶2/信号转导及转录活化因子3、磷脂酰肌醇3激酶（STAT3）/蛋白激酶B和丝裂原活化的蛋白激酶等通路发挥抑制肿瘤细胞增殖的作用；通过调控B细胞淋巴瘤2相关X蛋白、Notch信号通路、铁摄取调控蛋白、焦孔素D等蛋白表达诱导多种形式的细胞死亡；可通过上调磷酸化组蛋白H2AX表达、抑制促癌基因表达等影响细胞遗传；还可通过靶向STAT3位点、抑制血管内皮生长因子受体2、下调P-糖蛋白等调节肿瘤免疫微环境、抑制血管生成和迁移侵袭、改善肿瘤耐药。但其口服生物利用度低，不少学者通过研制其衍生物和前体药物、纳米递送系统和制作分子探针等方法提高了其利用效率和安全性。后续仍需开展更深入的机制研究及临床试验，为其新药研发与临床应用提供理论依据。

关键词　葫芦素B；抗肿瘤；分子机制；临床转化；毒性

Research progress on the antitumor mechanisms and clinical translation of cucurbitacin B

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ABSTRACT　Cucurbitacin B has been demonstrated to exhibit significant antitumor activity against various types of tumors. Its antiproliferative effects were mediated through the regulation of multiple signaling pathways, including the Janus kinase 2/signal transducer and activator of transcription 3 (STAT3) pathway, the phosphoinositide 3-kinase/protein kinase B pathway, and the mitogen-activated protein kinase pathway. Diverse forms of cell death were induced by modulating the expression of proteins such as B-cell lymphoma-2-associated X protein, Notch signaling components, iron uptake regulatory proteins, and gasdermin D. Genetic effects were exerted through upregulation of phosphorylated histone H2AX expression and suppression the expression of oncogenes. Furthermore, the tumor immune microenvironment was modulated, angiogenesis and migration/invasion were inhibited, and tumor drug resistance was ameliorated via targeting of the STAT3 site, inhibition of vascular endothelial growth factor receptor 2, and downregulation of P-glycoprotein. However, the oral bioavailability of cucurbitacin B has been found to be low; therefore, various strategies, including the development of derivatives and prodrugs, construction of nano-drug delivery systems, and fabrication of molecular probes, have been employed to improve its utilization efficiency and safety. In the future, more in-depth mechanistic investigations and clinical trials are still required to provide a theoretical basis for novel drug development and clinical application of this compound.

KEYWORDS　cucurbitacin B; antitumor; molecular mechanisms; clinical translation; toxicity

恶性肿瘤是严重危害人类生命健康的重大公共卫生问题之一。尽管近年来肿瘤领域的研究进展迅速，但肿瘤的异质性、耐药性及治疗毒性仍是临床治疗中的棘手问题。从天然产物中寻找高效、低毒的多靶点药物一直是其中的研究热点。葫芦素B是从葫芦科植物中提取的四环三萜化合物[1]，因具有较强的抗肿瘤、抗炎、抗氧化、抗病毒、降血糖、保肝、神经保护等生物活性而受到广泛关注。研究表明，葫芦素B对肝癌、乳腺癌、结肠癌、非小细胞肺癌、前列腺癌、鼻咽癌、舌癌等均有显著的抗肿瘤活性[2]。然而，葫芦素B溶解性差并且有潜在的肝脏和胃肠道毒性，严重阻碍了其临床应用。本文系统梳理了近年来葫芦素B抗肿瘤作用机制和临床转化

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