·REVIEWS· ·综 述·

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FBXW7在非小细胞肺癌治疗耐药中的研究进展

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[摘要] 非小细胞肺癌(non-small cell lung cancer，NSCLC)是全球范围内最常见的恶性肿瘤之一。NSCLC治疗耐药严重影响了预后，研究NSCLC治疗耐药的分子机制非常必要。泛素-蛋白酶体系统(ubiquitin-proteasome system，UPS)能够通过选择性降解短期蛋白调节细胞内重要过程，如周期调控、转录调控、信号转导、凋亡和分化等，其表达的异常影响肿瘤的发生、发展及预后。F-box家族蛋白是UPS的重要组成部分，而F框/WD-40域蛋白7(F-box and WD-40 domain protein 7，FBXW7)是F-box家族蛋白中研究的经典蛋白之一。研究表明FBXW7与NSCLC耐药有关，主要机制是FBXW7突变减少其下游蛋白的泛素化降解，导致NSCLC患者药物治疗耐药，其下游蛋白包括Snail蛋白、骨髓细胞白血病因子1(myeloid cell leukemia sequence 1，MCL-1)、雷帕霉素靶蛋白(mammalian target of rapamycin，mTOR)、卷曲螺旋结构域6(coiled-coil-domain containing 6， CCDC6)。雷帕霉素、组蛋白脱乙酰酶抑制剂MS-275及冬凌草素对治疗耐药的FBXW7突变的NSCLC患者有效。

[关键词] 非小细胞肺癌；泛素蛋白酶体系统；F框/WD-40域蛋白7；耐药

Research progress in the role of FBXW7 in drug resistance against non-small cell lung cancer

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ABSTRACT Non-small cell lung cancer (NSCLC) is one of the most common malignant tumors in the world. NSCLC shows serious effect on prognosis for drug resistance, and it is necessary to study the molecular mechanism for drug resistance in NSCLC. Ubiquitin-proteasome system (UPS) can regulate some important cellular processes by degrading short-term protein, and the abnormal expression is closely related to the occurrence, development and prognosis of tumor. The F-box family protein is an important component of the ubiquitin proteasome, such as cycle regulation, transcriptional regulation, signal transduction, apoptosis and differentiation. F-box and WD-40 domain protein 7 (FBXW7) is just the classic protein components among F-box family protein.

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Studies have shown that FBXW7 is related to drug resistance in NSCLC. The main mechanism is that FBXW7 mutation leads to drug resistance by reducing ubiquitination and degradation of its downstream proteins, including Snail protein, myeloid cell leukemia sequence 1 (MCL-1), mammalian target of rapamycin (mTOR), and coiled-coil-domain containing 6 (CCDC6). Rapamycin, histone deacetylase inhibitor MS-275, and rabdosia are effective in drug-resistant NSCLC patients with FBXW7 mutation.

KEY WORDS non-small cell lung cancer; ubiquitin-proteasome system; F-box and WD-40 domain protein 7; FBXW7; drug resistance

泛素-蛋白酶体系统(ubiquitin-proteasome system，UPS)是一种重要的选择性蛋白质调控体系，包括调控细胞周期、转录、信号转导、凋亡和分化等[1]。UPS主要通过一系列泛素酶介导的多步级联反应来发挥作用，涉及的泛素酶包括泛素激活酶 (ubiquitin-activating enzyme，E1)、泛素结合酶(ubiquitin-conjugating enzyme，E2)及泛素连接酶(ubiquitin ligase，E3)[2]，而E3在此过程中发挥特异性作用。SCF (Skp1-cullin-F-box protein)是E3的最大家族成员，简称SCFE3，由连接蛋白(Skp1)、支架蛋白(Cullin)、环指蛋白及F-box蛋白组成[3]，其中F-box蛋白决定了底物蛋白泛素化降解的特异性[4]，因此F-box蛋白在肿瘤发生和发展中起重要作用[5]。F框/WD-40域蛋白7(F-box and WD-40 domain protein 7，FBXW7)是F-box蛋白的最典型代表之一，作为肿瘤抑制因子，能够降解多种肿瘤因子[6]。研究[7-8]证明FBXW7蛋白不仅在非小细胞肺癌(non-small-cell lung carcinoma，NSCLC)的发生、发展、转移中发挥抑制作用，而且与NSCLC药物治疗耐药有关。

1 FBXW7概述

FBXW7又名hCDC4，由10个共有的外显子及1个特异性的外显子组成，根据特异性的外显子不同，可将其分为3种亚型，即FBXW7α，FBXW7β和FBXW7γ，其中FBXW7α在细胞中含量最多[9-10]。这3种蛋白亚型的羧基端均由F-box和WD-40重复结构域组成，其氨基末端结构不同决定这3种蛋白亚型的表达和功能的特异性[11]。不同的蛋白亚型定位在细胞的位置不同：FBXW7α主要位于细胞核内，FBXW7β主要定位胞质的内质网上，而FBXW7γ主要位于核仁[12]。FBXW7具有3个保守的结构域，即F-box蛋白、D结构域及WD-40重复序列，是蛋白质-蛋白质相互作用的区域。FBXW7具有两种形式，即单体和二聚体，它们降解的底物不同，如cyclin E和c-myc等底物可以被FBXW7单体形式高效降解，而其他底物的CDC4磷酸-降解决定子(CDC4 phosphodegron，CPD)与FBXW7的亲和力较弱，需要在FBXW7二聚体的作用下才能降解[13-14]。进一步研究发现F-box是通过与Skp1结合，进而募集SCFE3其他组分发挥作用。D结构域的功能是促进FBXW7的二聚化。FBXW7的WD40第三及第四重复序列含有高度保守的精氨酸残基，能与靶蛋白上的CPD磷酸化氨基酸相互作用，从而介导FBXW7与靶蛋白结合[15]。FBXW7与靶蛋白结合使靶蛋白泛素化降解，从而发挥调控细胞周期、分化、凋亡的作用[16]。目前研究认为FBXW7是一种抑癌因子[17]，因为FBXW7能够促进一些肿瘤因子的泛素化降解，如EN01[18]，ZNF322A[19]，以及miR-223[20]，miR-25[21]，miR367[22]。FBXW7在多种肿瘤中是突变或缺失的，如结肠癌[23]、胃癌[24]及肝癌[25]等，FBXW7的突变或缺失与这些肿瘤的不良预后有关。FBXW7突变在NSCLC中的发生频率较高[26]，且这种突变与缺失与NSCLC的预后相关[27]。以上结果表明FBXW7突变可能是NSCLC患者预后的生物标志之一。

2 FBXW7 突变产生NSCLC耐药的机制

随着对NSCLC治疗研究的深入，NSCLC药物治疗取得了很大进步，但仍逃脱不了耐药的发生。目前常见的耐药机制有：PI3K/Akt，Notch-1，JAK/STAT，Wnt，TGF-β等信号通路的激活[28-33]，表皮生长因子受体(epidermal growth factor receptor，EGFR)-T790M[34]，ALK-C1156Y及ALK-L1196M基因的突变[35]，旁路激酶c-Met，ErbB2及c-kit的活化[36]。许多研究[37-38]表明FBXW7在很多人类肿瘤中可以调节化学药物治疗(以下简称化疗)的敏感性，其突变与NSCLC等肿瘤的耐药密切有关。

2.1 通过减少Snail蛋白的泛素化降解导致铂类化疗药物耐药

上皮-间充质转化(epithelial-to-mesenchymal

transition，EMT)是指上皮细胞在特定程序的作用下向具有间质表型细胞转化的生物学过程，在胚胎的发育、慢性炎症的产生、组织重建、肿瘤转移及多种纤维化疾病中发挥重要作用。上皮细胞通过EMT失去了细胞极性及与基底膜的连接等上皮表型的特征，获得了迁移与侵袭能力[39]，因此EMT可以看成是上皮细胞来源的恶性肿瘤细胞获得了迁移和侵袭能力的重要生物学过程。Yu等[40]发现FBXW7的上调会增加铂类药物在NSCLC中的细胞毒性，其机制与EMT有关。最近有实验[41]证明：FBXW7通过诱导转录因子Snail蛋白的泛素化水解，阻碍了EMT过程的发生，从而抑制了肿瘤细胞的原始转变。相反，在FBXW7突变的NSCLC中Snail蛋白越稳定越会促使EMT过程的发生，导致NSCLC对铂类化疗药物耐药。以上证据表明EMT可能在恶性肿瘤化疗药物耐药中发挥重要作用。

2.2 通过减少MCL-1蛋白的泛素化降解导致抗微管蛋白化疗药物耐药

骨髓细胞白血病因子1(myeloid cell leukemia sequence 1，MCL-1)是一种抗凋亡蛋白，MCL-1减少会阻滞有丝分裂，从而诱导细胞凋亡。研究[42-43]表明MCL-1在肿瘤中高表达，并且与肿瘤的耐药性有关。有研究[44]发现紫杉醇、长春新碱等抗微管蛋白化疗药物治疗可诱导MCL-1蛋白磷酸化，而这种磷酸化修饰可被FBXW7识别并泛素化和降解，从而导致细胞内MCL-1蛋白含量明显下降和细胞凋亡显著增加。当肿瘤细胞中FBXW7突变时，会增加MCL-1蛋白稳定性，阻止细胞凋亡，进而使NSCLC患者对抗微管蛋白化疗药物产生耐药性。

2.3 通过减少MCL-1蛋白及mTOR的泛素化降解导致TKIs药物耐药

研究[45]报道FBXW7突变的NSCLC组织中会出现酪氨酸激酶抑制剂(tyrosine kinase inhibitors，TKIs)耐药，其主要机制是TKIs可以通过PI3K/Akt信号通路诱导MCL-1在糖原合成激酶3β(glycogen synthase kinase 3β，GSK3β)作用下发生磷酸化及核转移，MCL-1转移到细胞核后被细胞核中的FBXW7泛素化降解，当FBXW7突变时，MCL-1不能被泛素化降解，MCL-1的稳定性增加，因此NSCLC患者对TKIs产生了耐药性。最近也有研究[46]证明增加miR-223的表达而减少FBXW7的表达会提高NSCLC细胞对TKIs厄洛替尼的耐药性，其可能的机制是通过调控PI3K/Akt和Notch-1通路促进miR-223的表达，降解FBXW7，进而对厄洛替尼产生耐药性。此外，FBXW7通过抑制雷帕霉素靶蛋白(mammalian target of rapamycin，mTOR)达到抑制EMT的作用，增强NSCLC对吉非替尼的敏感性[47]，进一步说明FBXW7突变会导致NSCLC患者对TKIs产生耐药。

2.4 通过减少CCDC6的泛素化降解导致PARP抑制剂耐药

卷曲螺旋结构域6(coiled-coil-domain containing 6，CCDC6)的表达与NSCLC的预后相关，其在DNA修复过程发挥重要作用[48]。研究[49]表明低水平CCDC6蛋白的NSCLC细胞对聚腺苷酸二磷酸核糖转移酶[poly (ADP-ribose) polymerase，PARP]抑制剂奥拉帕尼敏感，而高水平CCDC6蛋白的NSCLC细胞对奥拉帕尼耐药，CCDC6敲除后的NSCLC细胞对奥拉帕尼敏感，其原因是CCDC6使DNA修复受损，抑制肿瘤细胞的转移，从而增强对奥拉帕尼的敏感性。另有研究[50]表明CCDC6是E3泛素连接酶FBXW7泛素化降解的靶蛋白，FBXW7突变的NSCLC细胞中CCDC6泛素化降解减少，CCDC6的稳定性增加，导致对PARP抑制剂耐药。

2.5 通过减少MCL-1的泛素化降解导致BH3类似物ABT-737耐药

靶向细胞凋亡是目前治疗癌症的方法之一。BCL-2家族蛋白成员中的BH3结构域蛋白是一种促凋亡蛋白，可使细胞程序性凋亡。研究[51]发现BH3类似物ABT-737可以靶向Bcl-2家族，但不能作用于MCL-1，而在FBXW7突变的鳞状细胞肺癌中容易产生对BH3类似物ABT-737的耐药，其机制是FBXW7突变的鳞状细胞肺癌中FBXW7减少，而ABT-737不能作用于MCL-1，导致MCL-1聚集，因此产生了对BH3类似物ABT-737的耐药性。

3 FBXW7突变的NSCLC的治疗进展

Villaruz等[52]报道了一位63岁的白人女性肺腺癌患者，存在肿瘤转移，在经过一系列治疗后出现耐药，但在其后的治疗中发现mTOR抑制剂雷帕霉素对这位患者仍有作用，其作用机制是该患者因发生FBXW7突变导致mTOR的增加，对治疗产生耐药性，而雷帕霉素有抑制mTOR的作用，所以雷帕霉素的治疗给这位患者带来了希望。该研究也强调了NSCLC中FBXW7突变是一种新型的肿瘤基因突变亚型，首次证明FBXW7突变在NSCLC治疗耐药中的作用。FBXW7突变能提高NSCLC患者对紫杉醇的耐药性，其原因是FBXW7突变使MCL-1表达增多，而组蛋白脱乙酰酶(histone deacetylases，HDAC)抑制剂MS-275能够抑制MCL-1的表达，在FBXW7突变的NSCLC中MS-

275治疗能恢复紫杉醇的敏感性[53]。此外，研究[51]表明在FBXW7突变的鳞状细胞肺癌中HDAC与BH3类似物ABT-737协同治疗能显著提高ABT-737的疗效，提示HDAC抑制剂在FBXW7突变的NSCLC耐药患者中具有一定的治疗前景。另有研究[45]证明在NSCLC中FBXW7的兴奋剂冬凌草素与TKIs联合作用对FBXW7突变的NSCLC治疗是有效的，提示冬凌草素对TKIs治疗耐药的FBXW7突变的NSCLC患者有效。

4 展 望

药物治疗在NSCLC治疗中起越来越重要的作用，但目前面临耐药带来的巨大挑战，探讨NSCLC对药物产生耐药性的机制以寻求逆转药物耐药的治疗手段具有重要的临床意义。FBXW7被认为是一种抑癌基因，对NSCLC的发生、发展及转移起抑制作用，且与NSCLC药物治疗耐药有关。FBXW7基因突变不仅有助于NSCLC预后的判断，而且FBXW7突变的NSCLC患者对药物治疗会产生耐药，提示对于FBXW7突变的NSCLC患者，针对FBXW7表达来增强药物治疗NSCLC的敏感性将会是一种新型靶向治疗策略。目前FBXW7作为抑癌基因的信号通路和增强对NSCLC药物敏感性的机制仍需进一步研究。

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参考文献

[1] Genschik P, Sumara I, Lechner E. The emerging family of CULLIN3-RING ubiquitin ligases (CRL3s): cellular functions and disease implications[J]. EMBO J, 2013, 32(17): 2307-2320.

[2] Hershko A. The ubiquitin system for protein degradation and some of its roles in the control of the cell division cycle[J]. Cell Death Differ, 2005, 12(9): 1191-1197.

[3] Zhou W, Wei W, Sun Y. Genetically engineered mouse models for functional studies of SKP1-CUL1-F-box-protein (SCF) E3 ubiquitin ligases[J]. Cell Res, 2013, 23(5): 599-619.

[4] Cardozo T, Pagano M. The SCF ubiquitin ligase: insights into a molecular machine[J]. Nat Rev Mol Cell Biol, 2004, 5(9): 739-751.

[5] Wang Z, Liu P, Inuzuka H, et al. Roles of F-box proteins in cancer[J]. Nat Rev Cancer, 2014, 14(4): 233-247.

[6] Cao J, Ge MH, Ling ZQ. Fbxw7 tumor suppressor: A vital regulator contributes to human tumorigenesis[J]. Medicine (Baltimore), 2016, 95(7): e2496.

[7] Xu J, Wu W, Wang J, et al. MiR-367 promotes the proliferation and invasion of non-small cell lung cancer via targeting FBXW7[J]. Oncol Rep, 2017, 37(2): 1052-1058.

[8] Chang H, Liu YH, Wang LL, et al. MiR-182 promotes cell proliferation by suppressing FBXW7 and FBXW11 in non-small cell lung cancer[J]. Am J Transl Res, 2018, 10(4):1131-1142.

[9] Spruck CH, Strohmaier H, Sangfelt O. hCDC4 gene mutations in endometrial cancer[J]. Cancer Res, 2002, 62(16): 4535-4539.

[10] Crusio KM, King B, Reavie LB, et al. The ubiquitous nature of cancer: the role of the SCF (Fbw7) complex in development and transformation[J]. Oncogene, 2010, 29(35): 4865-4873.

[11] Welcker M, Orian A, Grim JE, et al. A nucleolar isoform of the Fbw7 ubiquitin ligase regulates c-Myc and cell size[J]. Curr Biol, 2004, 15(24): 1852-1857.

[12] Ye X, Nalepa G, Welcker M, et al. Recognition of phosphodegronmotifs in human cyclinE by the ScFFbw7 ubiquitin ligase[J]. J Biol Chem, 2004, 279(48): 50110-50119.

[13] Zhang W, Koepp DM. Fbw7 isoform interaction contributes to cyclin E proteolysis[J]. Mol Cancer Res, 2006, 4(12): 935-943.

[14] Tang X, Orlicky S, Lin Z, et al. Suprafacial orientation of the SCFCdc4 dimer accommodates multiple geometries for substrate ubiquitination[J]. Cell, 2007, 129(6): 1165-1176.

[15] Kimura T, Gotoh M, Nakamura Y, et al. hCDC4b, a regulator ofcyclin E, as a direct transcriptional target of p53[J]. Cancer Sci, 2003, 94(5): 431-436.

[16] Xu W, Taranets L, Popov N. Regulating Fbw7 on the road to cancer[J]. Semin Cancer Biol, 2016, 36: 62-70.

[17] Yeh CH, Bellon M, Nicot C. FBXW7: a critical tumor suppressor of human cancers[J]. Mol Cancer, 2018, 17(1): 115.

[18] Zhan P, Wang Y, Zhao S, et al. FBXW7 negatively regulates ENO1 expression and function in colorectal cancer[J]. Lab Invest, 2015, 95(9): 995-1004.

[19] Liao SY, Chiang CW. δ/GSK3β/FBXW7α axis promotes degradation of the ZNF322A oncoprotein to suppress lung cancerprogression[J]. Oncogene, 2017, 36(41): 5722-5733.

[20] Eto K, Iwatsuki M, Watanabe M, et al. The sensitivity of gastric cancer to trastuzumab is regulated by the miR-223/FBXW7 pathway[J]. Int J Cancer, 2015, 136(7): 1537-1545.

[21] Xiang J, Hang JB, Che JM, et al. miR-25 is up-regulated in non- small cell lung cancer and promotes cell proliferation and motility by targeting FBXW7[J]. Int J Clin Exp Pathol, 2015, 8(8): 9147-9153.

[22] Xu J, Wu W, Wang J, et al. miR-367 promotes the proliferation and invasion of non-small cell lung cancer via targeting FBXW7[J]. Oncol Rep, 2017, 37(2): 1052-1058.

[23] Korphaisarn K, Morris VK, Overman MJ, et al. FBXW7 missense mutation: a novel negative prognostic factor in metastatic colorectal adenocarcinoma[J]. Oncotarget, 2017, 8(24): 39268-39279.

[24] Zhou X, Jin W, Jia H, et al. MiR-223 promotes the cisplatin resistance of human gastric cancer cells via regulating cell cycle by targeting FBXW7[J]. J Exp Clin Cancer Res, 2015, 34(1): 28.

[25] Sun XF, Sun JP, Hou HT, et al. MicroRNA-27b exerts an oncogenic function by targeting Fbxw7 in human hepatocellular carcinoma[J]. Tumour Biol, 2016, 37(11): 15325-15332.

[26] Youssef O, Knuuttila A, Piirila P, et al. Hotspot mutations detectable by next-generation sequencing in exhaled breath condensates from patients with kung cancer[J]. Anticancer Res, 2018, 38(10): 5627-5634.

[27] Min SH, Lau AW, Lee TH, et al. Negative regulation of the stability and tumor suppressor function of Fbw7 by the Pin1 prolyl isomerase[J]. Mol Cell, 2012, 46(6): 771-783.

[28] Han J, Zhao F, Zhang J, et al. MiR-223 reverses the resistance of EGFR-TKIs through IGF1R/PI3K/Akt signaling pathway[J]. Int J Oncol, 2016, 48(5): 1855-1867.

[29] Xie M, He CS, Wei SH, et al. Notch-1 contributes to epidermal growth factor receptor tyrosine kinase inhibitor acquired resistance in non-small cell lung cancer in vitro and in vivo[J]. Eur J, 2013, 49(16): 3559-3572.

[30] Theys J, Yahyanejad S, Habets R, et al. High NOTCH activity induces radiation resistance in non-small cell lung cancer[J]. Radiother Oncol, 2013, 108(3): 440-445.

[31] Shen H, Guan D, Shen J, et al. TGF-β1 induces erlotinib resistance in non-small cell lung cancer by down-regulating PTEN[J]. Biomed Pharmacother, 2016, 77(1): 1-6.

[32] Hu Y, Hong Y, Xu Y, et al. Inhibition of the JAK/STAT pathway with ruxolitinib overcomes cisplatin resistance in non-small-cell lung cancer NSCLC[J]. Apoptosis, 2014, 19(11): 1627-1636.

[33] Li Y, Ma C, Shi X, et al. Effect of nitric oxide synthase on multiple drug resistance is related to Wnt signaling in non-small cell lung cancer[J]. Oncol Rep, 2014, 32(4): 1703-1708.

[34] Kobayashi S, Boggon TJ, Dayaram T, et al. EGFR mutation and resistance of non-small cell lung cancer to gefitinib[J]. N Engl J Med, 2016, 352(8): 786-792.

[35] Katayama R, Shaw AT, Khan TM, et al. Mechanisms of acquired crizotinib resistance in ALK-rearranged lung cancers[J]. Sci Transl Med, 2012, 4(120): 120ra17.

[36] Engelman JA, Zejnullahu K, Mitsudomi T, et al. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling[J]. Science, 2007, 316 (5827): 1039-1043.

[37] Gombodorj N, Yokobori T, Tanaka N, et al. Correlation between high FBXW7 expression in pretreatment biopsy specimensand good response to chemoradiation therapy in patients with locally advanced esophageal cancer: A retrospective study[J]. J Surg Oncol, 2018, 118(1): 101-108.

[38] Lin J, Ji A, Qiu G, et al. FBW7 is associated with prognosis, inhibits malignancies and enhances temozolomide sensitivity in glioblastoma cells[J]. Cancer Sci, 2018, 109(4): 1001-1011.

[39] Yeung KT, Yang J. Epithelial-mesenchymal transition in tumor metastasis[J]. Mol Oncol, 2017, 11(1): 28-39.

[40] Yu HG, Wei W, Xia LH, et al. FBW7 upregulation enhances cisplatin cytotoxicity in non-small cell lung cancer cells[J]. Asian Pac J Cancer Prev , 2013, 14 (11): 6321-6326.

[41] Zhang Y, Zhang X, Zhao S, et al. FBW7 loss promotes epithelial-to-mesenchymal transition in non-small cell lung cancer through the stabilization of Snail protein[J]. Cancer Lett, 2018, 419(8): 75-83.

[42] Leverson JD, Zhang H, Chen J, et al. Potent and selective small-molecule MCL-1inhibitors demonstrate on-target cancer cell killing activity as single agents and in combination with ABT-263 (navitoclax)[J]. Cell Death Dis, 2015, 6(1): e1590.

[43] Lin KH, Winter PS, Xie A, et al. Targeting MCL-1/BCL-XL forestalls the acquisition of resistance to ABT-199 in acute myeloid leukemia[J]. Sci Rep, 2016, 6: 27696.

[44] Wertz IE, Kusam S, Lam C, et al. Sensitivity to antitubulin chemotherapeutics is regulated by MCL-1 and FBW7[J]. Nature, 2011, 71(7336): 110-114.

[45] Ye M, Zhang Y, Zhang X, et al. Targeting FBXW7 as a strategy to overcome resistance to targeted therapy in non-small cell lung cancer[J]. Cancer Res, 2017, 77(13): 3527-3593.

[46] Zhang H, Chen F, He Y, et al. Sensitivity of non-small cell lung cancer to erlotinib is regulated by the Notch/miR-223/FBXW7 pathway[J]. Biosci Rep, 2017, 37(3): BSR20160478.

[47] Xiao Y, Yin C, Wang Y, et al. FBXW7 deletion contributes to lung tumor development and confers resistance to gefitinib therapy[J]. Mol Oncol, 2018, 12(6): 883-895.

[48] Morra F, Luise C, Visconti R, et al. New therapeutic perspectives in CCDC6 deficient lung cancer cells[J]. Int J Cancer, 2015, 136(9): 2146-2157.

[49] Zhao J, Tang J, Men W, et al. FBXW7-mediated degradation of CCDC6 is impaired by ATM during DNA damage response in lung cancer cells[J]. FEBS Lett, 2012, 586(24): 4257-4263.

[50] Morra F, Luise C, Merolla F, et al. FBXW7 and USP7 regulate CCDC6 turnover during the cell cycle and affect cancer drugs susceptibility in NSCLC[J]. Oncotarget, 2015, 6(14): 12697-12709.

[51] He L, Torres-Lockhart K, Forster N, et al. Mcl-1 and FBW7 control a dominant survival pathway underlying HDAC and Bcl-2 inhibitor synergy in squamous cell carcinoma[J]. Cancer Discov, 2013, 3(3): 324-337.

[52] Villaruz LC, Socinski MA. Temsirolimus therapy in a patient with lung adenocarcinoma harboring an FBXW7 mutation[J]. Lung Cancer, 2014, 83(2): 300-301.

[53] Yokobori T, Yokoyama Y, Mogi A, et al. FBXW7 mediates chemotherapeutic sensitivity and prognosis in NSCLCs[J]. Mol Res, 2014, 12(1): 32-37.

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