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Commentary

Dioscin: A new potential inhibitor of Skp2 for cancer therapy

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Emerging evidence has demonstrated that S-phase kinase associated protein 2 (Skp2) functions as an oncogenic protein in carcinogenesis and tumor progression [1]. Skp2, a subunit of the Skp1-Cul1-F-box protein (SCF) E3 ubiquitin ligase, exerts its oncogenic function via promotion of the ubiquitination and subsequent proteasomal degradation of various substrates including p27, FOXO1, p21 and p57 [1]. A wealth of evidence has revealed that Skp2 is critically involved in regulation of cellular physiological and pathological processes such as cell proliferation, cell cycle, apoptotic death, differentiation, migration and invasion, angiogenesis, and metastasis [1]. Therefore, due to the pivotal role of Skp2 in controlling cellular processes, dysregulated expression of Skp2 contributes to oncogenesis and tumor progression in a wide spectrum of cancers. In line with this, high expression of Skp2 is observed to be correlated with poor overall survival in a range of human malignancies [1]. Since Skp2 is characterized as a key oncoprotein in carcinogenesis, inactivation of Skp2 might be a novel strategy for the treatment of human cancers.

Accordingly, several research groups have designed and developed the inhibitors of Skp2. For example, the compound SZL-P1-41 blocked Skp2 and Skp1 interaction, and subsequently attenuated the oncogenic function of Skp2 [2]. Moreover, a couple of natural compounds have been validated to suppress the expression of Skp2 in various types of human malignancies. Longikaurin A, a kauranoid diterpenoid, reduced Skp2 expression and contributed to cell cycle arrest in liver cancer cells [3]. Curcumin, a substance from curcuma longa, decreased the Skp2 expression levels in multiple cancer types [4]. A study reported that quercetin, curcumin and lycopene downregulated Skp2 expression, leading to promotion of cell cycle arrest in breast cancer cells [5]. Rottlerin, a polyphenolic substance in the fruits of mallotus philippinensis, exerts its anticancer activity via the suppression of Skp2 in breast and pancreatic cancer cells [6,7]. Nitidine chloride, a bioactive phytochemical alkaloid, was found to repress the expression of Skp2 in ovarian cancer cells. Flavokawain A, a chalcone produced from the kava plant, decreased Skp2 expression in prostate cancer [8].

In the current issue of EBioMedicine, Zhou et al. validated a new Skp2 inhibitor, dioscin, which is obtained from a natural steroid saponin, for potential use in colorectal cancer (CRC) treatment in the future [9]. The authors first exploited the expression of Skp2 in CRC tissues by immunohistochemical staining and observed that Skp2 was highly expressed in CRC tumor samples compared with the adjacent tissues [9]. Keeping abreast with this finding, overexpression of Skp2 was observed in various CRC cell lines compared with normal colon epithelial cells. Biologically, the results from MTS, EdU and colony formation showed that Skp2 downregulation by CRISPR-Cas9-based gene knockout inhibited cell proliferation [9]. Moreover, *in vivo* experiment supported that Skp2 depletion retarded tumor growth in a xenograft mouse model. Furthermore, this study revealed that Skp2-induced glycolysis was due to inactivation of Akt and Hexokinase 2 (HK2) in CRC cells [9].

Strikingly, the authors utilized a natural product library with 88 products to screen natural compounds that regulated Skp2 expression and glycolysis. Dioscin, a steroid saponin in plants, was validated to efficiently repress glucose consumption and lactate production [9]. Concurrently, dioscin reduced the expression of Skp2, pAkt, and HK2

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in CRC cell lines. To determine the molecular mechanism by which dioscin inhibited Skp2 expression, the authors performed multiple experiments including half-life assay and *in vivo* uiquitination assay, and demonstrated that dioscin enhanced ubiquitination and degradation of Skp2 [9]. Intriguingly, co-immunoprecipitation data showed the Skp2 and Cdh1 interaction. Notably, this study confirmed that Cdh1 is needed for dioscin-mediated degradation of Skp2 in CRC cells. Specifically, dioscin blocked the S72 phosphorylation of Skp2, leading to enhanced binding between Skp2 and Cdh1, and subsequently increased ubiquitination and degradation of Skp2 [9]. Lastly, this group noted that dioscin retarded tumor growth *in vivo* nude mouse model. Consistently, immunohistochemical staining data from the tumor tissues showed that dioscin induced Skp2 ubiquitination and inhibition of HK2, suggesting that dioscin exerts its antitumor growth partly via modulation of Skp2 destruction and HK2 activation [9].

In summary, this work clearly identified dioscin as a new Skp2 inhibitor in CRC. Compared with synthetic chemical inhibitors of Skp2, dioscin might have lower toxicity and fewer side effects. However, several critical concerns are needed to be addressed. A growing body of data implicates that dioscin performed its anticancer activities via modulation of numerous targets and multiple signaling pathways [10]. It remains to be ascertained whether Skp2 is one of the important targets of dioscin? Which dose of dioscin is safe for treating patients with CRC? How can dioscin be delivered to tumor organs? Is dioscin the better agent to inhibit Skp2 compared with other natural compounds such as curcumin and rottlerin? It is also important to solve the bio-solubility of dioscin in human body. Taken together, this work might stimulate the researchers to discover and develop Skp2 inhibitors for potential cancer prevention and therapy.

Declaration of Competing Interest

The authors declare no conflicts of interest.

References

[1] Wang Z, Liu P, Inuzuka H, et al. Roles of F-box proteins in cancer. Nat Rev Cancer 2014;14(4):233–47.
[2] Chan CH, Morrow JK, Li CF, et al. Pharmacological inactivation of skp2 SCF ubiquitin ligase restricts cancer stem cell traits and cancer progression. Cell 2013;154(3):556–68.
[3] Liao YJ, Bai HY, Li ZH, et al. Longikaurin A, a natural ent-kaurane, induces G2/M phase arrest via downregulation of skp2 and apoptosis induction through ROS/JNK/c-Jun pathway in hepatocellular carcinoma cells. Cell Death Dis 2014;5:e1137.
[4] Su J, Zhou X, Wang L, et al. Curcumin inhibits cell growth and invasion and induces apoptosis through down-regulation of skp2 in pancreatic cancer cells. Am J Cancer Res 2016;6(9):1949–62.
[5] Huang HC, Lin CL, Lin JK. 1,2,3,4,6-penta-O-galloyl-beta-D-glucose, quercetin, curcumin and lycopene induce cell-cycle arrest in MDA-MB-231 and BT474 cells through downregulation of skp2 protein. J Agric Food Chem 2011;59(12):6765–75.
[6] Yin X, Zhang Y, Su J, et al. Rottlerin exerts its anti-tumor activity through inhibition of skp2 in breast cancer cells. Oncotarget 2016;7(41):66512–24.
[7] Su J, Wang L, Yin X, et al. Rottlerin exhibits anti-cancer effect through inactivation of S phase kinase-associated protein 2 in pancreatic cancer cells. Am J Cancer Res 2016;6(10):2178–91.
[8] Li X, Yokoyama NN, Zhang S, et al. Flavokawain A induces deNEDDylation and skp2 degradation leading to inhibition of tumorigenesis and cancer progression in the TRAMP transgenic mouse model. Oncotarget 2015;6(39):41809–24.
[9] Zhou L, Yu X, Li M, et al. Cdh1-mediated skp2 degradation by dioscin reprogrammes aerobic glycolysis and inhibits colorectal cancer cells growth. EBioMedicine 2019 In press. doi: 10.1016/j.ebiom.2019.11.031.
[10] Tao X, Yin L, Xu L, et al. Dioscin: a diverse acting natural compound with therapeutic potential in metabolic diseases, cancer, inflammation and infections. Pharmacol Res 2018;137:259–69.