Ricolinostat

Ricolinostat is the first orally available, selective inhibitor of histone deacetylase 6 (HDAC6), currently under evaluation in clinical trials in patients with various malignancies. It is likely that the inevitable emergence of resistance to ricolinostat is likely to reduce its clinical effectiveness in cancer patients.

In a study, Wu et al. investigated the potential impact of multidrug resistance-linked ATP-binding cassette (ABC) transporters ABCB1 and ABCG2 on the efficacy of ricolinostat, which may present a major hurdle to its development as an anticancer drug in the future.

They demonstrated that the overexpression of ABCB1 or ABCG2 reduces the intracellular accumulation of ricolinostat, resulting in reduced efficacy of ricolinostat to inhibit the activity of HDAC6 in cancer cells. Moreover, the efficacy of ricolinostat can be fully restored by inhibiting the drug efflux function of ABCB1 and ABCG2 in drug-resistant cancer cells. In conclusion, our results provide some insights into the basis for the development of resistance to ricolinostat and suggest that co-administration of ricolinostat with a modulator of ABCB1 or ABCG2 could overcome ricolinostat resistance in human cancer cells, which may be relevant to its use in the clinic [1].

Histone deacetylase 6 (HDAC6) activity contributes to the malignant proliferation, invasion and migration of glioma cells (GCs), but the molecular mechanisms underlying the processes remains elusive. Huang et al. reported that HDAC6 inhibition by Ricolinostat (ACY-1215) or CAY10603 led to a remarkable decrease in the phosphorylation of JNK and c-Jun, which preceded its suppressive effects on glioma cell growth. Further investigation showed that these effects resulted from HDAC6 inhibitor-induced suppression of MKK7, which was identified to be critical for JNK activation and exerts the oncogenic roles in GCs. Selectively silencing HDAC6 by siRNAs had the same responses while transient transfections expressing HDAC6 promoted MKK7 expression. Interestingly, by performing Q-PCR, HDAC6 inhibition did not cause downregulation of MKK7 mRNA level, whereas the suppressive effects on MKK7 protein can be efficiently blocked by the proteasomal inhibitor MG132. As a further test, elevating MKK7-JNK activity was sufficient to rescue HDAC6 inhibitor-mediated-suppressive effects on c-Jun activation and the malignant features. The suppression of both MKK7 expression and JNK/c-Jun activities was involved in the tumour-growth inhibitory effects induced by CAY10603 in U87-xenograft mice. Collectively, our findings provide new insights into the molecular mechanism of glioma malignancy regarding HDAC6 in the selective regulation of MKK7 expression and JNK/c-Jun activity. MKK7 protein stability critically depends on HDAC6 activity, and inhibition of HDAC6 probably presents a potential strategy for suppressing the oncogenic roles of MKK7/JNK/c-Jun axis in GCs [2].

References

1)
Wu CP, Hsieh YJ, Murakami M, Vahedi S, Hsiao SH, Yeh N, Chou AW, Li YQ, Wu YS, Yu JS, Ambudkar SV. Human ATP-binding cassette transporters ABCB1 and ABCG2 confer resistance to histone deacetylase 6 inhibitor ricolinostat (ACY-1215) in cancer cell lines. Biochem Pharmacol. 2018 Sep;155:316-325. doi: 10.1016/j.bcp.2018.07.018. Epub 2018 Jul 17. PubMed PMID: 30028995.

2)
Huang Z, Xia Y, Hu K, Zeng S, Wu L, Liu S, Zhi C, Lai M, Chen D, Xie L, Yuan Z. Histone deacetylase 6 promotes growth of glioblastoma through the MKK7/JNK/c-Jun signaling pathway. J Neurochem. 2019 Aug 7. doi: 10.1111/jnc.14849. [Epub ahead of print] PubMed PMID: 31390677.

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