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HZ-6d targeted HERC5 to regulate p53 ISGylation in human hepatocellular carcinoma

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Manipulating the posttranslational modulator of p53 is central in the regulation of its activity and function. ISGylated p53 can be degraded by the 20S proteasome. During this process, HERC5/Ceb1, an IFN-induced HECT-type E3 ligase, mediated p53 ISGylation. In this study, we indicated that HERC5 was over-expressed in both HCC tissue samples and cell lines. Knockdown of HERC5 significantly induced the expression of p53, p21 and Bax/Bcl-2 in HCC cells, resulting in apoptosis augment. Whereas, opposite results were obtained by using HERC5 over-expression. On this basis, we screened a 7, 11-disubstituted quinazoline derivative HZ-6d that could bind to the HERC5 G-rich sequence *in vitro*. Interestingly, HZ-6d injection effectively delayed the growth of xenografts in nude mice. *In vitro*, HZ-6d significantly inhibited cell growth, suppressed cell migration, induced apoptosis in HCC cells. Further studies demonstrated the anti-cancer effect of HZ-6d was associated with down-regulation of HERC5 and accumulation of p53. Collectively, we demonstrated that HZ6d is a HERC5 G-quadruplex ligand with anti-tumor properties, an action that may offer an attractive idea for restoration of p53 function in cancers.

Recent Publications

1. Wang Y, Ding Q, Xu T, Zhang L (2017) HZ-6d targeted HERC5 to regulate p53 ISGylation in human hepatocellular carcinoma. *Toxicology & Applied Pharmacology*; 334.
2. Du Y, Li J, Xu T, Zhang L (2017) MicroRNA-145 induces apoptosis of glioma cells by targeting BNIP3 and Notch signaling. *[J]. Oncotarget;* 8(37): 61510.

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