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802.CHEMICAL BIOLOGY AND EXPERIMENTAL THERAPEUTICS

Study on the Synthetic Lethal Mechanism of Selective Killing of ALDH2 Deficient Acute Myeloid Leukemia Cells By Inhibiting BRIP1

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Background and objective: Although targets related to DNA double strand damage repair have clear tumor therapeutic potential, few have identified DNA double strand damage repair dependence in AML cells through genetic screening to date. In our previous experiments, we found that ALDH2 showed low expression in most newly diagnosed AML, and their unique ALDH2 vulnerability may make them preferentially dependent on BRIP1 by the DNA double-strand damage repair pathway, and have more synthetic lethal effects than other normal cells. Therefore, this study explored whether blocking BRIP1-mediated DNA double-strand damage repair could selectively eliminate AlDH2-deficient AML cells while preserving AlDH2-expressing normal cells present in most human tissues.
Methods: We examined the dependence of ALDH2-expressing cells on BRIP1 and methylation levels of ALDH2 promoters in different AML cell lines. The expressions of BRIP1 and ALDH2 in 6 AML cell lines and clinical samples were detected by Real-time PCR and Western blot, and the reverse expression pattern between the two was studied, and the correlation between the expression of ALDH2 and DNA base excision repair was analyzed. By targeting the inhibition of ALDH2 and BRIP1, in vitro and in vivo models were constructed to observe the proliferation and apoptosis of different AML cell lines and primary cells.
Results: In the group of AML cells with low expression of ALDH2, we found that BRIP1 showed a certain high expression compared with other groups. Among the 46 newly diagnosed AML samples, we divided the clinical samples into high and low groups based on the difference in the expression level and methylation degree of ALDH2. Compared with the group with high expression of ALDH2, BRIP1 in the group with low expression of ALDH2 was significantly increased ($P < 0.01$). The proliferation level of AML cells was significantly decreased ($P < 0.01$). BRIP1 inhibition induced apoptosis of U937 and TPH1 cells (AML cell lines with low expression of ALDH2) in a dose - and time-dependent manner ($P < 0.05$). In addition, in AML cell lines with high expression of ALDH2, we inhibited the expression of both ALDH2 and BRIP1, and the growth of AML cells was significantly down-regulated ($P < 0.01$). Similarly, we observed the same results when constructing an in vivo AML infiltration model in mice using AML primary cells.
Conclusion: The dependence of ALDH2-deficient cells on BRIP1 and the effect of targeting BRIP1 on the proliferation of AML cells could provide new ideas for finding new molecular targets for the treatment of AML.

Disclosures No relevant conflicts of interest to declare.

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