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POSTER ABSTRACTS

617.ACUTE MYELOID LEUKEMIAS: BIOMARKERS, MOLECULAR MARKERS AND MINIMAL RESIDUAL DISEASE IN DIAGNOSIS AND PROGNOSIS

ALDH3A2 Regulates Ferroptosis By Participating in Fatty Acid Synthesis and Finally Lead to Chemotherapy Resistance in Acute Myeloid Leukemia

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Chemotherapeutic resistance is a major challenge in the treatment of acute myeloid leukemia (AML). Although increasing the dose of anthracycline drugs improve chemotherapy efficacy and reduce drug resistance, the side effects limit the increase of their dosage. One strategy to improve the therapeutic effects is to improve the efficacy in their limited doses. Ferroptosis is one important way in which Adriamycin exerts cytotoxic effects on AML cells, which was also associated with resistance to Adriamycin. ALDH3A2 is a fatty aldehyde dehydrogenase related to the conversion of fatty aldehydes and fatty acids. Here, we found that ALDH3A2 is a biomarker for chemotherapy-resistant AML, increased expression of ALDH3A2 reduced ferroptosis and cytotoxicity induced by Adriamycin in AML cells. In our studies, we demonstrated that ALDH3A2 regulated ferroptosis and AML drug resistance by participating in fatty acid synthesis.

By analyzing the data from TCGA and GTEx databases, we found that ALDH3A2 expression varied in different types of tumor cells. AML patients had higher ALDH3A2 expression than normal tissues. We analyzed the RNA-seq results of 88 leukemia cell lines from the HPA database, and found that 15 out of the top 25% highest ALDH3A2 expression cell lines were AML cell lines, indicating that AML cells had higher ALDH3A2 expression than other types of leukemia cells. We plotted survival curves based on the gene data and clinical survival data from TCGA and GTEx databases. It showed that AML patients with high ALDH3A2 expression had shorter overall survival (OS) than those with low expression. We detected the expression of ALDH3A2 in AML cell lines and primary cells from patients using Western blot and RT-qPCR, respectively. Our data showed that drug-resistant AML cell lines had higher ALDH3A2 expression than their parental cells. The expression of ALDH3A2 in primary cells from AML patients achieving continuous complete remission (CR) within two years was significantly lower than that in the first-line non-remission(C1NR) group and the relapsed/refractory (R/R) group. Besides, the expression of ALDH3A2 is related to certain types of mutation such as CEBPα, FLT3-ITD and RUNX1. To investigate the function of ALDH3A2, we constructed AML cell lines with ALDH3A2 knockdown or overexpression. We found that the increasing ferroptosis level and decreasing cell activity after treatment with the same concentration of Adriamycin was observed in the knockdown group, and overexpression group had the *opposite* effect. By ELISA and GC-MS, we discovered that there were differences in 4-HNE and fatty acid content between the overexpression group and the control group. It suggested that ALDH3A2 overexpression reduced the cytotoxic 4-HNE and increased the content of heptadecanoic acid, oleic acid, and linoleic acid. We further pretreated AML cells with heptadecanoic acid, oleic acid, and linoleic acid, and found that pretreatment with heptadecanoic acid and oleic acid reduced ferroptosis level and cytotoxicity induced by Adriamycin in AML cells. We also tried to find the regulatory mechanism of ALDH3A2 expression and found that acetylation plays a certain role in it.

In conclusion, our studies found that increased expression of ALDH3A2 was related to poor chemotherapy efficacy in AML patients and clarifies the mechanism of ALDH3A2 regulating chemosensitivity in AML. ALDH3A2 degraded the cell toxic product 4-HNE of lipid peroxidation and regulated the proportion and content of heptadecanoic acid, oleic acid, and linoleic acid in cells, which related to ferroptosis and resistance to anthracycline drugs. Downregulating ALDH3A2 could increase AML's susceptibility to chemotherapy which may make it a promising therapy.

Disclosures No relevant conflicts of interest to declare.

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