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605.MOLECULAR PHARMACOLOGY AND DRUG RESISTANCE: LYMPHOID NEOPLASMS

Voltage-Dependent Anion Channel 2 (VDAC2) Drives Rituximab Resistance Via Inhibiting Ferroptosis in Diffuse Large B Cell Lymphoma

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Background: The underlying mechanism of rituximab resistance is still unclear; it is important to explore novel therapeutic targets to improve the outcomes of the patients. Here, we tried to identify the effects of Voltage-dependent anion channel 2 (VDAC2) on rituximab resistance as well as its therapeutic value in diffuse large B-cell lymphoma (DLBCL).
Methods: VDAC2 was identified by transcriptome and proteome sequencing analysis of rituximab-resistance cells. The effects of VDAC2 in rituximab resistance were investigated by gain-of-loss function experiments. The effects of VDAC2 regulating ferroptosis was evaluated with lipid ROS, MDA and GSH detection assays. Evaluate effect of VDAC2 on therapeutic efficacy was performed by Xenograft mouse model.
Results: Transcriptome and proteome sequencing analysis of rituximab-resistance and control DLBCL cells identified that VDAC2 was highly expressed in rituximab-resistance cells, and we found that VDAC2 could predict the prognosis of patients treated with RCHOP regimens, but not CHOP regimen. Knock-down of VDAC2 significantly inhibited cell proliferation and arrested cell cycle in S phase, as well as enhanced sensitivity to rituximab. Moreover, we found that knockdown expression VDAC2 significantly repressed lactate production, the extracellular acidification rate, treatment with exogenous lactate could abrogated the effects mediated by VDAC2. Meanwhile, we further found that ferroptosis was responsible for VDAC2 mediated rituximab resistance. Knockdown expression of VDAC2 increased lipid ROS and MDA levels, decreased the GSH levels, and repressed expression of SLC7A11 and Gpx4. Moreover, the lactate administration could rescue ferroptosis and sensitivity to rituximab induced by knockdown expression of VDAC2.
Conclusions: This study revealed a novel mechanism of rituximab resistance mediated by VDAC2 via inhibiting ferroptosis, which provides a potential therapeutic target for overcoming rituximab resistance in DLBCL patients.
Keywords: Diffuse large B cell lymphoma, rituximab resistance, VDAC2, Ferroptosis

Disclosures No relevant conflicts of interest to declare.

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