Inhibition of PKM2 promotes chemosensitivity of DOX in ABC-DLBCL via imbalance of GSH/ROS and inhibition of the NF-κB pathway

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Some patients with activated B-cell-like diffuse large B-cell lymphoma (ABC-DLBCL) remain insensitive to R-CHOP. Doxorubicin (DOX), a core agent of R-CHOP, induces reactive oxygen species (ROS) accumulation in ABC-DLBCL. PKM2 is key in glycolysis and tumour development. The present study demonstrated that PKM2 targeting attenuated cell proliferation, triggered cell apoptosis and synergised with DOX chemotoxicity. Mechanistically, PKM2 inhibition and knockdown inhibited glycolysis, disrupted glutathione (GSH)/ROS balance and activated oxidative stress-related pathways. And PKM2i synergised DOX to suppression of the nuclear factor κB (NF-κB) signalling pathway. In summary, PKM2 targeting promotes DOX chemosensitivity via metabolic (glycolysis) and non-metabolic (NF-κB modulation) pathways, positioning PKM2 as a therapeutic lever to boost R-CHOP efficacy in ABC-DLBCL.

Keywords: DLBCL, DOX, glycolysis, PKM2, ROS.

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ROS rather than on DDR in ABC-DLBCLs[4]. Besides its anti-tumour effect, DOX also inhibits energy metabolism and counteracts oxidative stress. DOX induces disturbances in the expression of mRNA related to energy metabolism, including glycolysis[6]. Consequently, targeted investigations are warranted to optimise DOX efficacy in ABC-DLBCL, with a focus on overcoming subtype-specific resistance mechanisms. In the 1920s, Otto H. Warburg first described a phenomenon in malignant tumours characterised by enhanced and accelerated conversion of glucose to lactate known as aerobic glycolysis or Warburg effect[7,8]. Pyruvate kinase (PK), including four different subtypes: PKL, PKR, PKM1, and PKM2, catalyses the glycolytic conversion of phosphoenolpyruvate (PEP) to pyruvate and acts as a key enzyme in glycolysis[9,10]. PKM2 is highly expressed in proliferating cells and various aggressive tumour cells, participating in glycolysis and also functioning as a protein kinase in cellular processes[9,11–13]. Moreover, total lesion glycolysis can be used to assess tumour burden and metabolism, acting as an effective biomarker for evaluating DLBCL prognosis[14]. This emerging evidence implicates that PKM2 is a potential oncogenic driver in DLBCL pathogenesis, fuelling lymphomagenesis