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Reviewing the IDH1 Mutation-Mediated Mechanism of Drug Resistance and Revisiting Its Overcoming Strategies

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Abstract

Isocitrate dehydrogenase 1 (IDH1) is a pivotal enzyme in cellular energy metabolism, playing a crucial role in the conversion of isocitrate into α-ketoglutarate (α-KG). When IDH1 undergoes mutation, it catalyzes the conversion of α-KG into the oncogenic metabolite 2-hydroxyglutarate (2-HG). Subsequently, 2-HG competitively suppresses a range of α-KG-dependent dioxygenase activities, ultimately leading to hypermethylation of DNA or histones, which in turn causes the occurrence of various malignant tumors, including acute myeloid leukemia (AML), glioma, and chondrosarcoma. Currently, the FDA has granted approval for the use of the small molecule inhibitor Ivosidenib (AG-120) in the treatment of IDH1-mutated AML and cholangiocarcinoma. Although AG-120 has benefited patients clinically, drug resistance has gradually emerged and has become a major problem in the treatment of mutant IDH1 (mIDH1) diseases. In this review, we highlighted the function of IDH1 mutations in cancer treatment and described detailed resistance mechanisms in terms of IDH1-specific mutation sites. Representative mIDH1 inhibitors and their binding modes were also discussed. In particular, we summarized seven strategies to overcome drug resistance, which provide a basis for understanding the mechanism of drug resistance for IDH1 mutations and exploring guidance to overcome drug resistance.

Keywords: 2-HG; AML; IDH1; IDH1 mutant; mechanism of drug resistance.