Abstract

The development of therapy resistance is a long-standing problem in treating cancer, particularly in the treatment of myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML), where the hypomethylating agent 5-azacytidine (AZA) is the first choice of treatment. To enhance therapeutic efficacy, AZA is often combined with other agents such as pevonedistat (Pevo), a NEDDylation inhibitor targeting the ubiquitin-proteasome system. While initial results showed a synergistic effect of the AZA and Pevo combination in treating MDS and AML, dual resistance has been described, underlining the importance of understanding the mechanisms behind the resistance development.

Our previous data demonstrated an essential role of redox homeostasis and antioxidant system represented by Nuclear factor erythroid 2-related factor 2 (NRF2) in AZA resistance. The Kelch-like ECH-associated protein 1 (KEAP1)-NRF2 pathway is the master regulator of antioxidative defence in cells crucial for maintaining redox balance. However, hyperactivation of NRF2 has been implicated in therapy resistance and cancer progression. We hypothesised that NRF2 is crucial in MDS/AML therapy resistance, particularly in resistance to combined AZA and Pevo therapy.

We worked with cells sensitive and resistant to AZA and Pevo and monitored their redox state and NRF2 activity through flow cytometry and immunodetection techniques. Our findings revealed that the development of resistance to AZA and Pevo is associated with redox changes and persistent NRF2 activation. Paradoxically, our results underscore an important role for NRF2 both in the mechanism of action of AZA and Pevo and in the resistance to this combined therapy. Additionally, using a mass spectrometry-based redox proteomics method, we analysed specific oxidative modifications of protein thiols and we found that Pevo resistance is accompanied by significant changes in the redox state of proteins regulating key survival pathways.

Key words:

Acute myeloid leukaemia (AML), myelodysplastic syndrome (MDS), Kelch-like ECH-associated protein 1 (KEAP1), Nuclear factor erythroid 2-related factor 2 (NRF2), Isocitrate dehydrogenase 1 (IDH1) gene, Isocitrate dehydrogenase 2 (IDH2) gene, mutations, redox homeostasis, antioxidant pathway, mass spectrometry, proteomics, flow cytometry