Unlocking acid ceramidase: a new weapon against proteasome chemoresistance in myeloma

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The development of proteasome inhibitors (PI) has significantly enhanced treatment responses and survival rates in patients with multiple myeloma (MM),[1,2] a hematologic cancer characterized by the growth of malignant plasma cells in the bone marrow. Despite the high initial response rates to PI, myeloma patients often experience relapses due to the development of drug resistance, preventing these therapies from achieving sustained or complete remission. The precise cellular and molecular mechanisms underlying PI chemoresistance in MM are not fully understood. While myeloma relapse and resistance to PI can be linked to genetic mutations in proteasomal components or drug efflux pumps, these events are relatively rare in patients.[3] Growing evidence suggests that non-mutational processes, including changes in the expression of genes related to survival signaling pathways, may play a significant role in PI chemoresistance.[4]

The balance within sphingolipid metabolism plays a crucial role in regulating cell survival by modulating pro-apoptotic molecules such as ceramide and prosurvival factors such as sphingosine-1-phosphate.[5] Disruption of this balance has been shown to promote cancer cell survival, thereby contributing to chemotherapy resistance by inhibiting cell death pathways. In this issue of *Haematologica*, Bishop *et al*. present their research that identified acid ceramidase, an enzyme encoded by the gene *ASHA1* which catalyzes the hydrolysis of ceramide into sphingosine and fatty acids, as a key driver of PI resistance in MM.[6]

Utilizing RNA sequencing data from CD138$^+$ cells isolated from MM patients, the authors demonstrated that genes involved in sphingolipid metabolism are more highly expressed in refractory/relapsed patients compared to newly diagnosed individuals, correlating with worse survival outcomes. Among these genes, *ASAH1* was significantly upregulated in the relapsed patients, and high ASAH1 expression was associated with increased levels of the anti-apoptotic genes *MCL1* and *BCL2*. Through elegant mechanistic studies, the team showed that ASAH1 activates PP2A phosphatase activity, which in turn phosphorylates MCL1 and BCL2, thereby enhancing their anti-apoptotic effects.

While MCL1 and BCL2 have been previously linked to MM cell survival, pharmacological targeting of these anti-apoptotic molecules remains challenging.[7] The team built on their discoveries to explore the efficacy of targeting the ASAH1-PP2A anti-apoptotic signaling axis. They utilized ceranib-2, a potent ceramidase inhibitor, to treat PI-resistant MM cell lines in mouse models, observing significant reductions in tumor burden. These results mirrored those obtained with genetic knockdown of *ASAH1* in MM cells. To further explore the clinical relevance of their findings, the investigators utilized a platform called "*Ex Vivo* Mathematical Myeloma Advisor" (EMMA), created to advance clinical-informed decisions, research, and preclinical compound testing in primary samples from MM patients.[8] Remarkably, the addition of ceranib-2 improved responses to PI and resensitized cells from relapsed MM patients to PI treatment.

This work has both basic/translational and clinical implications for the treatment of MM. First, it identifies a new mechanism of PI chemoresistance in patients with relapsed/refractory MM. Second, it provides compelling evidence that ceramide metabolism enhances survival pathways and contributes to chemotherapy resistance, with the data providing a rationale for clinical testing of ceranib-2 and PI combination therapy in MM patients with relapsed/refractory disease. These exciting discoveries also raise several clinically relevant questions for translating these findings into clinical practice. For instance, what is the optimal combination of sphingolipid-targeting agents with other therapies? Can biomarkers of ceramide metabolism be identified for patient stratification? What are the efficacy and safety profiles of ceranib-2 and similar agents in combination with PI? Ultimately, the studies by Bishop *et al*. deepen our understanding of the non-mutational molecular mechanisms of PI chemoresistance in MM and also

provide a rationale for clinical trials exploring combination treatment that include novel sphingolipid-targeting agents to improve clinical outcomes for patients with relapsed/refractory MM.

Disclosures

No conflicts of interest to disclose.

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