Altering Mitochondrial Bioenergetic Pathways to Overcome Melphalan Resistance in Multiple Myeloma, Year 2

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Cancer cells develop resistance to chemotherapy by rewiring their metabolism. In Year-1 of our project, we showed that melphalan-resistant multiple myeloma (MM) cells had higher amounts of mitochondrial ATP and mitochondrial mass compared to isogenic melphalan-sensitive cells. Our next aim was to characterize the activity of the mitochondrial bioenergetic pathway (Krebs cycle) in MM cells and determine whether mitochondrial disruption increases melphalan cytotoxicity. Using variable doses of melphalan in the 72-hour MTT viability assay, we classified different MM cell lines (MM1S, KMS11, RPMI-8226, and H929) as de novo “sensitive” or “less sensitive” to melphalan. To determine synergistic cytotoxicity, melphalan was combined with mitochondrial inhibitors (IACS-010759 or IM156, complex I inhibitors in the electron transport chain, or CB-839, a glutaminase inhibitor that disrupts glutamine anaplerosis). Mitochondrial activity in the “sensitive” vs “less sensitive” cell lines was compared using 13C-stable isotope labeling (SIL). RPMI-8226 was found to be “less sensitive” to melphalan than other cell lines. Addition of IACS-010759 and IM156 to melphalan did not affect viability across all cell lines. However, addition of CB-839 significantly decreased the viability of the “less sensitive” cell line (RPMI-8226). Additionally, CB-839 exhibited synergism with melphalan even in “sensitive” cell lines. Finally, SIL studies supported our findings by demonstrating that RPMI-8226 had a substantial amount of glutamine anaplerosis into the Krebs cycle via the conversion of glutamine to glutamate compared to “sensitive” cells. The glutaminase inhibitor, CB-839, synergizes with melphalan in MM cell lines and should be studied further in clinical trials.