Overcoming Melphalan Resistance in the Treatment of Multiple Myeloma

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Multiple myeloma (MM), an incurable cancer of the plasma cells in the bone marrow, is the 2nd most common hematological malignancy. Melphalan is an alkylator chemotherapy and an effective treatment of MM, but MM cells often develop resistance to it. Cancer cells develop resistance to different therapies by rewiring their cellular metabolism to deal with the stress induced by various chemotherapies. The goal of this project was to characterize the alterations in cellular metabolism present in melphalan-resistant MM cells. We created an isogenic melphalan-resistant MM cell line from a melphalan sensitive RPMI-8226 MM cell line to serve as an in vitro model for melphalan resistance. We performed intracellular metabolite profiling using mass-spectrometry techniques. We subsequently performed bioenergetic assessments using an extracellular flux analyzer to validate differences in the bioenergetics between the two isogenic melphalan sensitive and resistant cell lines. The intracellular metabolite profiles of melphalan-resistant MM cells showed higher amounts of metabolites involved in bioenergetic pathways compared to their isogenic sensitive cell lines. The melphalan-resistant cells had a higher generation of mitochondrial ATP and a higher spare respiratory capacity suggestive of an increased mitochondrial biomass. This novel finding was confirmed by observing a higher amount of mitochondrial proteins in the resistant compared to sensitive MM cells. While limitations of in vitro assays not completely reflecting human biology exist, our current data provide strong evidence that melphalan-resistant MM cells have altered mitochondrial bioenergetics, and this may be a potential target for interventions to improve the cytotoxicity of melphalan in MM cells.

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