The Potential Role of Drug Transporters in Resistance to Immunomodulatory Drugs (IMiDs) Therapy in Multiple Myeloma

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The immunomodulatory drugs (IMiDs), thalidomide, lenalidomide and pomalidomide, play a critical role in the treatment of multiple myeloma (MM). In combination with other agents, outcomes for MM patients have been greatly improved with IMiD therapy. Unfortunately, patients will ultimately develop resistance to these agents, though the mechanisms of resistance remain largely uncharacterized. It was previously reported that both lenalidomide and pomalidomide are substrates of P-glycoprotein (MDR1, ABCB1), though their clinical relevance remain unclear. Thalidomide was reported not to be a substrate for P-gp. Despite nearly identical chemical structures and similar binding affinities, the ADME and pharmacokinetic characteristics of the three approved IMiDs are dramatically different. Data from our lab showed difference between these agents with respect to brain penetration in mice, apparent permeability (Papp) across MDCKII-WT and Caco-2 cell monolayers, and uptake in various leukemic cells, independent of P-gp expression. Collectively, these data point to other, yet undetermined transporters that differentially modulate membrane permeability and which may be involved in development of resistance to these agents. To characterize differences in uptake in MM cell lines, we performed uptake studies for all three IMiDs in several MM cell lines both sensitive and resistant to dexamethasone and lenalidomide. The result showed lenalidomide has the highest uptake followed by pomalidomide then thalidomide consistently across all MM cell lines tested. We further tested the uptake of the three IMiDs in several adherent cell lines, a higher uptake for lenalidomide compared with pomalidomide was observed in the hCMEC/D3 and HEK-293 cell lines, while this trend was reversed in the Caco-2 and MDCKII-Pgp cell lines. ATP depletion study suggested the enhanced pomalidomide and thalidomide uptake into the hCMEC/D3 cells by cold pomalidomide was dampened by both 2-DG and NaN3, especially NaN3. Result from bidirectional permeability studies suggested that pomalidomide has a higher Papp (Apparent permeability coefficient) compared to lenalidmide which PAMPA (Parallel Artificial Membrane Permeability Assay) showed a similar trend. The mechanisms for such effect are not clear and further studies to understand such phenomenon will be carried out soon. After literature review, we decided to test the effect of three transporters (ABCC4, ABCC5, SLCO4C1) on the transport of the IMiDs due to their expression and location. We are also proceeding with a screen assay using endoribonuclease prepared transporter siRNA library to identify new transporters responsible for the observed differences in uptake and transport among the three IMiDs.