Development of Differentiation Therapies for NPM1 Mutated AML

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The most common cause of Acute Myeloid Leukemia is the mutation of the NPM1 protein. Cells can only differentiate when NPM1 is in the nucleus because the protein NPM1 carries with it master transcription factor PU1, which can only transcribe the code to differentiate in the nucleus; however, when mutated, exporting protein XPO1 delocalizes NPM1 to the cytoplasm. Currently there are no successful, noninvasive drugs for AML; the most effective drug, Selinexor, results in a relapse after a couple years of treatment because XPO1 cannot continue to be inhibited by the drug. This study attempts to investigate whether resistance to Selinexor is due to altered transporting pathways because Selinexor cannot inhibit the delocalization. After this is tested, I will attempt to find an alternative treatment focused on targeting the mechanism of transport for NPM1. After Selinexor resistant NPM1 mutated AML cell line OCI3 is developed, Immuno-Fluorescent Imaging and Western Blots are used to check the localization of Pu1 and NPM1. I used Geimsa Stains and Flow Cytometry to check the state of differentiation. Two alternative drugs, ATRA and Decitabine, are tested on the resistant and control cell line to find a secondary treatment after Selinexor. I found that on the resistant cell line, NPM1 and Pu1 return to the cytoplasm and the cell cannot differentiate due to alternating transporting pathways. In addition, ATRA and Decitabine both work as effective treatments on resistant cell lines, but ATRA is the most potent. The combination of Selinexor and ATRA had never been used. It is in clinical trials now.