

Thomas Schmidt

Biology, CBS, 2009

Mentor: Dr. Gregory M Vercellotti

Department of Medicine, Division of
Hematology, Oncology, and Transplantation

Acute Promyelocytic Leukemia (APL): NB4 cells differentiated by All-trans retinoic acid (ATRA) and Arsenic Trioxide (ATO).

Acute Promyelocytic Leukemia (APL) is a myeloid derived leukemia characterized by a block of differentiation at the promyelocytic stage of development. APL is associated with a translocation involving the retinoic acid receptor-alpha (RAR-alpha, RAR α) locus and the Promyelocytic Leukemia locus (PML) forming a new fusion gene, PML/RAR α . From ancient Chinese medicine, cures have been found using all-trans retinoic acid (ATRA) and arsenic trioxide (ATO). ATRA degrades the PML/RAR fusion protein to release the differentiation block caused by the fusion protein. ATO leads to the degradation of the PML/RAR α oncoprotein, which then leads to differentiation of the cell. ATO also induces the heme-catabolising enzyme heme-oxygenase-1 (HO-1). HO-1, and its downstream products carbon monoxide and biliverdin/bilirubin have documented anti-inflammatory effects. Downstream of HO-1, the enzyme responsible for converting biliverdin to bilirubin is biliverdin reductase (BVR.) BVR also has the ability to serve as a soluble tyrosine kinase, with signal transduction functions with multiple pathways, including the MAPK kinase member ERK. This mechanism is primarily thought to occur through stimulation of protein kinase C (PKC). This provocative evidence gives rise to the possibility that HO-1 and/or BVR may be critical factors mediating ATO-induced APL treatment response. Therefore our hypothesis is that induction of HO-1 or the downstream BVR enzyme is critical for APL differentiation in response to ATO.

Using a NB4 cell line we were able to maintain a culture of APL cells, and experiments on cell differentiation were conducted. We measured differentiation by assessing the ability of the NB4 cells to produce superoxide, assessed with nitroblue tetrazolium (NBT) reduction. Untreated cells produce no superoxide while ATRA and ATO were shown to differentiate cells. ATO also induced apoptosis. A PKC stimulatory peptide enhanced cell viability and differentiation in ATO treated cells. Western blots for HO-1 revealed no induction of protein expression. We conclude that ATRA and ATO can differentiate APL cells in vitro but have differential effects on cell viability. Further work is being conducted to unravel the mechanisms of differentiation of these agents.

Poster Number: Session:

