The Role of Oxidative Stress in Chemotherapy-Resistant Human Acute Myeloid Leukemia

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Despite a high rate of complete remission after conventional front-line induction chemotherapy, the prognosis is very poor in AML. To date, the 5-year overall survival is only about 30 to 40% in patients younger than 60 years old and less than 20% in patients over 60 years (Tallman et al. 2005; Burnett et al. 2011). This is due to the high frequency of relapses (50% and 85% before and after the age of 60, respectively) caused by tumor regrowth initiated by chemoresistant leukemic clones (RLCs). Thus, chemotherapy resistance is the major therapeutic barrier in AML that is one of the malignant hemopathies for which therapy has not significantly improved during the past 30 years despite intense research efforts. Therefore, a paramount issue in the eradication of RLCs is to elucidate the molecular basis of chemoresistance. Many hypotheses have been proposed to explain therapeutic resistance (drug efflux, detoxification enzymes, poor accessibility of the drug to the leukemic niche) (3,4), but none led to a complete understanding of the molecular mechanisms of AML resistance especially in vivo nor to new therapies, which would effectively eradicate RLCs.

Contrasting with formerly held views, our previous and current works have demonstrated that while leukemic stem cells (LSCs) are rare and enriched in more immature populations, they are heterogeneous for their cell surface phenotype (Sarry et al. JCI. 2011) and their sensitivity to chemotherapies (Farge et al. Cancer Discovery. 2017). This has been addressed in vivo using patient-derived xenograft in our highly immunodeficient mouse model (NOD/LtSz-scid IL2Rγc null, NSG). More strikingly, cytarabine-resistant pre-existing and persisting cells displayed upregulated myeloperoxidase (MPO) expression and activity, high levels of reactive oxygen species and high rate of oxygen consumption.

Furthermore, this changes could be consider as a predictive for treatment response in PDX and AML patients, and HIGH MPO but not LOW MPO human AML cell lines were chemoresistant in vivo. Actually we are targeting myeloperoxidase activity in order to induce a shift towards LOW MPO and enhanced anti-leukemic effects of cytarabine.

Along with this line, our preliminary data have thus shown that high MPO activity are related to cytarabine resistance in AML and manipulating MPO activity or MPO expression can have clinical benefits. Based on our current work (Hosseini et al. In preparation), inhibition of MPO activity by 4-Aminobenzoic hydrazide induced rapid and profound changes in respond to Arac. This strongly alters redox homeostasis and mitochondrial functions (pro/anti-oxidant pathways, ROS production, oxygen consumption, oxidative phosphorylation) leading to a rapid cell death of AML cells.

Based on the above-mentioned results, our working hypothesis is that inhibition of MPO activity sensitizes to cytarabine in AML in vitro and in vivo as a promising therapeutic avenue to overcome patient relapses.
Literature/ Key References


