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Insulin/IGF1 Pathway Inhibition in Combination with All-Trans Retinoic Acid in Acute Promyelocytic Leukemia

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Abstract

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Chemotherapy-free regimens are now a realistic goal in Acute Promyelocytic Leukemia (APL), as demonstrated by recent studies combining All-Trans Retinoic Acid (ATRA) with Arsenic Trioxide and Gemtuzumab Ozogamicin. Combinations of ATRA with kinase inhibitors, which have shown tremendous efficacy in several malignancies, are interesting alternatives but remain poorly characterized in APL. The Insulin-like growth factor 1 (IGF1) pathway is an attractive drug target because of its pervasive involvement in cell proliferation and metabolism of cancer cells. A variety of strategies to target the Insulin/IGF1 axis have been developed, but trials have struggled to demonstrate real efficacy over standard treatments, probably due to our still incomplete understanding of the intricacies of the downstream signalling cascade. Importantly, recent evidence suggests that inhibition of the sole IGF1 receptor may be inadequate because the structurally similar insulin receptor (IR) or IGF1R/IR heterodimeric receptors may be sufficient to support tumour growth.

We dissected the IGF1R/IR pathway in the well established APL cell line NB4. IGF1 and insulin, but not the structurally similar IGF1R ligand IGF2, significantly increased NB4 growth in serum-free medium. ATRA treatment resulted in the downregulation, at both transcript and protein level, of several components of the proximal IR/IGF1R pathway: IGF1R (down by 64,9 ±1,7%), IR (down by 82,5 ±4,9%), the transducer proteins insulin receptor substrate 1 (IRS1) (down by 85,7 %) and IRS2 insulin receptor

IRS2) by 98,1% (+/– 0,8). However, the downstream cascade remained ligand-responsive: stimulation of serum-starved cells with IGF1 induced a dose-dependent phosphorylation of AKT, FOXO, the mTOR target ribosomal protein S6 and ERK1-2. In addition, baseline levels of phospho-ERK were elevated after ATRA treatment. This suggested that ATRA-treated cells may increase their dependence on IGF1R for their survival. In agreement with this model, NB4 cell growth was completely inhibited by the anti-IGF1R antibody aIR3, but concomitant treatment with ATRA halved the half-maximal dose (IC50) of aIR3 to 1 ug/ml and promoted apoptosis (as assessed by flow cytometry). To identify IGF1R-targeting compounds with higher efficacy we screened novel small molecule inhibitors and found that the imidazopyrazine-derivative OSI-906 stopped NB4 cell growth with an IC50 of 1.5 μM in IGF1-supplemented serum-free medium. This compound is an orally available dual IR/IGF1R inhibitor, currently on trial for several solid tumours.

In conclusion, we show that the Insulin/IGF1 signalling pathway is modulated at different levels by ATRA in APL cell lines and that this pathway represents a suitable and attractive drug target in combination with ATRA treatment. On the basis of data presented here we are currently testing the in vivo efficacy of ATRA/OSI906 combinations in *in vivo* models of APL.

Disclosures:

Off Label Use: Linsitinib (OSI-906) is a potent, selective orally active inhibitor of the insulin-like growth factor-1 receptor (IGF-1R).

Author notes

* Asterisk with author names denotes non-ASH members.