Pharmacological IGF1R/IRS signaling inhibition reduces cell viability in acute lymphoblastic leukemia cells

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BACKGROUND: Acute lymphoblastic leukemia (ALL) is a neoplasm of lymphoid precursors that present deregulation in PI3K/Akt/mTOR and MAPK pathways. The IGF1/IGF1R signaling pathway is initiated through binding of the ligand (IGF1) to its transmembrane receptor (IGF1R), and subsequent activation of IRS1 and IRS2 proteins, which transmit mitogenic and antiapoptotic signals, modulating PI3K/Akt/mTOR and MAPK pathways. However, IGF1R/IRS signaling is still little explored in ALL. **AIM:** We herein aimed to investigate the effects of the pharmacological IRS1/2 (NT157) and IGF1R/IR (OSI-906) inhibition in ALL cells. **METHODS:** Jurkat, Molt-4, Namalwa and Raji cell lines, and ALL primary cells (n=2) were treated or not with NT157 or OSI-906, and evaluated for cell viability (MTT), clonogenicity (colony formation), apoptosis (annexin-V/PI and caspases cleavage), protein expression/activation (Western blot) and PCR-array for MAPK signaling. Statistical analyses were performed by ANOVA test. **RESULTS:** In ALL cell lines, NT157 decreased cell viability and clonogenicity, and increased apoptosis in a dose and time-dependent manner (all $p<0.05$). NT157 treatment induced IRS1 downregulation in a dose-dependent manner. More importantly, in primary ALL cells, NT157 reduced cell viability and was a potent apoptosis inductor. OSI-906 treatment reduced cell viability, but did not induce apoptosis in ALL cell lines. In primary cells, OSI-906 did not modulate cell viability and apoptosis. PCR-array reveals that NT157 modulates 25 genes, including downregulation of c-MYC (proliferation-related genes) and upregulation of CDKN1A, CDKN1C, CDKN2A and CDKN2B (cell cycle arrest-related genes). **CONCLUSION:** Pharmacological inhibition of IRS1/2, by NT157, exerts a cytotoxic effect in ALL cell lines and primary ALL cells, while IGF1R/IR inhibition, by OSI-906, has a predominant cytostatic effect. These data indicate that direct inhibition of IRS proteins by NT157 results in a better anti-leukemia effects, and targeting IRS proteins may be an effective anti-ALL approach.

Key words: Acute lymphoblastic leukemia; IGF1R/IRS; NT157
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