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Implications and Potential Therapeutic Targeting of Insulin-Like Growth Factor Type 1 Receptor (IGF-IR) in Adulthood Acute Lymphoblastic Leukemia

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Abstract: Background: A greater understanding of the pathogenesis of malignancy has led to the development of novel therapies designed to target aberrant molecular pathways that characterize and distinguish cancer cells from normal tissue. Small molecules are being designed to interfere with specific steps along the deregulated signaling cascade from the cytoplasmic membrane to the nucleus. Viable targets include growth factor receptors and their downstream second messengers, modulators of the cell cycle or apoptosis, regulators of protein trafficking and degradation and transcription regulators. Many reviews had discussed the small molecule signal transduction inhibitors in various stages of development and address the strategic issues relating to clinical trial design with these novel targeted agents. *Aim of Work:* To verify the Insulin-Like Growth Factor Type 1 Receptor (IGF-IR) and its impact on proliferation of lymphoblasts in Adulthood Acute Lymphoblastic leukemia (ALL). Bone marrow samples from 30 patients with ALL were examined along with 10 healthy donors as controls, a quantitative real time reverse transcriptase polymerase chain reaction (Real time R.T PCR) used to evaluate the concentration of (IGF-IR) correlated with the blast concentration in marrow samples. In our assay (IGF-IR) appeared to have higher to lower expression rate in turn from ALL (27.897) if compared with normal controls (37.883) ($p<0.01$). This work was carried out to prive the effect of IGF-IR on hematopoie- tic cells in ALL and its relation to the diseases progress. *Patients and Methods:* The expression of IGF-IR was analyzed in 30 patients with ALL, The patient work over a 3 month's period from February 2008 to May 2008. They were 18 males and 12 females with a male to females' ratio 1.5: 1.0. Their ages ranged from 12 - 51 years. All patients were diagnosed as ALL by the routine diagnosis in Egypt national cancer institute with 10 normal age and sex matched healthy controls using a Real-Time Quantitative Reverse- Transcriptase Polymerase Chain Reaction (qRT-PCR) to assess the possible relation, association or correlation between IGF-IR expression and ALL clinical and laboratory features at diagnosis. *Results:* IGF-IR was expressed in all 30 patients with ALL; the expression levels of IGF-IR was significantly higher in newly diagnosed patients than in patients in complete remission (CR) and controls ($p<0.001$). There were statistically significant differences in the expression of IGF-IR between patients with blast concentration. Conclusion: IGF-1R seems to play a crucial role in patients with Adulthood and over expression of (IGF-IR) existed in hematopoietic cells in ALL marrows which appeared to be contributed to disease progress. 1- Over expression of (IGF-IR) existed in hematopoietic cells in ALL marrows which appeared to be contributed to disease progress. 2- Over expressed in our patient. 3- Over express contributed to disease progress.

Key words: IGF-IR · Adult ALL · RT- PCRT · Prognosis

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INTRODUCTION

Insulin-like growth factor-1 (IGF) and its receptor (IGF-1R) play an important role in mitogenesis, apoptosis, growth and proliferation of several types of cancers. Overexpression of IGF-1R in many cancers is associated with increase of cancer cell proliferation and migration as well as inhibition of apoptosis and the correlations between IGF-1R and apoptosis were demonstrated in previous reports. Results may suggest that the insulin-like growth factor system is involved in regulation of apoptosis in many cancer cells [1, 2].

Insulin-like growth factor type 1 receptor (IGF-1R) plays critical roles in cancer cell development, proliferation, motility and survival and new therapeutic agents targeting IGF-1R are in development. Many studies was undertaken to determine the effects of anti-IGF-1R therapeutic targeting on cell signaling and cancer cell phenotypes in different cell carcinomas. The therapeutic efficacy of the human anti-IGF-1R antibody was tested in many cell lines and in tumor xenografts and IGF-1R was overexpressed in human cancer cell lines and tumors. It was observed the overexpression of IGF-1R and the effective therapeutic targeting of the receptor in human cancer xenografts [3,4].

It was demonstrated that IGF-1 mediates the sustained phosphorylation of PI3K, which is essential for long term survival and protection of progenitors from glutamate toxicity [5]. These prosurvival effects correlated with prolonged activation and stability of the IGF-1R. It was investigated, in many studies, the mechanisms whereby IGF-1 signaling, through the IGF-1R, mediates the sustained phosphorylation of PI3K [5].

As cancer cell proliferation can be abrogated by blocking mRNA or protein products of the IGF genes, tumors with extensive involvement of the IGF pathway would be candidates for the therapeutics strategies aimed at interference with this pathway [6].

Several type-1 membrane proteins undergo regulated intramembrane proteolysis resulting in the generation of biologically active protein fragments. It was found that IGF-1R undergoes regulated intramembrane proteolysis, a metalloprotease-dependant ectodomain-shedding event generates an approximately 52 kDa IGF-1R-carboxyl terminal domain (CTD) [7]. he IGF-1R-CTD is consequentially a substrate for gamma-secretase cleavage, liberating an approximately 50 kDa intracellular domain (ICD) that can be inhibited by a specific gamma-secretase inhibitor [7]. Studies suggest that the IGF-1R is a substrate for gamma-secretase and may mediate a function independent of its role as a receptor tyrosine kinase [7].

The IGF-1R is overexpressed in many tumors including hematological cancers. It is a critical signaling molecule for tumor cell proliferation and survival. In many studies, IGF-1R expression was down-regulated by antisense oligonucleotides to evaluate their specific effects on growth of cancer cells *in vitro* and *in vivo.* Data suggest that IGF-1R antibodies can effectively and specifically inhibit cancer cell growth *in vitro* and *in vivo*. Blockage of IGF-1R expression could be a promising therapeutic approach for the management of patients with cancers [8].

The IGF-1R mitogenic signaling mediates malignant cell survival by many complex and redundant pathways. Many studies compared the effects of IGF-1R inhibition on viability and apoptosis of human cell lines, using different methods for the impairment of IGF-1R function [9].

A lot of studies have found that down-regulation of IGF-1R could reverse the neoplastic phenotype and sensitize malignant cells to antitumor agents [10 - 20].

In this study, we analyzed the expression level of type 1 insulin like growth factor receptor in 30 patients with acute lymphoblastic leukemia (ALL), adult type, with 10 normal healthy age matched controls, using a Quantitative Real Time Reverse Transcriptase Polymerase Chain Reaction qRT-PCR technique with a specific aim of determining their role in the development and progression of ALL.

MATERIAL AND METHODS

Patients: The study included 30 patients with adult ALL and 10 normal age and sex matched controls. Patients were recruited from the National Cancer Institute (NCI), Cairo University. The diagnosis of ALL was made based on the morphology from Geimsa stained smears of bone marrow (BM) aspirates, cytochemical stains criteria such as: Negativity for myeloperoxidase (MPO) and Sudan black B (SBB) and a positivity for acid phosphatase for (T-ALL) and immunophenotyping.

The study included 18 males and 12 female, with a males to females ratio 1.5 to 1.0. their ages ranged from 12 - 51 years. The qRT- PCR was used to assess the expression rates and levels of IGF-IR and to investigate a

possible relation, association, or correlation with the clinical features of ALL patients at diagnosis such as: Sex, age, lineage (B or T), hemoglobin (HB), TLC, platelets count and BM blast cell infiltration.

RNA Isolation and Real-Time qRT-PCR: Mononuclear cells (MNCs) were isolated from 2ml BM aspirate which separated by Ficoll density gradient centrifugation. Total RNA was extracted from MNCs using a QIAamp RNA blood kit (Qiagen, Germany) according to manufactures criteria. Complementary DNA (cDNA) was synthesized using (dt) 15-mer primer by superscript III Reverse transcriptase and stored at -20°C till use.

The mRNA expression levels of type I insulin like growth factor receptor (IGF-IR) and glyceralde-hydes-3-phosphate dehyrogenase (GAPDH) were measured by qRT- PCR using an ABI PRISM 7000 Sequence Detector System (Applied Biosystems, Foster City, CA), using gene expression reagent which divided in to two steps, first step reagent (synthesizing cDNA from total RNA using high capacity cDNA archive kit) (PN:4322171) containing RT Buffer, dNTP'S mix, random hexamers and RT enzyme, second step reagent (PN:4352533) Taq Man Gene Expression Assay 20X.The qRT-PCR amplification was performed using the predeveloped Assays-on-demand Gene Expression Set for the IGF-IR and Taq Man GAPDH control reagents (Ap-plied Biosystems) for the GAPDH gene (Specific primers) in combination with the Taq Man Universal PCR Master Mix (Applied Bio systems). The sequences of the primers: IGF IR forward (5' AGGCTGAATACCGCA AAGTC 3'), reverse (5' GTGAAA GGCCGAAGGTTAGA 3'); GAPDH forward (5' GTCCATGCCATCACT GCCAC 3'), reverse (5' ATGACCT TGCCCACAGCCTT 3').

All reactions were performed in triplicate using 20µl samples containing 50ng cDNA. The reaction protocol used involved heating for 2 minutes at 50°C and 10 minutes at 95°C, followed by 40 cycles of amplification (15 seconds at 95°C and 1 minute at 60°C). Analysis was performed using ABI PRISM 7000 Sequence Detection Software (Applied Bio systems).

The expression levels of IGF-IR gene in all tested samples and healthy controls were expressed in the form of CT (cycle threshold) level. A negative control without template was included in each experiment.

The expression rates of IGF-IR were recorded as a percentage (%) of patients with IGF-IR expression among total patients regardless of the expression level and the expression levels were represented as the mean values ± SD. Results were considered significant at $p<0.01$.

RESULTS

Clinical Characteristics of Adult ALL Patients: There were 30 adult patients, 18 males and 12 females. The following table appear general data and blast concentration percent of adult ALL, Table (1).

In this study 100 % of Adult ALL are newly diagnosed, The mean age 28.4±1.92 years, the mean TLC was 73.9±38x/L, the mean Hb was 7.9±2gm/dl, the mean platelet count was 55±29x/L, the mean BM blast concentration was 71.5±3.9%.

There was a higher IGF-IR expression rate in Adult ALL marrows than that in normal controls.

The expression levels of IGF-IR were higher in newly diagnosed ALL patients adulthood than patients in controls ($p<0.001$), this appear when act correlations between ALL patients adulthood with normal control patients with Use t Test for estimation of Significant or nonsignificant appear (ts = 14.08) in (P 0.05 = 1.684) highly significant and in (P 0.01= 2.423) highly significant, Fig. (1).

Relationship Between IGF-IR Expression and Blast Concentration: Nucleated IGF-IR positive cell number in Adult ALL marrows showed a positive correlation to their lymphoblast count (r= 0.667; P 0.01), (F. value = 154.254), The mean expression level of IGF-IR was 28.4156±0.598 for newly diagnosed adulthood cases compared to 71.5 ±3.909 in case blast concentration, which showed positive correlation, (i.e.) when increase the yield of gene expression depend on the increase of blast concentration, Table (2), Curve (1).

Relationship Between Blast Concentration and Age: Relationship between blast concentrations with age of patients appear negative correlation, mean ± SD (71.5 ± 3.909) in case blast concentration, while it is (28.43± 1.92) in case age, which showed negative correlation, (i.e) the blast concentration increased in small old than adult and show strong relations- hip between this items. (r= 0.158; P 0.01), (F. value = 39.499) highly significant, Table (2), Curve (2).

There were no statistically significant differences in the expression levels of IGF-IR between patients with

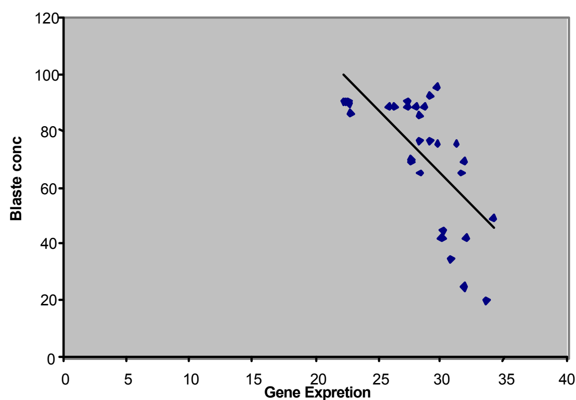
Table 1: General data and blast concentration of Adult ALL Patients.

Code	Housekeep-ping genes (GAPDH)	Geneexpression (IGF-IR)	Δct	Blast Conc. %	Age
1	20.171	22.441	2.27	90	24
2	28.173	33.682	5.509	20	18
3	19.371	30.113	10.742	42	18
4	23.192	34.191	10.999	49	24
5	24.677	29.127	4.45	76	19
6	18.633	28.687	10.054	88	14
7	21.506	28.403	6.894	65	22
8	32.332	31.287	-1.045	75	23
9	25.755	28.021	2.266	88	27
10	23.362	32.101	8.739	42	19
11	34.191	31.912	-2.278	69	35
12	23.187	29.181	5.994	92	24
13	21.651	29.773	8.122	75	29
14	23.344	31.887	8.543	25	24
15	20.481	30.145	9.664	45	18
16	22.249	27.364	5.115	90	40
17	24.212	25.826	1.614	88	51
18	21.135	22.641	1.506	90	30
19	24.245	28.291	4.046	85	28
20	28.952	29.693	0.741	95	23
21	31.299	30.873	-0.426	35	50
22	23.069	31.652	8.583	65	45
23	20.139	28.283	8.144	76	18
24	25.881	27.627	1.746	70	19
25	20.278	22.834	2.556	86	23
26	22.249	27.386	5.137	88	19
27	24.212	26.361	2.149	88	40
28	21.237	22.731	1.494	89	50
29	25.872	27.627	1.755	69	35
30	20.183	22.328	2.145	90	38

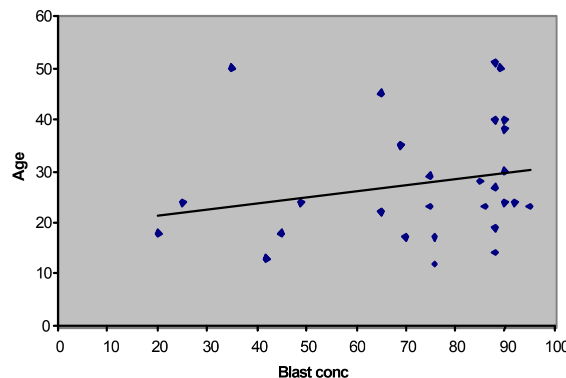
NB: ΔCT = CT1 Target gene Gene expression (IGF-IR) _ CT2 Normalizing gene housekeeping genes (GAPDH)

Table 2: Statistical data for Adult ALL Patients and Normal patients.

	Adult ALL. Patients				Normal Patients	
	Housekeeping genes (GAPDH)	Geneexpression (IGF-IR)	Blast conc.	Age	Housekeeping genes (GAPDH)	Geneexpression (IGF-IR)
Sum	715.238	852.468	2145	853	278.628	378.832
Mean	23.84126667	28.4156	71.5	28.4333	27.862	37.8832
Σ(X)2	17453.703	24441.932	164528	27489	7770.018	14363.685
Variance	14.677	10.97632694	471.0862069	111.56	0.74	1.368
S.Deviation	3.831	3.277	21.413	10.56	0.86	1.169
S. Error	0.699	0.598	3.909	1.92	0.272	0.369
C.F	17028.061	24130.503	151230	24253.63	7763.356	14351.368
S.S	425.642	311.4288	13298	3235.37	6.662	12.31
Max	34.191	34.191	95	51	29.296	39.832
Min	18.633	22.328	20	18	26.797	36.434
Range	18.633 - 33.688	22.328 - 33.719	25 - 95	18 - 51	26.797 - 29.296	36.434 - 39.832
Count	30	30	30	30	10	10



Curve 1: Correlation between IGF-IR expression and blast concentration.



Curve 2: Correlation between blast concentrations and age.

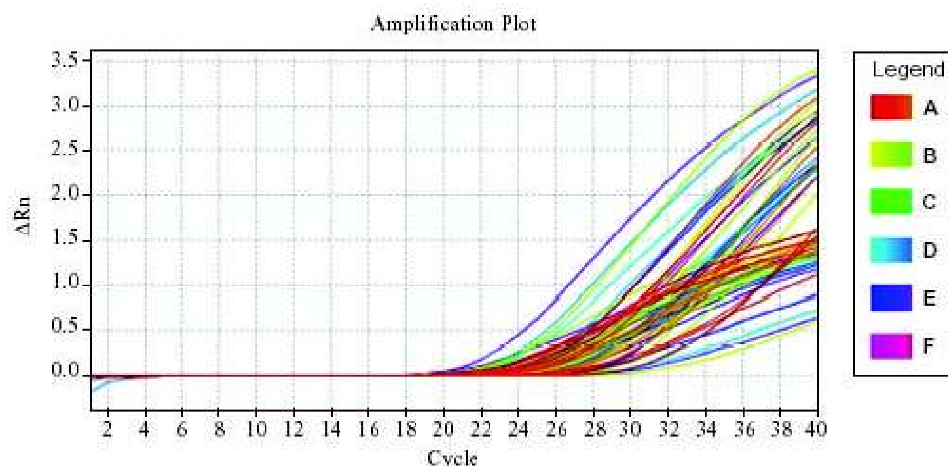


Fig. 1: Curve of IGF-IR gene in ALL cases and control by RT-PC.

different clinical and laboratory features including sex, age, lineage, hemoglobin, TLC, platelets and BM blast concentration (p>0.05).

DISCUSSION

Although IGFs might not be considered classical hematopoietic growth factors, some reports have shown that IGFs played a crucial role in the process of erythropoiesis, mye- lopoiesis and lymphopoiesis and regulated the proliferation and differentiation of hematopoietic cells via the IGF-IR [21]. Our study shows that nucleated cells in normal marrow expressed a relatively low level of IGF-IR, which suggested that IGF-IR participated in hematopoietic regul- ation under physiological conditions. ALL marrow cells cases, IGF-IR expression was higher in advanced than that in less advanced subgroup, which was further identified by real-time quantitative RT-PCR in this assay. Finally, the most compelling discovery was that the IGF-IR positive rate among nucleated cells in ALL marrow showed an evident positive correlation to their lympho- blast numbers. All of these indirect indices pointed to the consideration that IGFIR overexpression predicts malignant proliferation in hematopoi-etic cells, which harbinges transform- ation from MDS to AML. This viewpoint could be supported by some previous research, which showed low-level expression of IGF-IR in normal hematopoietic progenitor cells [22], but increased expression in malignant cells [21].

In other words, the cells expressing IGF-IR excessively perhaps represent malignant clone-original hematopoi- etic cells in MDS. Some previous reports considered that IGF-IR overexpression was commonly found in lymphocytic leukemia, seldom in myeloid leukemia [23, 24].

Otherwise, a few researches including our previous paper [25-27] showed that high IGF-IR expression could also be found in AML cases. In this assay, all the bone marrows from ALL contained > 50% of lymphoblast (even

>90% in some cases). So it is impossible that so many IGF-IR positive cells (mean 71.5%) came from lymphocytes or some other cells. It should be believable that IGF-IR overexpression works during occurrence and development in lymphoblastic leukemia.

Otherwise Several studies indicate that blocking IGF-1R expression can inhibit tumour cell proliferation and metastasis [28].

In this study, the expression level of type 1 insulin like growth factor receptor (IGF-IR) was analyzed in 30 patients with ALL Adulthood with 10 normal age matched healthy controls.

IGF-IR was expressed in all 30 patients with ALL adulthood. The expression levels of IGF-IR were higher in newly diagnosed ALL patients than in controls. Also, there were no statistically significant differences between ALL patients adulthood regarding gender, age, lineage, hemoglobin, TLC, platelets and BM blast infiltration.

Several studies have shown that high concentrations of serum IGFs and/or lower levels of IGFBPs are associated with increased risk for several cancers [29-37].

In 2008 Whelan *et al*. [38] mentioned the homeobox (Hox) gene family, which encodes a group of transcription factors that are preferentially expressed during embryonic development and hematopoiesis and are commonly deregulated in acute lymphoblastic leukemia (ALL). They studied whether HoxA9 gene can induce IGF-IR expression in B-lineage ALL or not. They found that HoxA9 over expression induces IGF-1R expression and subsequently promotes leukemic cell growth. As for IGF-I, their results suggest that HoxA9 may not regulate the expression of IGF-1, but this growth factor is expressed by both the leukemic cells and the supporting stromal cells [38].

IGF-1R expression has been reported in AML blasts and IGF-1 is capable of stimulating 242 AML cell proliferation. Several studies have indicated that inhibition of IGF-1R signaling results in a reduction of cell proliferation and induction of apoptosis, particularly in AML [39,40].

In 2007, Ciampolillo *et al*. [41] demonstrated that IGF-IR is involved in the pathogenesis of a variety of human neoplasia via the mitogenic and anti-apoptotic properties of its cognate receptor.

Several lines of evidence suggest a role for IGF-1 and IGF-1R in leukemia. High levels of serum IGF-1 correlate with childhood leukemia and high birth weight [42]. Signaling via IGF-1/IGF-1R interactions has been shown to participate in the growth and survival of multiple myeloma cells [43,44].

We conclude IGF-1R seems to play a crucial role in patients with ALL. Since, all cases of ALL patients expressed IGF-1R and that the IGF-1R level is higher in newly diagnosed cases than in controls. Therefore, new therapeutic agents targeting IGF-1R may provide a better chance for those patients. However, Over expression of (IGF-IR) existed in hematopoietic cells in ALL marrows which appeared to be contributed to disease progress, Over expressed in our patient and Over express contributed to disease progress.

And I want to recommended to point out the following important points.

1- The long study to confirm this study by increasing the number of patients and increasing the number of correlations related with them. 2-Using various analyses and more correlations to involve this point at a large scale. 3-The importance of the topic and paying the attention for it from other researchers specially immunology researchers and 4- Can anti- IGF-IR therapy be theoretically apoptosis-promoting and hence therapeutic?

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