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EFFECT OF A20 ON GLUCOSE DEPENDENT CELL MIGRATION IN ACUTE LYMPHOBLASTIC LEUKEMIA

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SUMMARY

Acute lymphoblastic leukemia (ALL) is the most common pediatric hematologic malignancy characterized by aberrant proliferation of immature lymphoid cells. A20 is a deubiquitinase gene that inhibits functional activation of immune cells mediated through nuclear factor κB (NFκB)/signal transducers and activators of transcription (STAT) pathways. A20 is frequently inactivated in leukemia/lymphoma. Little is known about the involvement between A20 and STAT signalling in regulating the function of ALL blasts. The present study, therefore, explored whether migration and apoptosis of peripheral blood mononuclear cells (PBMCs) and ALL blasts in high glucose conditions is regulated by A20. To this end, ALL blasts from blood samples of fifteen patients and PBMCs from healthy individuals in the absence of A20 were examined. Gene expression profile was determined by quantitative RT-PCR, cell apoptosis by flow cytometry, and cell migration by a transwell migration assay. As a result, the expression of A20 was inactivated in ALL blasts. Cell migration, but not apoptosis of ALL-blasts was enhanced when the cells were exposed to high glucose and dependent on A20 expression, the effects were abolished by using Nifuroxazide, a STAT inhibitor. In conclusion, A20 inhibited glucose-induced migration of ALL blasts through the STAT pathway. The effect might contribute to poorer survival of ALL patients, who develop hyperglycemia during therapy.

Keywords: *Acute lymphoblastic leukemia, A20, apoptosis, migration, PBMCs.*

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common pediatric hematologic malignancy defined by clonal expansion of lymphocytic population with arrested maturation in the blood and bone marrow (Chen *et al.*, 2007; Troeger *et al.*, 2008). Despite notable improvements in the long-term survival rate, about 10% to 15% of patients develop the relapsed ALL due to drug resistance or toxicity (Uderzo *et al.*, 2001). ALL blast cells are characterized by hyper-activation of intracellular signalling pathways including signal transducers and activators of transcription (STATs) (Furqan *et al.*, 2013; Irving, 2016; Tovar *et al.*, 2016) that regulate cellular physiological processes such as growth, migration, and cell survival. Therefore, the STAT inhibitor Nifuroxazide is used to exert anti-tumor immunity and anti-metastasis activity in multiple cancers including ALL (Zhu *et al.*, 2016; Ye *et al.*, 2017).

ALL treatment induces metabolic abnormalities, such as impaired glucose tolerance and diabetes (Barbosa-Cortes *et al.*, 2017). Hyperglycemia is common with ALL therapy within the first phase of chemotherapy (Tsai *et al.*, 2015) and the patients with hyperglycemia are associated with risk of infection and poorer survival (Dare *et al.*, 2013). Glucose is an energy-rich molecule and cells use glucose to generate ATP through glycolysis and oxidative phosphorylation. In contrast to normal cells, cancer cells exhibit elevated levels of glucose consumption and produce excessive lactic acid by glycolysis even in aerobic conditions (Warburg, 1956). Therefore, a glucose starvation medium inhibits cancer cell growth and viability through activated AMPK pathway and inactivated mTOR signalling (El Mjiyad *et al.*, 2011).

Abnormal activation of functional genes involved in the development and pathogenesis of cancers have been extensively indicated in multiple studies. A recent study indicated that inactivated expression of A20 results from genetic aberrations including gene deletions and/or mutations linked to hematologic malignancies (Kato *et al.*, 2009). A20 is considered as a negative regulator of the inflammatory response and cell migration mediated through activation of nuclear factor (NF)-κB signalling (Kato *et al.*, 2009). A20-deficient mice display severe inflammation, cachexia and premature mortality (Lee *et al.*, 2000).

Although A20 loss has been identified in many cancers, little is known regarding its role in the regulation of migration and apoptosis of leukemic blasts in high glucose conditions. The present study has thus been performed to elucidate whether A20 participates in modulating the physiological processes of leukemic cells. To this end, A20 gene expression, migration, and apoptosis of ALL blasts and A20-silenced PBMCs were investigated.

MATERIALS AND METHODS

Patients and control subjects

Fresh peripheral blood samples were collected from untreated 15 patients aged from 20–45 years, who were diagnosed with ALL based on cytomorphology and cytochemistry according to the WHO (Harris *et al.*, 2000) classification, at the 103 Hospital, Military Medical University, Hanoi, Vietnam. The control group comprised 16 healthy subjects. No individuals in the control population took any medication or suffered from any known acute or chronic disease. All patients and volunteers gave a written consent to participate in the study. Person care and experimental procedures were performed according to the Vietnamese law for the welfare of humans and were approved by the Ethical Committee of Institute of Genome Research, Vietnam Academy of Science and Technology.

Isolation of peripheral blood mononuclear cells (PBMCs) and leukemic blasts

PBMCs from whole blood samples of healthy donors and leukemic cells from ALL patients were collected by venipuncture and transferred to sterile tubes containing EDTA as an anticoagulant. The cells were isolated via density gradient centrifugation (Ficoll-Paque Plus, GE Healthcare Life Sciences) using Hank's buffer (Gibco). Freshly isolated PBMCs and leukemic cells were obtained by centrifuging at 400 g for 30 min at room temperature. The cells were counted in a Neubauer chamber and washed with PBS, the final cell pellet was resuspended in RPMI 1640 medium (Gibco) with 10% FBS, L-glutamine (Gibco), Antibiotic-Antimycotic Solution (Sigma), and MEM NEAA (Gibco) at a density of 2×10^6 cells/ml and cultured for 48 h. The cells were treated with *Escherichia coli* lipopolysaccharide, which is used as a positive control for physiological activation of PBMCs (LPS, 500 ng/ml, Sigma-Aldrich) or high glucose (30 mM, Sigma Aldrich) in the presence or absence of Nifuroxazide (10 µM, Sigma-Aldrich).

Transfection of PBMCs with siRNA

Human *A20*-targeted and control siRNAs (pre-designed siRNA, Thermo Scientific) were transfected into PBMCs (2 x 10^6 cells/1ml) with the help of Lipofectamine RNAiMAX Reagent (Invitrogen) according to the manufacturer's recommendations. Cells were incubated for 24 h at 37ºC, 5% CO_2. After washing three times with PBS, the cells were used for further experiments.

RNA extraction and real-time RT-PCR

Total mRNA was isolated using the Qiashredder and RNeasy Mini Kit from Qiagen according to the manufacturer's instructions. For cDNA first-strand synthesis, 1 µg of total RNA in 12.5 µL DEPC-H_2O was mixed with 1 µL of oligo-dT primer (500 µg/mL, Invitrogen) and heated for 2 min at 70°C. To determine the transcript level of A20, the quantitative real-time PCR with the LightCycler System (Roche Diagnostics) was applied. The following primers were used: A20 primers: 5'-TCCTCAGGCTTTGTATTTGA-3' (forward) and 5'- TGTGTATCGGTGCATGGTTTT-3' (reverse) and GAPDH primers: 5'-GGAGCGAGATCCCTCCAAA-3' (forward) and 5'-GGCTGTTGTCATACTTCTCAT-3' (reverse). PCR reactions were performed in a final volume of 20 µL containing 2 µL cDNA, 2.4 µL $MgCl_2$ (3 µM), 1 µL primer mix (0.5 µM of both primers), 2 µL cDNA Master SYBR Green I mix (Roche Molecular Biochemicals), and 12.6 µL DEPC-treated water. The target DNA was amplified during 40 cycles of 95ºC for 10 s, 62ºC for 10 s, and 72ºC for 16 s, each with a temperature transition rate of 20ºC/s, a secondary target temperature of 50ºC, and a step size of 0.5ºC. Melting curve analysis was performed at 95ºC, 0 s; 60ºC, 10 s; 95ºC, 0 s to determine the melting temperature of primer dimers and the specific PCR products. The ratio between the respective gene and corresponding GAPDH was calculated per sample according to the $\Delta\Delta$ cycle threshold method.

Migration assay

PBMCs and ALL blasts were washed twice with PBS and suspended in RPMI 1640 medium. Migration was assessed in triplicate in a multiwell chamber with a pore diameter size of 3 µm (BD Falcon). The cell suspension (2 x 10^6 cells/ml) was placed in the upper chamber to migrate into the lower chamber in which either CXCL12 (200 ng/ml, PeproTech) or medium alone as a control for spontaneous migration were included. The chamber was placed in a 5% CO_2, 37°C incubator for 24 h. The cells that migrated into the lower chamber were collected and counted under a light microscope using Trypan blue. The mean number of spontaneously migrated cells were subtracted from the total number of migrated cell and migration was considered by calculating the percentage of migrating cell related to the input.

Caspase 3 activity assay

Caspase 3 activity was determined using the caspase-3 activity assay kit from Biovision according to the manufacturer's instructions. Briefly, 5x10^6 cells were washed twice with cold PBS, fixed and permeabilized with 'Cytofix/Cytoperm' solution, and then by washing twice with 'Perm/ Wash' buffer. Then the cells were stained with FITC conjugated anti-active caspase 3 antibody in 'Perm/ Wash' buffer for 60 min. After 2 washing steps, the cells were analyzed by flow cytometry. The caspase 3-positive cells were considered as apoptotic cells.

Phosphatidylserine translocation

Apoptotic cell membrane scrambling was evidenced from annexin V binding to phosphatidylserine (PS) at the cell surface. The percentage of PS-translocating cells was evaluated by staining with FITC-conjugated Annexin V. In brief, 2 x10^6 cells were harvested and washed twice with annexin washing buffer (AWB, 10 mM Hepes/NaOH, pH 7.4, 140 mM NaCl, 5 mM $CaCl_2$). The cell pellet was resuspended in 100 µL of annexin-V-Fluos labelling solution (Roche) (20µl Annexin-V-Fluos labelling reagent in 1 ml AWB), incubated for 15 min at room temperature. After washing with AWB, they were analyzed by flow cytometry.

Statistics

Data are provided as means ± SEM, *n* represents the number of independent experiments. Differences were tested for significance using Student's unpaired two-tailed *t*-test or ANOVA, as appropriate. *P*<0.05 was considered statistically significant.

RESULTS AND DISCUSSION

Attenuated expression of A20 is reported in several lymphomas (Kato *et al.*, 2009). Firstly, we conducted experiments to ask whether the level of A20 is down-regulated in ALL patients. As expected, inactivation of A20 was observed in ALL patients (Figure 1). Moreover, A20 is considered as an inhibitor of migration through STAT signaling (Kato *et al.*, 2009), therefore, we performed transfection experiments using control or *A20* siRNA to block A20 expression and Nifuroxazide to inhibit expression of STAT activation. As shown in Figure 2, LPS treatment leads to increased migration of PBMCs and A20-silenced PBMCs in a greater number compared to control siRNA-treated PBMCs and the effect was abolished in the presence of Nifuroxazide. The evidence suggested that A20 sensitive migration in PBMCs was dependent on STAT signalling.

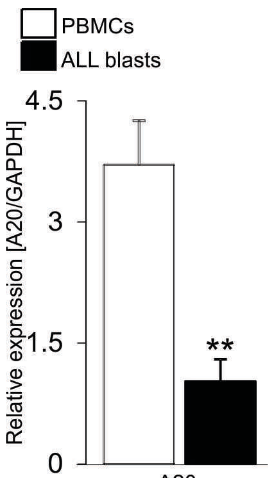

Figure 1. A20 expression in ALL patients. Arithmetic means ± SEM (n = 15) of the transcript level of A20 expression in control and patient groups. GAPDH was used as a reference gene for relative quantification. ** (p<0.01) indicates significant difference from control (*T*-test).

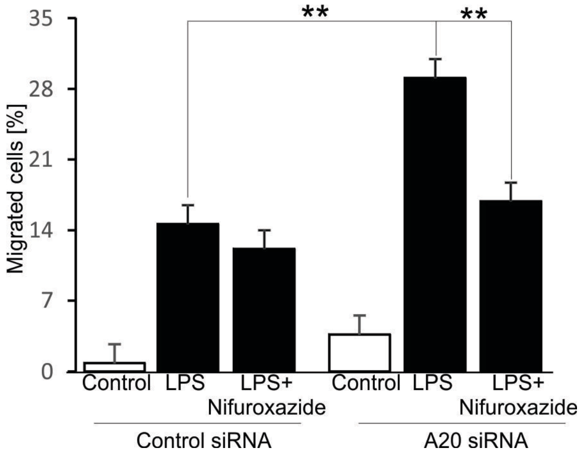

Figure 2. Effect of A20 on the migration of PBMCs. A. Arithmetic means ± SEM (n = 6) of percentages of migrated PBMCs, which were treated with control siRNA or A20 siRNA and followed by stimulating with LPS (500 ng/ml) in the presence or absence of Nifuroxazide (10µM). ** (p<0.01) indicates significant difference from LPS-stimulated PBMCs (ANOVA*)*.

Unlikely to PBMCs, LPS did not induce migration of ALL blast (data not shown). Cancer cells including leukemic blasts use glucose to produce a severely elevated level of lactic acid by switching the oxidative pathway to the glycolytic pathway even in the presence of oxygen, whereas in normal cells glucose generates lactate in anaerobic conditions (Warburg, 1956). Accumulation of lactic acid is associated with poor prognosis of ALL (Sayyed *et al.*, 2018), and hyperglycemia is found in about 10% ALL patients during chemotherapy treatment, who are associated with risk of infection and poorer survival (Panigrahi *et al.*, 2016). In this study, we used high glucose to stimulate this activation in the blasts. Treatment of high glucose significantly increased migration of the blasts compared to that of PBMCs and the difference was attenuated by using Nifuroxazide (Figure 3), although migration of the blasts in normal glucose condition was not different with PBMCs. The evidence revealed for the first time that in the exposure of high glucose, migration of blast cells in ALL patients was significantly increased and dependent on the presence of A20 through STAT signalling. It has been shown that glucose starvation results in cancer cell growth and viability through several different mechanisms, including cell death by activating the AMPK pathway and inactivating mTOR signalling (El Mjiyad *et al.*, 2011). A loss of A20 protein is also frequently found in several cell types upon high glucose treatment (Shrikhande *et al.*, 2010). Although, recent studies also reported the role of A20 as an inhibitor of migration of cancer cells (Kato *et al.*, 2009), and signalling molecules including STATs (Furqan *et al.*, 2013) are linked to cancer cell migration, the A20 sensitive regulation of migration of ALL blasts through STAT pathway is undefined.

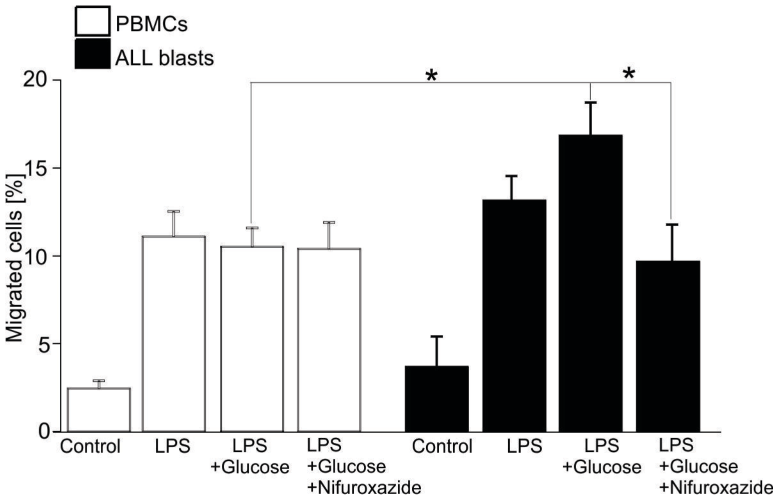

Figure 3. Effect of high glucose on the migration of ALL blasts. Arithmetic means ± SEM (n = 5) of percentages of migrated PBMCs (white bars) and ALL blasts (black bars), which were untreated or treated with LPS (500ng/ml) in the presence or absence of high glucose (30 mM) and/or Nifuroxazide (10μM). * ($p<0.05$) indicates a significant difference from high glucose-treated ALL blasts (ANOVA).

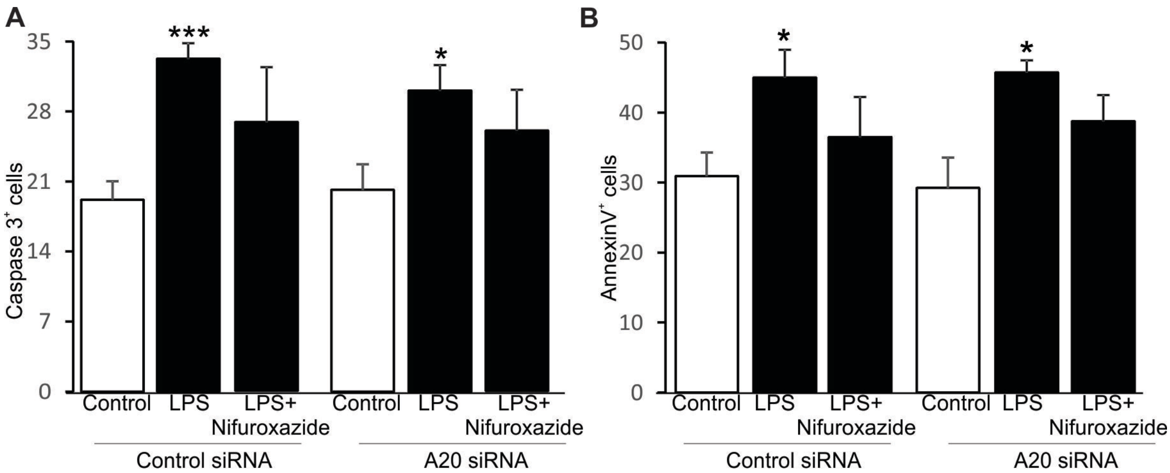

Figure 4. Effect of high glucose on apoptosis of PBMCs. A-B. The arithmetic mean ±SEM (n=5) of percentages of caspase 3^+ and annexin V^+ expressing PBMCs, which were treated with control siRNA or A20 siRNA in the presence or absence of high glucose (30 mM) and/or Nifuroxazide (10μM). * ($p<0.05$) and *** ($p<0.001$) indicate significant differences from control PBMCs (ANOVA).

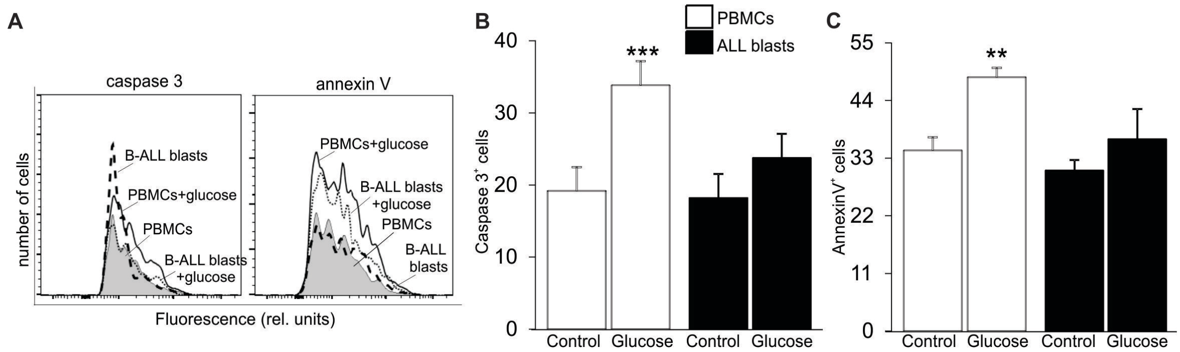

Figure 5. Effect of high glucose on apoptosis of ALL blasts. A. Representative FACS histograms depicting caspase 3 activity and annexin V binding were attained from PBMCs and ALL blasts, which were untreated or treated with high glucose (30 mM). B-C. Arithmetic means ± SEM (n=5) of caspase 3 activity and annexin V binding were attained from PBMCs (white bars) and ALL blasts (black bars), which were untreated or treated with high glucose (30 mM). ** (p<0.01) and ** (p<0.001) indicates significant differences from control PBMCs (ANOVA*)*.

Activation of immune cells leads to cell apoptosis; therefore, further experiments were performed to ask whether induction of cell apoptosis by high glucose is related to the expression of A20 and STAT signaling. PBMCs were transfected with control or *A20* siRNA and subsequently treated with high glucose for 24 h. Differently, the effect of high glucose on caspase 3 activity and annexin V binding of PBMCs was independent on the expression level of A20 and STAT signaling (Figure 4) as caspase 3 activity and annexin V binding of PBMCs were enhanced upon high glucose treatment and unaltered in the presence of Nifuroxazide in both genotypes.

In contrast to control PBMCs, high glucose did not affect cell apoptosis of leukemic blasts (Figure 5). The results attained pointed out that the inhibitory effect of apoptosis in high glucose-induced blast cells was independent on the presence of A20. Conversely, another study indicated that glucose deficit medium exerts apoptosis of cancer cells (El Mjiyad *et al.*, 2011). Therefore, the regulation of cell apoptosis in ALL patients might be mediated through other signaling pathways rather than STATs.

In conclusion**,** A20 participates in inhibiting ALL cell migration through STAT signaling in high glucose exposure. The effect might contribute to poorer prognosis and survival of ALL patients, who develop hyperglycemia during therapy.

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A20 ĐIỀU HÒA SỰ DI CƯ PHỤ THUỘC VÀO ĐƯỜNG GLUCOSE CỦA TẾ BÀO LEUKEMIA CẤP DÒNG LYMPHO

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TÓM TẮT

Bạch cầu lympho cấp (BCLC) là bệnh ung thư máu chủ yếu ở trẻ em, có đặc điểm điển hình là sự tăng sinh bất thường của tế bào non ác tính dòng lympho (lympho bào). Gen A20 thuộc nhóm gen deubiquitinase đóng vai trò điều hòa ngược các phản ứng miễn dịch thông qua ức chế một số tín hiệu nội bào như tín hiệu NF-κB và STAT. Biểu hiện của gen A20 bị bất hoạt trong một số bệnh nhân ung thư máu và ung thư hạch. Vai trò điều hòa chức năng lympho bào trong bệnh nhân BCLC thông qua biểu hiện gen A20 và tín hiệu nội bào STAT là ít được biết đến. Chính vì vậy, nghiên cứu này tiến hành xác định ảnh hưởng điều hòa của gen A20 tới khả năng di cư và sự chết apoptosis trên hai loại tế bào đơn nhân máu ngoại vi (PBMC) và lympho bào, khi tiếp xúc với đường glucose ở nồng độ cao. Thí nghiệm được tiến hành trên 15 mẫu máu của bệnh nhân BCLC và người khỏe để tách tế bào PBMC và lympho bào. Các tế bào sau đó bị bất hoạt gen A20. Mức độ biểu hiện gen được thực hiện bằng kỹ thuật realtime-PCR, sự chết tế bào được đo bằng kỹ thuật flow cytometry và sự di cư của tế bào bằng phương pháp đếm tế bào di chuyển từ màng trên xuống dưới. Kết quả nhận được cho thấy, biểu hiện gen A20 bị bất hoạt trên bệnh nhân BCLC Việt Nam. Sự di cư của của lympho bào tăng lên khi tiếp xúc với đường glucose ở nồng độ cao và phụ thuộc vào biểu hiện của gen A20. Ảnh hưởng này bị xóa bỏ khi xử lý lympho bào với chất ức chế tín hiệu STAT là Nifuroxazide, trong khi sự chết apoptosis của lympho bào không bị ảnh hưởng. Kết quả nghiên cứu cho thấy sự tăng cường di cư của lympho bào gây ra một phần bởi biểu hiện bất hoạt gen A20 thông qua tín hiệu STAT khi tiếp xúc với đường glucose. Ảnh hưởng này có thể liên quan đến thời gian sống sót ngắn hơn trên bệnh nhân BCLC bị tăng đường huyết trong quá trình điều trị bệnh.

Từ khóa: *A20, apoptosis, bạch cầu lympho cấp, sự di cư và tế bào đơn nhân máu ngoại vi.*