Int J Clin Exp Med 2016;9(6):11260-11267
www.ijcem.com /ISSN:1940-5901/IJCEM0023683

Original Article

High glucose induced human breast cancer cell MCF-7 viability, migration and invasion via the expression of AKT, MAPKs and STAT3

Qi Wu[1], Wenhuan Li[2], Shan Zhu[1], Juanjuan Li[1], Juan Wu[1], Xiang Li[1], Chuang Chen[1], Wen Wei[1], Shengrong Sun[1], Changhua Wang[3]

[1]Department of Breast and Thyroid Gland Surgery, Renmin Hosptial of Wuhan University, Wuhan 430060, Hubei Province, P. R. China; [2]Department of Thyroid and Breast Surgery, The Central Hosptial of Wuhan, Wuhan 430071, Hubei Province, P. R. China; [3]Department of Pathophysiology, Wuhan University School of Basic Medical Sciences, Wuhan 430060, Hubei Province, P. R. China

Received January 10, 2016; Accepted April 6, 2016; Epub June 15, 2016; Published June 30, 2016

Abstract: High glucose induces human breast cancer cell viability, migration and invasion in vitro and in vivo. However, the mechanism of high glucose induces human breast cancer cell viability, migration and invasion remains poorly understood. In our study, we investigate the effects of high glucose induces MCF-7 human breast cancer cell viability, migration and invasion in vitro experiments. High glucose induces activation of cell viability, migration and invasion in a time- and concentration-dependent manner. The mechanism reveals that high glucose significantly increases the phosphorylation of AKT, ERK1/2 and STAT3 and inhibits the phosphorylation of p38 MAPK. These results suggest that high glucose induces human breast cancer cell MCF-7 viability, migration and invasion via the expression of AKT, MAPKs and STAT3.

Keywords: High Glucose, MCF-7, AKT, MAPKs, STAT3

Introduction

Breast cancer is the most commonly occurring tumor among women worldwide. In China, approximately one in every ten women will develop the disease in their lifetime, and it is the second leading cause of cancer-related death in women [1]. Type2 diabetes (T2DM) is characterized by a chronic hyperglycemic state caused by insulin resistance in skeletal muscle, adipose tissue, the liver, and/or impaired insulin secretion [2]. It is now well-established that T2DM is linked to increasing breast cancer incidence and mortality [3-5]. According to recent studies, T2DM conferred as much as 37% increased risk of breast cancer in women [6] and both T2DM and breast cancer incidence are increasing at alarming rates worldwide. Even prediabetes may also increase the risk of breast cancer [7-9]. The detailed mechanisms remains unknown, however, that the hyperglycemia in T2DM patients may promote cancer progression is a possible mechanism.

The central role of AKT in the PI3Ks pathway makes it one of the most activated downstream effectors, the AKT kinase family includes three members AKT1, AKT2, and AKT3. It is becoming increasingly clear that AKT isoforms underline their distinct functional role in cancer development and progression [10-12]. Therefore, hyperglycemia enhances the viability of non-tumorigenic and malignant mammary epithelial cells through increased leptin/IGF1R signaling and activation of AKT/mTOR [13].

The mitogen-activated protein kinase (MAPK) pathway is an important signaling pathway in living beings in response to extracellular stimuli. There are 3 main subgroups manipulating by a set of sequential actions: ERK1/2, JNK/SAPK, p38 MAPK. ERK1/2 can be triggered by growth factors or the transcription factors involved in tumor cell differentiation, proliferation, survival, migration, and angiogenesis, meanwhile glucose uptake and metabolism are required for ERK1/2 activation [14, 15]. p38 MAPK that

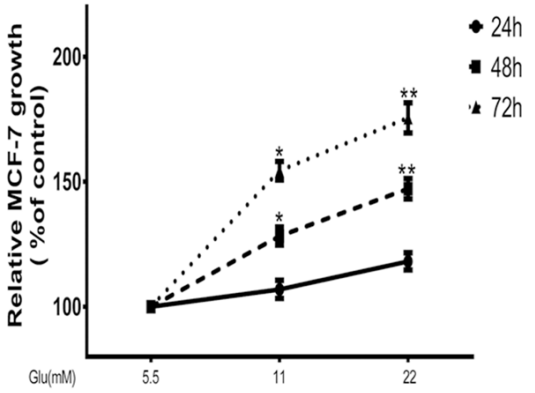

Figure 1. Effect of high glucose on cell viability in MCF-7 cells in a concentration- and time-dependent manner. Cell viability was analyzed using the MTT assay. Cells were incubated with at the concentrations indicated for 24, 48 and 72 h. The bars represent the mean values ± SD triplicate (n = 3). *P < 0. 05, **P < 0.01 versus control values.

mediates various cellular functions such as apoptosis, cell growth and differentiation are activated by inflammatory cytokines and a variety of environmental stresses. p38 MAPK activity play important roles in tumour progression [16, 17].

Of the seven members of signal transducer and activator of transcription (STAT) protein family, STAT3 has been demonstrated to be the most important for cancer progression [18, 19]. It's not only crucial for transducing signals from numerous receptor and non-receptor tyrosine kinases that are frequently activated in cancer cells, but they are also transcription factors that regulate the expression of a wide range of genes [20, 21], thereby contributing to tumour progression.

Taken together, this evidence suggests that high glucose induced human breast cancer cell viability, migration and invasion, but its possible mechanism have not been investigated. To our knowledge, this is the study demonstrating that high glucose induced human breast cancer cell MCF-7 viability, migration and invasion via the expression of AKT, MAPKs and STAT3.

Materials and methods

Materials

Tubulin, AKT and the phospho-AKT (Ser473) antibody, STAT3 and the phospho-STAT3 (Ser727), the MAPK family antibody sampler kit, and the phospho-MAPK family antibody sampler kit were purchased from Cell signaling Technology (USA). D-Mannitol were purchased from Sigma (USA).

Cell culture and treatment

Human breast cancer cell line, MCF-7 (ATCC, Manassas, USA) were cultured in RPMI 1640 (Gibco BRL, GrandIsland, NY, USA) containing 10% fetal bovine serum (FBS) (HyClone, Logan, UT, USA) and 1% penicillin/streptomycin (Invitrogen, Grand Island, NY) at 37°C in a humidified atmosphere of 5% CO_2. Cells were cultured in normal-glucose (5.5+16.5 mM D-Mannitol for osmotic balance) and high-glucose (11+11 mM D-Mannitol for osmotic balance or 22 mM) conditions. At 80-90% confluence, cells were subjected to serum starvation in serum-free RPMI 1640 overnight and then stimulated with wogonin under normal- and high-glucose conditions for 48 h.

MTT assay

The thiazolyl blue tetrazolium bromide (MTT) (Amresco, Solon, OH, USA) was dissolved in phosphate buffered saline (PBS) at a concentration of 5 mg/ml, filtered, and stored at 4°C. Cells were seeded into a 96-well plate, washed three times with PBS and starvation in serum-free RPMI 1640 overnight. Cells were treated with wogonin under normal- and high-glucose conditions for 24 h, 48 h, 72 h. For the viability assay, 20 μl MTT was added into each well. An ELISA plate reader (Biotek, Winooski, Vermont, USA) was used to measure the optical density at 490 nm. The viability of control cells was 100%.

TUNEL assay

The TUNEL assay was performed using an In Situ Cell Death Detection Kit (Roche, Basel, Switzerland) following the manufacturer's instructions. Cells that were cultured in serum-free RPMI 1640 containing 5.5 mM glucose were used as a negative control. Images were taken with the Olympus FluoView FV1000 Confocal Microscope.

Wound healing assay

MCF-7 cells were grown to confluent monolayers on 6-well plates and a pipette tip was used to create linear scratch wounds. Mitomycin C (Amresco) was used to inhibit cell viability. 1%

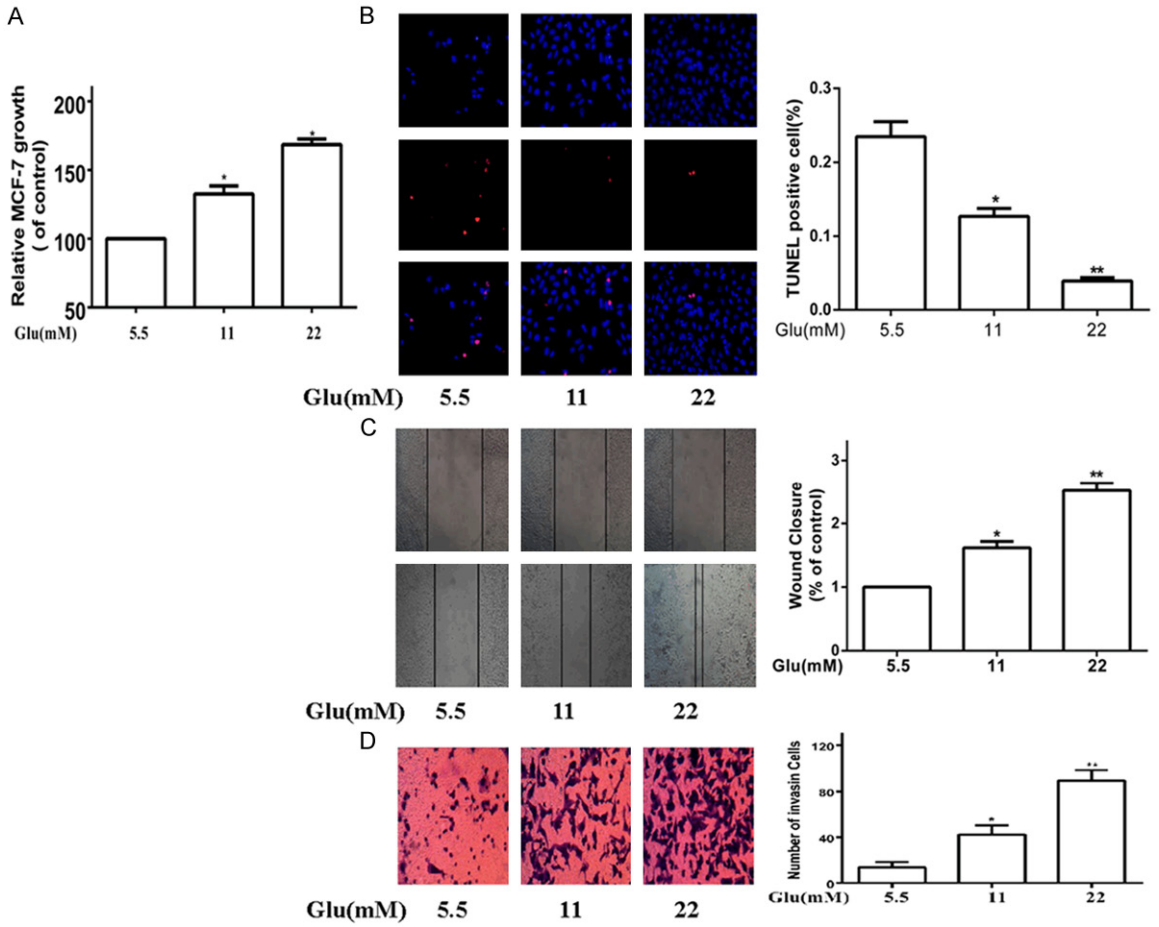

Figure 2. Effect of high glucose on MCF-7 cells viability, migration, invasion in vitro. Cells were exposed to different glucose concentrations for 48 h in 5% CO2 incubator at 37°C. A. MTT assay was used to exam the effects of high glucose on cells viability. B. TUNEL assay was used to exam the effects of high glucose on cells apoptosis. C. Confluent monolayer was scraped with a pipette tip and cells migrated into the wounded monolayer was assessed by microscope equipped with a camera. D. Cells were seeded in the upper chamber of transwell coated with matrigel, after 48 h incubation, invasive cells passed through the membrane and were measured by crystal violet staining. The bars represent the mean values ± SD triplicate (n = 3). *P < 0. 05, **P < 0.01 vs. the 5.5 mM group.

FBS also was used in the assay. Cells migrated into the wound surface and the relative wound closure were determined under an inverted microscopy at various times, five randomly chosen fields were analyzed for each well. The percentage of inhibition was expressed using control wells at 100%. Wound images were taken with a digital camera mounted on light microscope. The wound gap widths were measured using Image J software.

Transwell assay

The upper chamber of each 8.0 μm pore size Transwell apparatus (Corning, NY, USA) was coated with Matrigel (BD Biosciences, San Jose, CA). MCF-7 cells were added to the upper chamber at a density of $2*10^6$ cells/ml (100 μl per chamber) in serum-free RPMI 1640 and incubated for 48 h with 10% FBS and wogonin under normal- and high-glucose conditions in the lower compartment. Cells on the upper surface were removed by a cotton swab. Cells that penetrated to the lower membrane surface were fixed in 4% paraformaldehyde, stained with crystal violet, and quantified by manual counting and ten randomly chosen fields were analyzed for each group.

Western blots

Cells were collected with lysis buffer after being washed three times with ice-cold PBS. Lysates were boiled in SDS loading buffer for 10 min

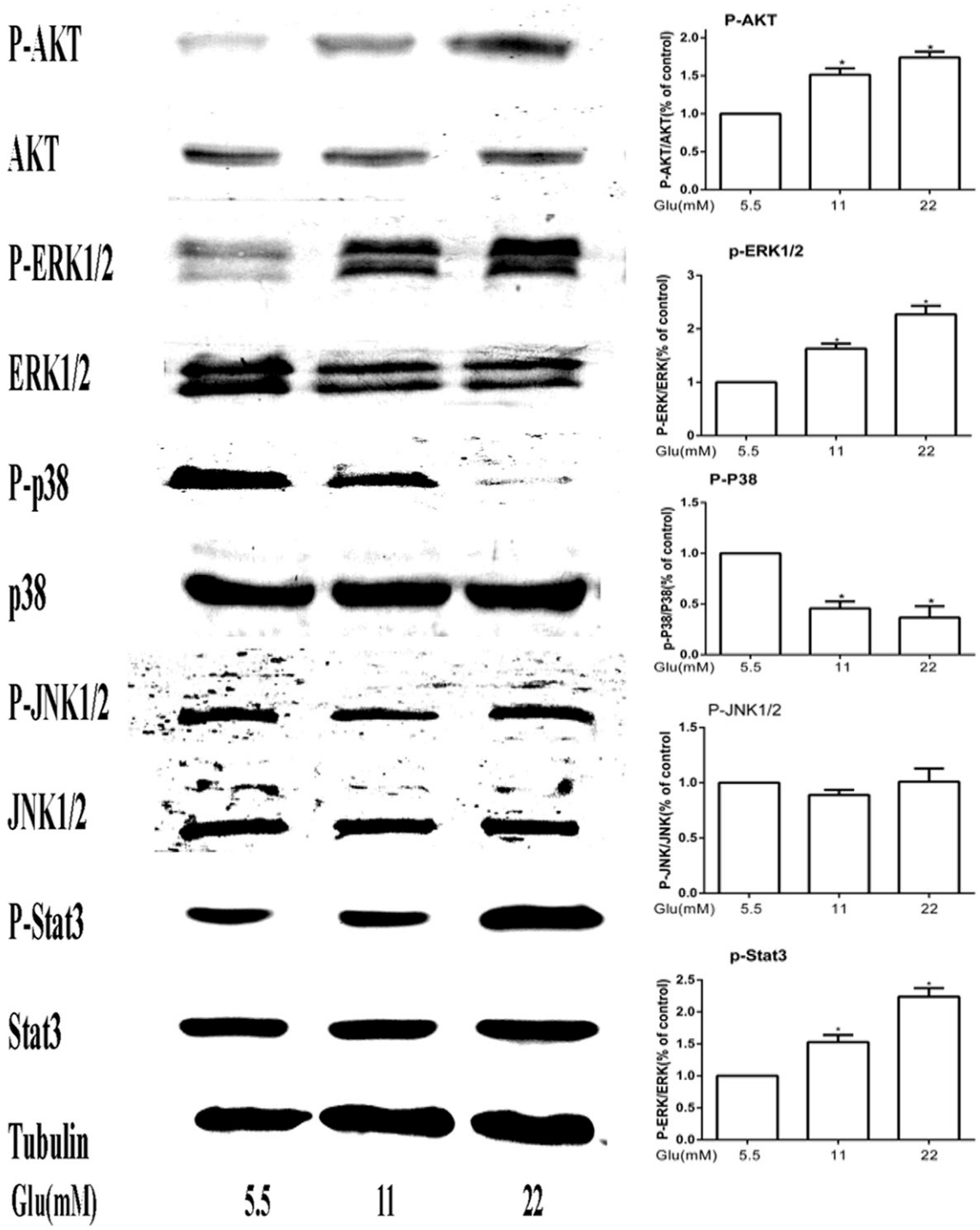

Figure 3. Effect of high glucose on MCF-7 cells via the expression of AKT, MAPKs and STAT3. Cells were exposed to different glucose concentrations for 48 h in 5 % CO_2 incubator at 37 °C. Cell lysates were then examined by Western blot analysis to verify the total and phosphorylation of AKT, MAPKs and STAT3. Band intensities were normalized to Tubulin and presented as a bar graph. The bars represent the mean values ± SD triplicate (n = 3). *P < 0. 05, **P < 0.01 vs. the 5.5 mM group.

then cleared by centrifugation (14,000 rpm, 10 min, 4°C). The proteins were separated by SDS-PAGE, transferred to a nitrocellulose membrane, and detected with specific antibodies.

Statistical analysis

All experiments were done independently at least three times. Results are represented as the mean ± SD. The quantification of the relative increase in protein expression and phosphorylation was performed using NIH Scion Image software and was normalized with the control protein expression in each experiment. Significant differences between groups were analyzed by using a r the paired t-test. A *P*-value of < 0.05 was considered statistically significant.

Results

Effect of high glucose on MCF-7 cell viability in a concentration-dependent and time-dependent manner

The overall effects of high glucose in MCF-7 cells was assessed using an MTT assay. As shown in **Figure 1**, high glucose promoted MCF-7 cell viability in a concentration-dependent and time-dependent manner when compared to the control. At glucose 22 mM group, cell viability after 48 h of treatment was promoted 153.2% compared to glucose 5.5 mM group.

Effect of high glucose on MCF-7 cells viability, migration, invasion in vitro

To investigate the effects of high glucose-induced MCF-7 cells growth, MCF-7 cells were incubated under normal- and high-glucose conditions for 48 h. MTT and TUNEL assays were performed to measure cell viability and apoptosis. As demonstrated in **Figure 2A**, high glucose improved MCF-7 cell viability, accordingly decreased MCF-7 cell apoptosis (**Figure 2B**). We used wound healing and transwell assays as described in the materials and methods section to test the effect of high glucose-induced MCF-7 cell migration and invasion. As shown in **Figure 2C**, after 48 h the wound was almost covered due to the influx of highly migratory cells in high glucose groups, whereas low glucose groups cells remained close to the initial state. As shown in **Figure 2D**, compared with the control, a dose-dependent augment in the number of invasive cells was seen in high glucose groups.

Effect of high glucose on MCF-7 cells via the expression of AKT, MAPKs and STAT3

AKT, MAPKs and STAT3, which are important glucose effectors in tumour progression, are involved in the regulation of MCF-7 growth, migration, invasion. Western blotting assay was also used to find out the mechanism of high glucose-induced MCF-7 cells growth, migration, invasion. We tested the total and phosphorylation of AKT expression in MCF-7 cells exposed under normal- and high-glucose conditions for 48 h. As shown in **Figure 3**, the phosphorylation of AKT was increased in high glucose groups. The amount of phosphorylation p38 reduced in high glucose groups, while ERK1/2 increased in high glucose groups. JNK1/2 was not significantly influenced under high glucose conditions. Also the phosphorylation of STAT3 was increased in high glucose groups.

Discussion

As cancer cells use glucose as the source of energy for their viability, high glucose provides a favorable environment for the growth and survival of breast cancer cells [22, 23]. Further, it has been reported that high glucose confers resistance to chemotherapy in malignant cancer cells but not in non-malignant cell [23, 24]. We demonstrate that high glucose induce MCF-7 viability, migration and invasion, moreover the mechanism study that the effect is associated with the expression of AKT, MAPKs and STAT3.

Viability, migration and invasion of tumor is the major cause of morbidity and mortality. The mechanism is a multistep and complex process involving the extracellular signalling, tumor microenvironment and stimulating factors. It is reported that activation of AKT plays a critical role in high glucose-induced cancer cell lines viability, migration and invasion [13, 25-29]. It is well-established that hyperglycemia enhances the viability of non-tumorigenic and malignant mammary epithelial cells through increased leptin/IGF1R signaling and activation of AKT/mTOR [13].

MAPKs are involved in a multitude of cellular pathways and functions in response to a variety of ligands and cell stimuli. In many cancer cell types, the ERK1/2 are linked to cell proliferation. ERK1/2 are thought to play a role in some cancers, because mutations in Ras and B-Raf, which can activate the ERK1/2, are found in many human tumor [15]. Reactive oxygen species (ROS) are well known to induce the activation of the Raf/MEK/ERK1/2 signaling pathways in a variety of cell types [30, 31]. In pancreatic cancer ROS intermediates act

directly on growth receptors, such as the high glucose [32], and that induce the activation of ERK1/2 and p38 signaling. p38 kinases are members of MAPK family that transduce signals from various environmental stresses, growth factors and steroid hormones. p38 has recently gained attention as a tumor suppressor. This effect is reported that increased tumorigenicity of the lack of p38 MAPK cells is caused mainly by a decrease in the apoptosis rate indicating that the lack of the p38 MAPK caused an imbalance to increase the ERα:ERβ ratio and a reduction in the activity of the p53 tumor suppressor protein [33]. Further, There is much evidence to support a role for p38α as a tumour suppressor, and this function of p38α is mostly mediated by both negative regulation of cell cycle progression and the induction of apoptosis, although the induction of terminal differentiation also contributes to tumour suppressive function [34]. These data suggest that high glucose can activate ERK1/2 and inhibit p38 that this may promote growth, migration, invasion and prevent apoptosis in MCF-7.

STATs are latent transcription factors that mediate cers are reported to contain constitutively activated cytokine- and growth factor-directed transcription [19, 20, 35]. In many human cancers and transformed cell lines, STAT3 is persistently activated, and in cell culture, active STAT3 is either required for transformation, enhances transformation or blocks apoptosis [36-38]. There is study provide evidence that glucose can promote both migration and invasion of CT-26 cells, and that the STAT3-induced MMP-9 signal pathway is involved in this process [39]. It is well-established that high glucose can increase mitochondria-derived ROS generation and subsequently upregulate VEGF expression possibly through JAK2/STAT3 activation [40]. It demonstrates that progestins (PR) also induce STAT3 phosphorylation at Ser727 residue, which occurs via activation of ERK1/2 pathways [41]. These data suggest that high glucose can activate STAT3 that this may promote growth, migration, invasion and prevent apoptosis in MCF-7.

In conclusion, this is the major study to show that high glucose induces human breast cancer cell MCF-7 viability, migration and invasion via the expression of AKT, MAPKs and STAT3. Nevertheless, we find that high glucose induces MCF-7 viability, migration and invasion just by the experiments in vitro, whether those need to be further investigated in vivo.

Acknowledgements

This work was partially supported by a NSFC grant to Prof. Shengrong Sun (Grant NO: 30701032), and a NSFC grant to Prof. Changhua Wang (Grant NO: 30770758/H0178). This work was also supported by a NSFC grant to Dr. Juanjuan Li (Grant NO: 81302314/H1622), the Fundamental Research Funds of Hubei Province Health and Family Planning Commission to Wen Wei (Grant NO: JS-20110118) and the Fundamental Research Funds for the Central Universities of China to Shan Zhu (Grant NO: 2042014kf0189).

Disclosure of conflict of interest

None.

Address correspondence to: Shengrong Sun, Department of Breast and Thyroid Surgery, Renmin Hosptial of Wuhan University, 99 Zhang Zhidong Road, Wuhan 430060, Hubei Province, P. R. China. E-mail: sun137@sina.com; Changhua Wang, Department of Pathophysiology. Wuhan University School of Basic Medical Sciences. Wuhan 430060, Hubei Province, P. R. China. E-mail: chwang0525@whu.edu.cn

References

[1] Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin 2014; 64: 9-29.

[2] Association. A D. Diagnosis and classification of diabetes mellitus. Diabetes Care 2010; 30: S42-S47.

[3] Boyle P, Boniol M, Koechlin A, Robertson C, Valentini F, Coppens K, Fairley LL, Boniol M, Zheng T, Zhang Y, Pasterk M, Smans M, Curado MP, Mullie P, Gandini S, Bota M, Bolli GB, Rosenstock J, Autier P. Diabetes and breast cancer risk: a meta-analysis. Br J Cancer 2012; 107: 1608-1617.

[4] Wolf I, Sadetzki S, Catane R, Karasik A, Kaufman B. Diabetes Mellitus and Breast Cancer. Lancet Oncol 2008; 6: 103-111.

[5] Lipscombe LL, Goodwin PJ, Zinman B, Mclaughlin JR, Hux JE. Diabetes mellitus and breast cancer: a retrospective population-based cohort study. Breast Cancer Res Treat 2006; 98: 349-356.

[6] Liao S, Li J, Wei W, Wang L, Zhang Y, Li J, Wang C, Sun S. Association between diabetes mellitus and breast cancer risk: a meta-analysis of the literature. Asian Pac J Cancer Prev 2011; 12: 1061-1065.

[7] Onitilo AA, Stankowski RV, Berg RL, Engel JM, Glurich I, Williams GM, Doi SA. Breast cancer incidence before and after diagnosis of type 2 diabetes mellitus in women: increased risk in the prediabetes phase. Eur J Cancer Prev 2014; 23: 76-83.

[8] Ji GY, Jin LB, Wang RJ, Bai Y, Yao ZX, Lu LJ, Huang JB, Liu SC, Li HY, Wang ZW, Ren GS, Wu KN, Kong LQ. Incidences of diabetes and prediabetes among female adult breast cancer patients after systemic treatment. Med Oncol 2013; 30: 687.

[9] Salinas-Martínez AM, Flores-Cortés LI, Cardona-Chavarría JM, Hernández-Gutiérrez B, Abundis A, Vázquez-Lara J, González-Guajardo EE. Prediabetes, diabetes, and risk of breast cancer: a case-control study. Arch Med Res 2014; 45: 432-438

[10] Gonzalez E, Mcgraw TE. The Akt kinases: isoform specificity in metabolism and cancer. Cell Cycle 2009; 8: 2502-2508.

[11] Martelli AM, Tabellini G, Bressanin D, Ognibene A, Goto K, Cocco L, Evangelisti C. The emerging multiple roles of nuclear Akt. Biochim Biophys Acta 2012; 1823: 2168-2178.

[12] Schmelzle T, Hall MN. TOR, a central controller of cell growth. Cell 2000; 103: 253-262.

[13] Lopez R, Arumugam A, Joseph R, Monga K, Boopalan T, Agullo P, Gutierrez C, Nandy S, Subramani R, de la Rosa JM, Lakshmanaswamy R. Hyperglycemia enhances the proliferation of non-tumorigenic and malignant mammary epithelial cells through increased leptin/IGF1R signaling and activation of AKT/mTOR. PLoS One 2013; 8: e79708.

[14] Mccubrey JA, Steelman LS, Abrams SL, Chappell WH, Russo S, Ove R, Milella M, Tafuri A, Lunghi P, Bonati A, Stivala F, Nicoletti F, Libra M, Martelli AM, Montalto G, Cervello M. Emerging MEK inhibitors. Expert Opin Emerg Drugs 2010; 15: 203-223.

[15] Mccubrey JA, Steelman LS, Chappell WH, Abrams SL, Wong EW, Chang F, Lehmann B, Terrian DM, Milella M, Tafuri A, Stivala F, Libra M, Basecke J, Evangelisti C, Martelli AM, Franklin RA. Roles of the Raf/MEK/ERK pathway in cell growth, malignant transformation and drug resistance. Biochim Biophys Acta 2007; 1773: 1263-1284.

[16] Shin I, Kim S, Song H, Kim HC, Moon A. H-Ras-specific activation of Rac-MKK3/6-p38 pathway: its critical role in invasion and migration of breast. J Biol Chem 2005: 14675-14683.

[17] Galliher AJ, Schiemann WP. Src phosphorylates Tyr284 in TGF-beta type II receptor and regulates TGF-beta stimulation of p38 MAPK during breast cancer cell proliferation and invasion. Cancer Res 2007; 67: 3752-3758.

[18] Snyder M, Huang J, Huang XY, Zhang JJ. A signal transducer and activator of transcription 3. Nuclear Factor kappaB (Stat3·NFκB) complex is necessary for the expression of fascin in metastatic breast cancer cells in response to interleukin (IL)-6 and tumor necrosis factor (TNF)-alpha. J Biol Chem 2014; 289: 30082-30089.

[19] Ren L, Wang X, Dong Z, Liu J, Zhang S. Bone metastasis from breast cancer involves elevated IL-11 expression and the gp130/STAT3 pathway. Med Oncol 2013; 30: 634.

[20] Yu H, Pardoll D, Jove R. STATs in cancer inflammation and immunity: a leading role for STAT3. Nat Rev Cancer 2009; 9: 798-809.

[21] Bromberg J, Darnell JJ. The role of STATs in transcriptional control and their impact on cellular function. Oncogene 2000; 19: 2468-2473.

[22] Takatani-Nakase T, Matsui C, Maeda S, Kawahara S, Takahashi K. High glucose level promotes migration behavior of breast cancer cells through zinc and its transporters. PLoS One 2014; 9: e90136.

[23] Wu Q, Li WH, Zhang TT, Zhu S, Li JJ, Wu J, Li X, Chen C, Sun SR, Wang CH. Wogonin attenuates high glucose-induced human breast cancer cell MCF-7 viability, migration and invasion via the expression of AKT, PKCδ and p38 MAPK. Int J Clin Exp Pathol 2016; 9: 684-694.

[24] Zeng L, Biernacka KM, Holly JM, Jarrett C, Morrison AA, Morgan A, Winters ZE, Foulstone EJ, Shield JP, Perks CM. Hyperglycaemia confers resistance to chemotherapy on breast cancer cells: the role of fatty acid synthase. Endocr Relat Cancer 2010; 17: 539-551.

[25] Coloff JL, Macintyre AN, Nichols AG, Liu T, Gallo CA, Plas DR, Rathmell JC. Akt-dependent glucose metabolism promotes Mcl-1 synthesis to maintain cell survival and resistance to Bcl-2 inhibition. Cancer Res 2011; 71: 5204-5213.

[26] Kiley SC, Clark KJ, Duddy SK, Welch DR, Jaken S. Increased protein kinase C delta in mammary tumor cells: relationship to transformtion and metastatic progression. Oncogene 1999; 18: 6748-6757.

[27] Liu PP, Liao J, Tang ZJ, Wu WJ, Yang J, Zeng ZL, Hu Y, Wang P, Ju H Q, Xu RH, Huang P. Metabolic regulation of cancer cell side population by glucose through activation of the Akt pathway. Cell Death Differ 2014; 21: 124-135.

[28] Okumura M, Yamamoto M, Sakuma H, Kojima T, Maruyama T, Jamali M, Cooper DR, Yasuda K. Leptin and high glucose stimulate cell proliferation in MCF-7 human breast cancer cells: reciprocal involvement of PKC-alpha and PPAR expression. Biochim Biophys Acta 2002; 1592: 107-116.

[29] Yamamoto M, Patel NA, Taggart J, Sridhar R, Cooper DR. A shift from normal to high glucose levels stimulates cell proliferation in drug sensitive MCF-7 human breast cancer cells but

not in multidrug resistant MCF-7/ADR cells which overproduce PKC-betaII. Int J Cancer 1999; 83: 98-106.
[30] Usatyuk PV, Vepa S, Watkins T, He D, Parinandi NL, Natarajan V. Redox regulation of reactive oxygen species-induced p38 MAP kinase activation and barrier dysfunction in lung microvascular endothelial cells. Antioxid Redox Signal 2003; 5: 723-730.
[31] Conde de la Rosa L, Schoemaker MH, Vrenken TE, Buist-Homan M, Havinga R, Jansen PL, Moshage H. Superoxide anions and hydrogen peroxide induce hepatocyte death by different mechanisms: involvement of JNK and ERK MAP kinases. J Hepatol 2006; 44: 918-929.
[32] Li W, Wu Z, Ma Q, Liu J, Xu Q, Han L, Duan W, Lv Y, Wang F, Reindl KM, Wu E. Hyperglycemia regulates TXNIP/TRX/ROS axis via p38 MAPK and ERK pathways in pancreatic cancer. Curr Cancer Drug Targets 2014; 14: 348-356.
[33] Mendoza RA, Moody EE, Enriquez MI, Mejia SM, Thordarson G. Tumorigenicity of MCF-7 human breast cancer cells lacking the p38alpha mitogen-activated protein kinase. J Endocrinol 2011; 208: 11-19.
[34] Hui L, Bakiri L, Stepniak E, Wagner EF. p38alpha: a suppressor of cell proliferation and tumorigenesis. Cell Cycle 2007; 6: 2429-2433.
[35] Frodin M, Sekine N, Roche E, Filloux C, Prentki M, Wollheim CB, Van Obberghen E. Glucose, other secretagogues, and nerve growth factor stimulate mitogen-activated protein kinase in the insulin-secreting beta-cell line, INS-1. J Biol Chem 1995; 270: 7882-7889.
[36] Huang S, Chen M, Shen Y, Shen W, Guo H, Gao Q, Zou X. Inhibition of activated Stat3 reverses drug resistance to chemotherapeutic agents in gastric cancer cells. Cancer Lett 2012; 315: 198-205.
[37] Zhao M, Gao FH, Wang JY, Liu F, Yuan HH, Zhang WY, Jiang B. JAK2/STAT3 signaling pathway activation mediates tumor angiogenesis by upregulation of VEGF and bFGF in non-small-cell lung cancer. Lung Cancer 2011; 73: 366-374.
[38] Lin L, Liu A, Peng Z, Lin H J, Li P K, Li C, Lin J. STAT3 is necessary for proliferation and survival in colon cancer-initiating cells. Cancer Res 2011; 71: 7226-7237.
[39] Lin CY, Lee CH, Huang CC, Lee ST, Guo HR, Su SB. Impact of high glucose on metastasis of colon cancer cells. World J Gastroenterol 2015; 21: 2047-2057.
[40] Zheng Z, Chen H, Zhao H, Liu K, Luo D, Chen Y, Chen Y, Yang X, Gu Q, Xu X. Inhibition of JAK2/STAT3-mediated VEGF upregulation under high glucose conditions by PEDF through a mitochondrial ROS pathway in vitro. Invest Ophthalmol Vis Sci 2010; 51: 64-71.
[41] Tkach M, Rosemblit C, Rivas MA, Proietti CJ, Diaz FM, Mercogliano MF, Beguelin W, Maronna E, Guzman P, Gercovich FG, Deza EG, Elizalde PV, Schillaci R. p42/p44 MAPK-mediated Stat3Ser727 phosphorylation is required for progestin-induced full activation of Stat3 and breast cancer growth. Endocr Relat Cancer 2013; 20: 197-212.