Type 2 diabetes promotes cell centrosome amplification and the role of AKT-ROS-dependent signalling of ROCK1 and 14-3-3σ

Pu Wang[1], Yu Cheng Lu[1], Jie Wang[2], Lan Wang[1], Hanry Yu[3], Yuan Fei Li[4], Alice Kong[5], Juliana Chan[5], Shao Chin Lee[1,*]

[1]: School of Life Sciences, Shanxi University, Taiyuan, Shanxi, PR China

[2]: Shanxi College of Traditional Chinese Medicine, Taiyuan, Shanxi, PR China,

[3]: Department of Physiology, National University of Singapore, Singapore.

[4]: Department of Oncology, the First Clinical Hospital of Shanxi Medical University, Taiyuan, Shanxi, PR China

[5]: Department of Medicine and Therapeutics, the Chinese University of Hong Kong, HKSAR, PR China

*: Correspondence: Dr. Shao Chin Lee, School of Life Sciences, Shanxi University, Taiyuan, Shanxi, PR China. Email: lee_shao@hotmail.com; Telephone: (86) 13485376021;

Running title:

Centrosome amplificationin type 2 Diabetes and its mechanisms

Abstract

Type2 diabetes is associated with oxidative stress which can cause cell centrosome amplification. The study investigated centrosome amplification in type 2 diabetes and the underlying mechanisms. We found that centrosome amplification was increased in the peripheral blood mononuclear cells (PBMC) from the type 2 diabetic patients, which correlated with the levels of fasting blood glucose and HbA1c. High glucose, insulin and palmitic acid, alone or in combinations, induced ROS production and centrosome amplification. Together, they increased AKT activation as well as the expression, binding and centrosome translation of ROCK1 and 14-3-3σ. Results from further analyses showed that AKT-ROS-dependent upregulations of expression, binding and centrosome translocation of ROCK1 and 14-3-3σ was the molecular pathway underlying the centrosome amplification induced by high glucose, insulin and palmitic acid. Moreover, the increases in AKT activation and ROS production as well as expression, binding and centrosome distribution of ROCK1 and 14-3-3σ were confirmed in the PBMC from the patients with type 2 diabetes. In conclusion, our results show that type 2 diabetes promotes cell centrosome amplification, and suggest that the diabetic pathophysiological factors-activated AKT-ROS-dependent signalling of ROCK1 and 14-3-3σ is the underlying molecular mechanism.

Key words: Centrosome amplification; Type 2 diabetes; AKT; ROS; ROCK1; 14-3-3σ; Pathophysiological factors.

INTRODUCTION

Type 2 diabetes is a common non-communicable disease. At certain stage of the disease development, patients present pathophysiological features such as hyperglycemia, hyperinsulinemia and increased plasma level of free fatty acids. At latter stage, patients may develop insulin deficiency, but continue to have hyperglycemia and increased plasma level of free fatty acids. These pathophysiological factors are able to trigger the production of reactive oxygen species (ROS) (Inoguchi et al., 2000; May and de Haen, 1979) and DNA damage (Lee and Chan, 2015) *in vitro*, which may explain why oxidative stress and DNA damage are increased *in vivo* in patients with type 2 diabetes (Lee and Chan, 2015; Orie et al., 1999).

Cell centrosome amplification refers to a cell with more than two centrosomes. There is evidence that oxidative stress and DNA damage can cause centrosome amplification (Chae et al., 2005; Dodson et al., 2004). At the molecular level, many signal mediators for cell centrosome amplification have been identified, which include those inside or outside the centrosomes. Overexpression of PLK4 (Basto et al., 2008) or aurora A (Castellanos et al., 2008), both are centrosome proteins, can cause centrosome amplification. Wang and co-workers show that Chk2 is located in centrosome, which controls centrosome amplification induced by sub-toxic concentrations of hydroxyurea (Wang et al., 2015). Overexpression of cyclin E (Bagheri-Yarmand et al., 2010) which can be in centrosome was also to promote centrosome amplification. Ras (Zen et al., 2010) which is a protein outside the centrosomes has been shown to cause centrosome amplification. Interestingly, BRCA1 promotes centrosome amplification when is translocated to centrosome (Zou et al., 2014), which shows a dynamic communication between centrosome and its surrounding environment for centrosome amplification. At the cellular and organismal levels, centrosome amplification regulates cell division, movement and intracellular transport (Anderhub et al., 2012), and increases cancer invasion potential (Godinho et

al., 2014). While robust centrosome amplification results in multipolar division follow by mitosis catastrophe (Pannu et al., 2012), there is evidence that moderate centrosome amplification can induce genome instability (Ganem et al., 2009) and tumorigenesis (Levine et al., 2017).

Since type 2 diabetes is associated with oxidative stress (Inoguchi et al., 2000; May and de Haen, 1979; Lee and Chan, 2015; Orie et al., 1999) which can cause centrosome amplification (Chae et al., 2005; Dodson et al., 2004), in the present study, we investigate cell centrosome amplification in type 2 diabetes and the underlying mechanisms.

RESULTS

Cell centrosome amplification is increased in patients with type 2 diabetes, which is in correlation with fasting blood glucose and HbA1c

To investigate whether centrosome amplification is associated with type 2 diabetes, first of all, we compared the extent of centrosome amplification in PBMCs from 32 patients with type 2 diabetes and 12 healthy subjects. The clinical characteristics of the volunteers were summarized in Table 1. Compared with the healthy subjects, the diabetic patients had higher body mass index, fasting blood glucose, HbA1c and triglyceride. Moreover, we compared the level of centrosome amplification between the healthy subject and diabetic patients. The images of centrosome and centrosome amplification were shown in Fig. 1A. The patients had a greater degree of cell centrosome amplification than the healthy subjects (8.7 % v.s.3.4%; $p<0.01$) (Fig. 1B); there was a 2.6-fold increase in centrosome amplification in PBMCs from the patients. When the diabetic patients were divided into two groups according to their fasting blood glucose level less or greater than 10mM, there was a step-wise increase in centrosome amplification ($p<0.01$; Fig. 1C). Indeed, in all the volunteers, correlation analysis showed that the extent of cell centrosome amplification was correlated with the fasting blood glucose level ($R^2 = 0.7$; $p<0.01$; Fig. 1D) and HbA1c ($R^2=0.7$;

p<0.01; Fig. 1E). Similarly, in the patients alone, the level of centrosome amplification was also correlated with fasting blood glucose (R^2 = 0.5; p <0.01; Fig. 1F) and HbA1c (R^2=0.4; p<0.01; Fig. 1G).

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High glucose, insulin and palmitic acid, alone or in combinations, induce centrosome amplification via ROS production

We then investigated whether the pathophysiological factors in type 2 diabetes could induce centrosome amplification via specific molecular pathway using colon cancer cells as an experimental model. Some results were verified in normal human breast epithelial cells wherever it was considered to be meaningful, which was to verify findings from experiments using cancer cells in non-cancerous cell model. Palmitic acid, the most common saturated free fatty acid, was used to represent free fatty acids. We tested ROS pathway to start with. Fluorescent spectrophotometry was used to quantify the level of ROS when experiments involved more than three samples. Otherwise, flow cytometry analysis was employed. The results showed that high glucose, insulin and palmitic acid, alone or in combinations, significantly induced ROS production (Fig. 2A) and centrosome amplification (Figs. 2C) in the cancer cells. High glucose, insulin and palmitic acid individually induced centrosome amplification in concentration-dependent manners (figures not shown). They, together, also triggered ROS production (Fig. 2B) and centrosome amplification (Fig. 2D) in the normal human breast epithelial cells. Antioxidant N-acetylcysteine (NAC) was able to inhibit the ROS production and the centrosome amplification (Figs. 2A -2D). The potential of high glucose, insulin and palmitic acid in inducing centrosome amplification was three factors > two factors > single factor (all at p<0.05; Fig. 2C).

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Functional transcriptomic analysis identifies AKT, ROCK1 and 14-3-3σas signal mediators for the centrosome amplification

To further identify the molecular signals for the centrosome amplification, we performed a functional transcriptomic analysis between the control samples and those treated with high glucose, insulin and palmitic acid. The differentially expressed genes were summarized in the supplementary data sheet (Table S1). In total, 729 genes were differentially expressed, with 508 upregulated and 221 downregulated. Results of bioinformatic annotation were included in supplementary figures S1-S5. Functional enrichment using GO analysis assigned the genes to 37 terms in three categories of molecular component, molecular function and biological process (Fig. S1). The top terms were molecular function, cellular component, biological process and cell, which had 9%, 9%, 8.4% and 8.3% of the genes, respectively. KEGG annotation identified 37 pathways which were related to different functional groups (Fig. S2). The top pathways were signal transduction, infectious diseases, cancer, immune system and endocrine system, which had 15.6%, 11.6%, 11.1%, 7.4% and 7.0% of the genes, respectively. Notably, AKT (Fig.S3), ROCK (Fig. S4) and 14-3-3σ (Fig.S5) pathways were activated, which were chosen for further functional analysis. Western blot analyses confirmed that high glucose, insulin and palmitic acid activated AKT, which was inhibited by AKT inhibitor Ly294002 or siRNA (Fig. 3A). Similarly, ROCK1 (Fig. 3B) and 14-3-3σ (Fig. 3C) protein levels were upregulated, which were inhibited their specific siRNA (Figs. 3B and 3C). We then performed functional analyses to examine whether AKT, ROCK1 and 14-3-3σ mediated the centrosome amplification. Indeed, inhibition of AKT using chemical inhibitor or siRNA could inhibit the centrosome amplification (Fig. 3D). Similarly, siRNA for ROCK1 (Fig. 3E) and siRNA for 14-3-3σ (Fig. 3F) were also able to inhibit the centrosome amplification. Moreover, AKR chemical inhibitor, AKT siRNA, ROCK1 siRNA and 14-3-3σsiRNA individually were all able to inhibit the centrosome in the normal human breast epithelial cells (Figs. 3G and 3H).

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AKT-ROS-dependent signaling of ROCK1 and 14-3-3σ is the molecular pathway for the centrosome amplification

We next delineated the signal transduction pathway for the centrosome amplification in the colon cancer cells. The logic was that inhibition of an upstream signal would inhibit downstream one(s), while inhibition of a downstream signal would not affect the upstream one(s). We observed that inhibition of AKT using chemical inhibitor (Fig. 4A) orsiRNA (Fig. 4B) was able to inhibit ROS production as well as the upregulations of ROCK1 (Figs. 4C) and 14-3-3σ (Fig. 4D). NAC was able to inhibit the upregulation of ROCK1 (Fig. 4E) and 14-3-3σ (Fig. 4F), but did not affect the activation of AKT (figure not shown). ROCK1 or 14-3-3σsiRNA did not affect AKT activation or ROS production (figures not shown).

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High glucose, insulin and palmitic acid increase the binding between ROCK1 and 14-3-3σ as well as their centrosome translocation

Next, we investigated the relationships amongst ROCK1, 14-3-3σand centrosome in the cancer cells by using ROCK1 and 14-3-3σ antibodies to pull down their binding partners, as well as to analyse the centrosome translocation of the two proteins. In pull-down samples using ROCK1 antibody, 14-3-3σ protein was detected, which was increased in the cells treated with high glucose, insulin and palmitic acid (Fig. 5A). Similarly, high glucose, insulin and palmitic acid increased the pull down ofROCK1 using 14-3-3σ antibody (Fig. 5A). AKT inhibitor and NAC were able to inhibit the increase in co-precipitation of ROCK1 and14-3-3σfrom the cells treated by high glucose, insulin and palmitic acid (Figs. 5A). These observations on the Western blot analysis images were confirmed when the images were quantified (Figs. 5B and 5C. As shown in confocal images in Figs. 5D and 5E respectively, ROCK1 and 14-3-3σ were localized in the centrosome in all the treated samples. In the cells with more than one centrosome, only half of the centrosomes had ROCK1, with another half of

centrosomes free of ROCK1 (Fig. 5D). The fluorescent intensity of ROCK1 staining, which indicates the level of ROCK1 in the centrosomes, was higher in the treated cells compared to that in the control cells, which was inhibited by AKT inhibitor or NAC but not 14-3-3σsiRNA (Fig. 5F). Comparing with that only 1% of the control cells had 14-3-3σ in the centrosomes, approximately 20% of the cells treated with high glucose, insulin and palmitic acid had 14-3-3σ in the centrosomes, which was inhibited by AKT inhibitor, NAC or ROCK1 siRNA (all at $p < 0.01$; Figs. 5E and 5G).

Suggested Figure 5 here

The increases in AKT activation and ROS production as well as expression, binding and centrosome distribution of ROCK1 and 14-3-3σ *in vitro* are verified in the PBMC from the volunteers

Finally, we investigated whether the molecular signalling events found *in vitro* occurred *in vivo* in patients with type 2 diabetes. We compared these molecular events between the PBMC from healthy volunteers and those from type 2 diabetic patients. The results showed that PBMC from the diabetic patients had increased level of AKT activation (Fig. 6A) and ROS production (Fig. 6B). The PBMC from the patients also had increased expression (Fig. 6A), binding (Figs. 6C) and centrosome distribution of ROCK1 and 14-3-3σ (Figs. 6D and 6E).

Suggested Figure 6 here

DISCUSSION

Our results showed that patients with type 2 diabetes had 2.6-fold increase in cell centrosome amplification *in vivo* in PBMC, which correlated with poor glycemic control (Fig. 1). Pathophysiological factors in type 2 diabetes, i.e., high glucose, insulin and palmitic acid, could trigger centrosome amplification (Figs. 2C and 3D). AKT-ROS-dependent upregulation of expression, binding and centrosome

translocation of ROCK1 and 14-3-3σ was the underlying molecular pathway (Figs. 3-6).

Type 2 diabetes increases the risk of developing all-site cancer, with the exception of prostate cancer (Giovannucci et al., 2010). Cancer patients with type 2 diabetes have poorer prognosis than those without diabetes (Mills et al., 2013). However, it remains unknown why and how type 2 diabetes favours cancer development. Centrosome amplification can initiate in animal model (Levine et al., 2017) and increase cancer cell invasion potential (Godinho et al., 2014). In the present study, we showed that patients with type 2 diabetes had increased level of cell centrosome amplification *in vivo* (Fig. 1). Thus, we speculate whether there is a link between the diabetes-associated centrosome amplification (Fig. 1) and the increased cancer risk in type 2 diabetes.

Our results (Figs. 3-6) support the findings that AKT (Na et al., 2015) and ROS (Chae et al., 2005) can mediate centrosome amplification, and further place AKT upstream of ROS. In an apoptosis model, activation of ROCK1 causes AKT inactivation (Zhang et al., 2016), which is different from our results that placed ROCK1 downstream of AKT activation (Figs. 4C). Our result (Fig. 4E) showed that ROS was upstream of ROCK1, which is in agreement with the observations by Shen and Wang (Shen and Wang, 2015). Oh and Jang showed that AKT can be upstream of 14-3-3σ (Oh and Jang, 2009), which is supported by our result (Figs. 4D) that AKT was upstream of 14-3-3σ.

As shown in Fig. 4, inhibition of AKR inhibits all other signals. Inhibition of ROS inhibits ROCK1 and 14-3-3σ but not AKT. Inhibition of ROCK1 or 14-3-3σ did not affect any other signals. This suggests that AKT-ROS-dependent signalling of ROCK1 and 14-3-3σis the pathway underlying the centrosome amplification by the experimental treatment. Our results (Figs. 5D and 5E) showed that ROCK1, but not 14-3-3σ, was a centrosome protein. ROCK1 was present in half of the centrosomes

when a cell had two or more centrosomes. Whether it is present only in the mother centrosomes remains to be clarified. In most cases, 14-3-3σ was present in the centrosomes only in the treated cells (Fig. 5E). Knockdown of ROCK1 inhibited 14-3-3σ translocation to centrosome, while knockdown of 14-3-3σ did not affect the translocation of ROCK1 to the centrosomes (Figs. 5F and 5G), which suggests that ROCK1 transports 14-3-3σ to centrosome or is involved in 14-3-3σ translocation to centrosome after treatment. Downregulation of either ROCK1 or 14-3-3σ inhibited the centrosome amplification (Figs. 3E and 3F), which suggests that the integrity of ROCK1 and 14-3-3σ complex is required for the centrosome amplification. These data suggest that the pathophysiological factors of type 2 diabetes activate AKT-ROS signalling which promotes the expression and binding of ROCK1 and 14-3-3σ as well as their translocation to centrosome to promote centrosome amplification.

High glucose, insulin and palmitic acid, alone or in combinations, did not affect the cell viability under the experimental conditions, with the exception that high glucose treatment increased cell viability (data not shown). In some cell line models, centrosome amplification is associated with cell cycle arrest (Yih et al., 2006). In our study, high glucose, insulin and palmitic acid, alone or in combination, did not disturb the cell cycle (data not shown), which suggests that cell cycle arrest is not a prerequisite for centrosome amplification under our experimental conditions. At the concentrations of 10, 20 and 30 μM, linoleic acid did not significantly affect the centrosome amplification (figure not shown), suggesting that unsaturated free fatty acids are unable to suppress the centrosome amplification.

In our study, 3.4% of the PBMC from the healthy subjects displayed centrosome amplification (Fig. 1B), which agrees with the finding by Dementyeva and do-workers that approximately 3% of the peripheral blood cells from healthy donors display centrosome amplification (Dementyeva et al., 2010).

It is known that obesity increases the risk for cancer (Mazzarella, 2005). There is also

evidence that type 1 diabetes modestly increases the risk for cancer (Zendehdel et al., 2003). Obesity is associated with increased plasma levels of insulin and free fatty acids (Golay et al., 1986).Type 1diabetes is associated with hyperglycaemia and increased free fatty acid level. All these pathophysiological factors were able to cause centrosome amplification (Figs. 2C-2D). Thus, we speculate whether centrosome amplification could play a role the cancer development in obesity and type 1 diabetes. Moreover, our results (Figs. 3B and 3C) showed that the diabetic pathophysiological factors could upregulate ROCK1 and 14-3-3σ which are associated with neurodegeneration (Joo et al., 2015; Hu et al., 2016), upon which we further speculate whether ROCK1 and/or 14-3-3σ could be new clues for the development of Alzheimer's disease which shows an increased risk in type 2 diabetes (Zhang et al., 2016).

The study involved limited number of subjects. Further analysis with large cohorts is required to confirm the findings. In the study, we used PBMC to demonstrate the increase in centrosome amplification in type 2 diabetes. This raises a concern of whether centrosome amplification occurs in other tissues prone to diabetes-related cancer.

In conclusion, our results show that type 2 diabetes promotes cell centrosome amplification, and suggest that activation of AKT-ROS-dependent upregulations in expression, binding and centrosome translocation of ROCK1 and 14-3-3σ by the pathophysiological factors in type 2 diabetes is the underlying molecular mechanism.

MATERIALS AND METHODS

Chemicals, antibodies and cells

All chemicals were purchased from Sigma (St. Louis, MO, USA). Gama-tubulin antibody (No. ab27074; mouse antibody) was purchased from Abcam (Cambridge, UK). Rock1 antibody (No. 4035; rabbit antibody) was provided by cell signaling technology (Boston, MA, USA). 14-3-3σ antibody (No. PLA0201; rabbit antibody) was purchased from Sigma (St. Louis, MO, USA). Other antibodies were provided by

Cell Signalling Technology (Boston, MA, USA). HCT116 colon cancer cells were kindly provided by Dr. B. Vogelstein of the Johns Hopkins University School of Medicine, who produced the cell line. Normal human breast epithelial cells (PCS-600-010) and culture medium were purchased from the American Type Culture Collection (ATCC, Manassas, VA, USA). The culture medium and reagents for the colon cancer cells were purchased from Gibco (Beijing, China). The palmitic acid stock was conjugated to fatty acid-free bovine albumin in a 3:1 molar ratio at 37 ℃ for 1 hour before use. Anti-gamma tubulin antibody was used to detect centrosome by innumofluorescent staining. ROCK1 siRNA treatment largely reduced the staining of ROCK1. 14-3-3 was seen in the centrosome only after experimental treatment. These observations showed that non-specific staining by the antibodies would not affect the experimental observations.

Clinical study

Institutional approval and written informed consent were obtained from the medical ethics committee and all participating subjects, respectively. All the volunteers were consecutively recruited during 2014 and 2016 at the Shanxi Hospital of Integrative Western and Chinese Medicine and Shanxi Medical University without any selection bias. Type 2 diabetes was diagnosed according to the 1999 WHO criteria. All healthy subjects were free hypertension. Each volunteer donated 5-ml blood sample. All the clinical data were collected by clinical doctors responsible for the clinical study.

Cell culture

HCT116 cells were maintained in DMEM (low glucose, 5mM) supplemented with 50 U/ml penicillin, 50 g/ml streptomycin and 10% (v/v) foetal calf serum. Human primary breast epithelial cells were cultured in basal medium (PCS-600-030) with a growth kit (PCS-600-040, ATCC, Manassas, USA) according to ATCC instructions. Epithelial cells from the second passage in our lab were used in the study. In cell model studies, cells treated for 12 hours were used for ROS quantification. Cells treated for 24 hours were harvested for co-immunoprecipitation assay. Those treated for 30 hours were used for transcriptomic analysis. Cells treated for 48 hours were used for quantification of centrosome number and protein distribution in centrosomes. We performed time course assays and the time points were chosen, since these time points produced the highest level of differences for the measurements between the

control and the treated samples.

Quantification of ROS

Changes in the intracellular ROS levels were determined using the 2,7'-dichlorofluorescein (DCFH-DA, Beyotime, Shanghai, China) probe on a spectrofluorometer (SpectraMax M5, Molecular Devices, Silicon Valley USA). Cells grown in a 24-well plate were treated, washed twice with PBS, and incubated with DCFH-DA for 20 min at 37 oC. Then, the cells were harvested, washed once in PBS, and transferred to a 96-well plate. Optical density values were obtained at an excitation wavelength of 488 nm and an emission wavelength of 525 nm. Alternatively, the ROS levels were quantified using a flow cytometer (FACSCalibur, BD, New Jersey, USA) according to the manufacturer's instructions.

Confocal microscopy

A cover slip was placed in a well of a 6-well plate. Cells were plated at a density of 50,000 cells per well. Cells grown on the cover slips were fixed in cold methanol and acetone (1:1; v:v) for 6 min at -20℃, followed by three washes with PBS (10 min each time). Then, the cells were incubated with 0.1% Triton X-100 for 15 minutes and 3% BSA for 1 hour. The cells were incubated with a primary antibody in 3% BSA in PBS overnight at 4 ℃, washed twice with PBS, and incubated with a FITC-conjugated secondary antibody in 3% BSA in 1×PBS for 1 hour at room temperature in the dark. Finally, the cells were mounted with mounting medium. Confocal microscopy was performed using the Zeiss LSM880 microscope (Oberkochen, Germany) with a 1.4 NA oil-immersion lens, and image processing was performed with Zen software (Oberkochen, Germany). One hundred cells were counted for their centrosome numbers for the percentage of centrosome amplification.

To separate peripheral blood mononuclear cells (PBMC), we loaded a 5-ml blood sample on the top of separation medium (LTS1077; TBD, Tianjin, China) in a centrifuge tube and centrifuged at 250 g for 20 min. The cells on the top were collected, washed twice in PBS, smeared onto a cover slip, and air dried for 24 hours at room temperature.

Transcriptomic profiling and bioinformatic annotation

The cells were harvested after treatment and total RNA was extracted. Two cDNA libraries (control or treatment with high glucose, insulin, and palmitic acid) were constructed using the Illumina TruSeq RNA Sample Preparation Kit (Illumina, USA) according to the manufacturer's instructions. After several steps of purification, adapter addition, and cDNA length selection, the two libraries were sequenced independently using an Illumina HiSeq™500 platform (Shanghai Personal Biotechnology Co., Shanghai, China). Pathway assignments were generated using GO (geneontology.org) and KEGG databases (www.kegg.jp).

Western blot analysis

The cells were lysed in RIPA buffer. Proteins were separated by polyacrylamide gel electrophoresis and transferred onto PVDF membrane. After blocking for 1 hour at room temperature with TBST containing 0.05% (v/v), Tween-20 and 5% (w/v) non-fat milk, the membranes were incubated with primary antibodies overnight at 4 ℃, followed by washes with TBST containing 0.05% Tween-20.The membranes were then incubated with a horseradish peroxidase-conjugated secondary antibody for 1 hour at room temperature. ECL reagents (Thermo Biosciences, Massachusetts, USA) were used to visualize the protein bands which were captured on X-ray film.

Co-immunoprecipitation

Cells were harvested under non-denaturing conditions, washed by ice-cold PBS for 3 times, lysed in 0.5 ml ice-cold cell lysis buffer and centrifuged. Supernatant was collected to a new tube and incubated with 20 ul Protein G Plus /Protein A agarose (Miliproe, IP05 USA) with gentle shaking for 2 hours at 4 oC. Protein G Plus /Protein A agarose was then removed by centrifuge for 10 min at 4 oC, and supernatant was incubated with primary antibody overnight at 4 oC with gentle shaking. After that, 30ul Protein G Plus /Protein A agarose were added and incubated under gentle shaking for 4 hours at 4 oC. Finally Protein G Plus /Protein A agarose was collected by centrifuge.

Knockdown of protein level

The pre-designed siRNA oligonucleotides (Songon Technology, Shanghai, China) for Akt1, ROCK1 and 14-3-3σ were:

GAGUUUGAGUACCUGAAGCUGUU (sense) and
AACAGCUUCAGGUACUCAAACUC (antisense);
UGAUCUUGUAGCUCCCGCAUGUGUC (sense) and
ACUAGAACAUCGAGGGCGUACACAG (antisense); and
ACCTGCTCTCAGTAGCCTA (sense) and TAGGCTACTGAGAGCAGGT (antisense), respectively. HCT116 cells (5×104 cells per well) were seeded in 6-well plates and cultured for 24 hours, and then were transfected with 200 pM siRNA oligonucleotides using Lipofectamine 2000 transfection reagent (Invitrogen, California, USA), according to the manufacturer's instructions. The total AKT protein level was evaluated by Western blot analysis 24 hours after transfection.

Statistical analysis

All the experiments including the transcriptomic profiling were performed in triplicate. The data are expressed as the mean ± SD. Student's t-test was performed to compare the difference between two groups. Multi-group comparisons were performed using one-way ANOVA analysis. Linear regression analysis was performed for correlations. The statistical analysis software package SPSS21 was employed for the statistical comparisons. A p value < 0.05 was considered statistically significant.

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Competing interests

The authors declare that there is no conflict of interest.

Author contribution

P Wang and YC Lu performed most of the experiments. J Wang and YF LI contributed the clinical studies. L Wang provided the technologies. H Yu was involved in grant applications and the study design. A Kong and J Chan contributed the ROS data set and were involved in designing the study. SC Lee was the principal investigator, who was in charge the whole project, from grant application and study design to manuscript preparation.

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Figure Legends

Fig. 1.

Cell centrosome amplification is increased in patients with type 2 diabetes, which is in correlation with fasting blood glucose and HbA1c. (**A**): image of centrosome amplification; (**B**): cell centrosome amplification is increased in patients with type 2 diabetes; (**C**): evidence that centrosome amplification correlates with the fasting blood glucose; (**D**) and (**E**): correlation analysis shows that the centrosome amplification correlates with the fasting blood glucose and HbA1c in all the volunteers; (**F**) and (**G**): in the diabetic patients alone, centrosome amplification also correlates with fasting blood glucose and HbA1c.Student t-test was used to compare the means between two groups. One way ANOVA analysis was used to compare multiple groups. Linear regression was performed for correlations. *: $p < 0.05$; **: $p < 0.01$, compared with

567 that in the control group.

568

569 **Fig. 2.**

570 **High glucose, insulin and palmitic acid, alone or in combinations, induce**
571 **centrosome amplification via ROS production.** (**A**): high glucose, insulin and
572 palmitic acid, alone or in combinations, triggers ROS production in the cancer cells;
573 (**B**): the pathophysiological factors, together, trigger ROS production in normal
574 human breast epithelial cell; (**C**): high glucose, insulin and palmitic acid, alone or in
575 combinations, can promote centrosome amplification in the cancer cells; (**D**): high
576 glucose, insulin and palmitic acid can trigger centrosome amplification in the normal
577 human breast epithelial cells. (**A**)-(**D**): NAC inhibits the ROS production and the
578 centrosome amplification. Glu: glucose, 15 mM; Ins: insulin, 5 nM; Pal: palmitic acid,
579 150 μM; NAC: 3 mM. One way ANOVA analysis was used to compare multiple
580 groups. *: $p < 0.05$; **: $p < 0.01$.

581

582 **Fig. 3.**

583 **Functional transcriptomic analysis identifies AKT, ROCK1 and 14-3-3σ as signal**
584 **mediators for the centrosome amplification.** (**A**), (**B**) and (**C**):the diabetic
585 pathophysiological factors activate of AKT, ROCK1 and 14-3-3σ, respectively; (**D**):
586 inhibition of AKT using chemical inhibitor or siRNA blocks the centrosome
587 amplification in the colon cancer cells; (**E**): ROCK1 siRNA inhibits the centrosome
588 amplification; (**F**): 14-3-3σ siRNA inhibits the centrosome amplification in normal
589 human breast epithelial cells. (G): AKT inhibitor inhibits centrosome amplification;
590 (H): AKT siRNA, ROCK1 siRNA and 14-3-3σ siRNA inhibit centrosome
591 amplification in normal human breast epithelial cells. One way ANOVA analysis was
592 used to compare multiple groups.**: $p < 0.01$, compared with that in the control group;
593 ##: $p < 0.01$, compared with that in the samples treated with Glu, Ins and Pal.Glu:
594 glucose, 15 mM; Ins: insulin, 5 nM; Pal: palmitic acid, 150 μM; Ly294002: 30 μM.

595

596

Fig. 4.

AKT-ROS-dependent signaling of ROCK1 and 14-3-3σ is the molecular pathway for the centrosome amplification. (**A**) and (**B**): AKT chemical inhibitor and siRNA inhibit ROS production, respectively; (**C**): AKT chemical inhibitor or siRNA inhibits ROCK1 upregulation; (**D**): AKT chemical inhibitor or SiRNA inhibits 14-3-3σ upregulation; (**E**) and (**F**): NAC inhibits the upregulation of ROCK1 and 14-3-3σ, respectively. Glu: glucose, 15 mM; Ins: insulin, 5 nM; Pal: palmitic acid, 150 μM; Ly294002, 30 μM; NAC: 3 mM.

Fig. 5.

High glucose, insulin and palmitic acid increase the binding between ROCK1 and 14-3-3σ as well as their centrosome translocation. (**A**): use of ROCK1 or 14-3-3σ antibodies to pull down their binding partner, and the influences of Ly294002 and NAC; (**B**) and (**C**): quantification of the gel images of Western blot analysis shown in Fig. 5A; (**D**): confocal image of ROCK1 localization in the centrosomes; (**E**): confocal image of 14-3-3σlocalization in the centrosomes; (**F**): high glucose, insulin and palmitic acid increases level of ROCK1 localization in the centrosomes, which is inhibited by AKT inhibitor and NAC but not 14-3-3σ siRNA; (**G**): experimental treatment increases the localization of 14-3-3σ to the centrosomes, which is inhibited by AKT inhibitor, NAC or ROCK1 siRNA. One way ANOVA analysis was used to compare multiple groups.**: $p < 0.01$, compared with that in the control group; ##: $p < 0.01$, compared with that in the samples treated with Glu, Ins and Pal.Glu: glucose, 15 mM; Ins: insulin, 5 nM; Pal: palmitic acid, 150 μM; Ly294002, 30 μM; NAC, 3 mM.

Fig. 6.

The increases in AKT activation and ROS production as well as expression, binding and centrosome distribution of ROCK1 and 14-3-3σ are confirmed in the PBMC from the patients with type 2 diabetes. (**A**): AKT activation as well as expressions of ROCK1 and 14-3-3σ are increased in PBMC from the patients; (**B**):

627 ROS production is increased in the PBMC from the patients; (**C**): binding between
628 ROCK1 and 14-3-3σ is increased in PBMC from the diabetic patients; (**D**) and (**E**):
629 centrosome distributions of ROCK1 and 14-3-3σ are increased in the PBMC from the
630 type 2 diabetic patients, respectively. For Western blot analyses and
631 co-immunoprecipitation, five clinical samples were randomly selected and combined
632 for the experiments. ROS quantification was performed in triplicate using different
633 samples.One way ANOVA analysis was used to compare multiple groups. **: $p <$
634 0.01.

Table 1. Clinical and biochemical characteristics of the volunteers

	Healthy subject	Diabetic patient
n	12	32
Age (years)	57±2	55±2
Sex ratio (male:female)	1:1	1:1
Body mass index (kg/m^2)	19.8±2.7	26.7±5*
Systolic blood pressure (mmHg)	133.3±5.7	131.7±17.2
Diastolic blood pressure (mmHg)	76.6±11.5	83.3±10.3
Fasting blood glucose (mmol/l)	5.3±0.3	10.1±3.7*
HbA1c (%)	5.6±	8.5±2.2*
Total cholesterol (mmol/l)	2.8±1.4	4.9±1.4
Triglyceride (mmol/l)	0.66(0.2-1.1)	2.3(1.2-3.5)*

Data are means±SD, or medians (range). *p<0.05

Fig. 1A

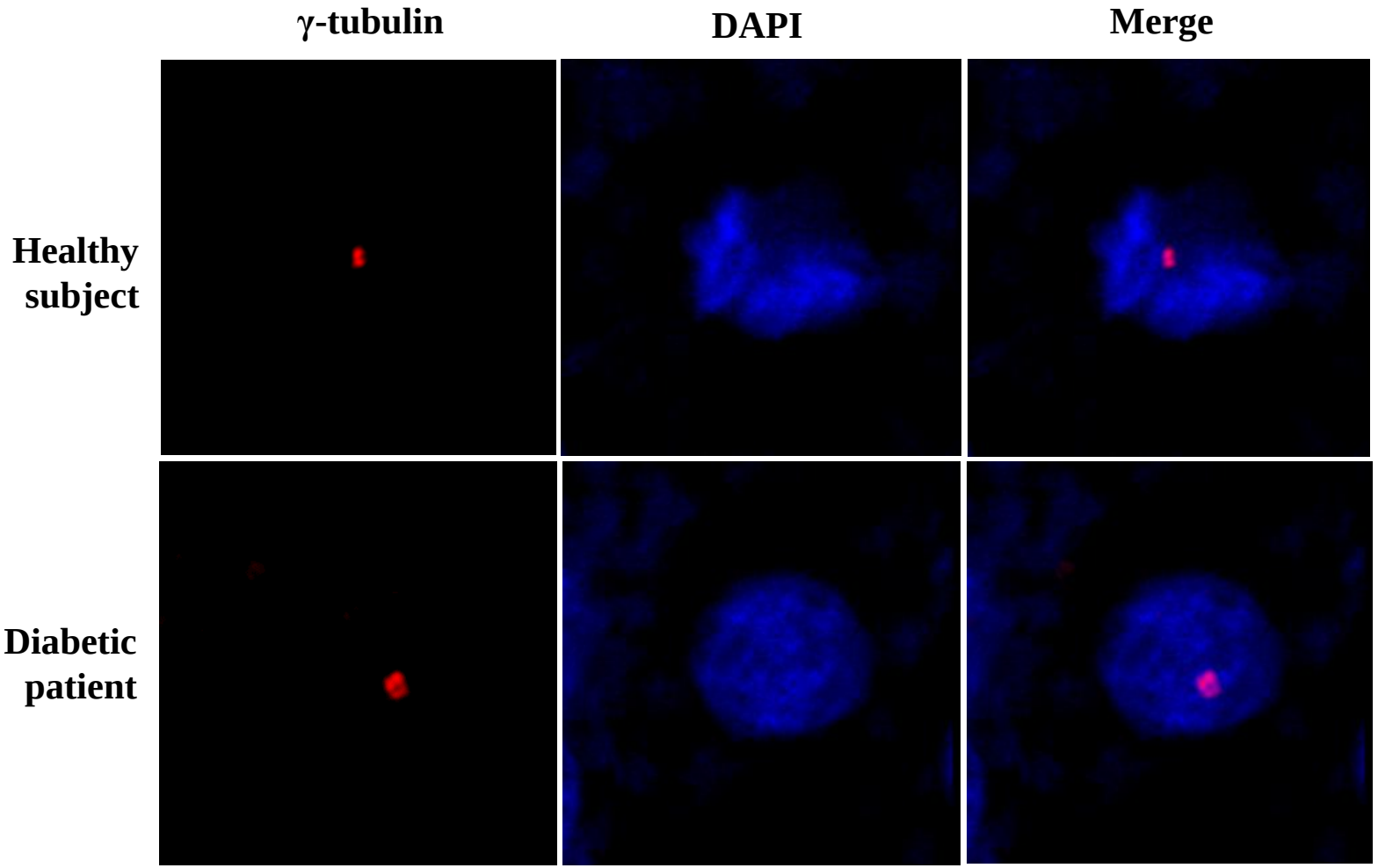

Fig. 1B

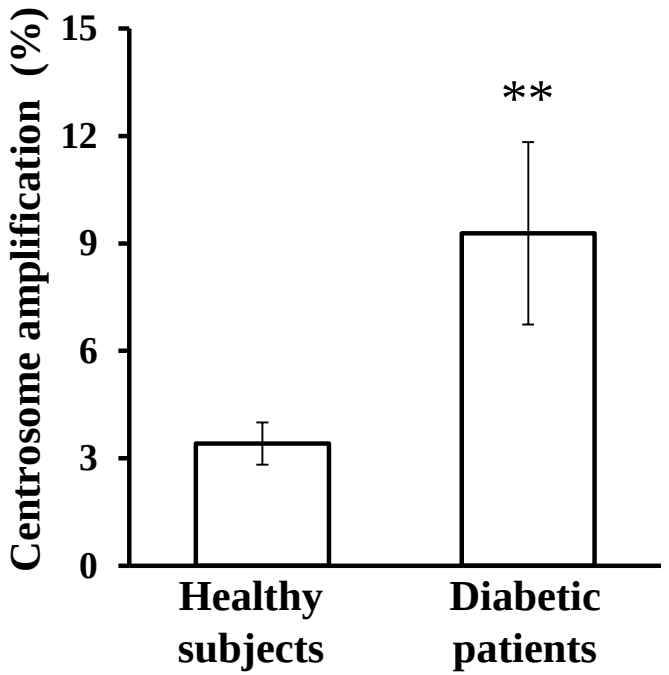
Centrosome amplification (%)
15
12
9
6
3
0
**
Healthy subjects
Diabetic patients

Fig. 1C

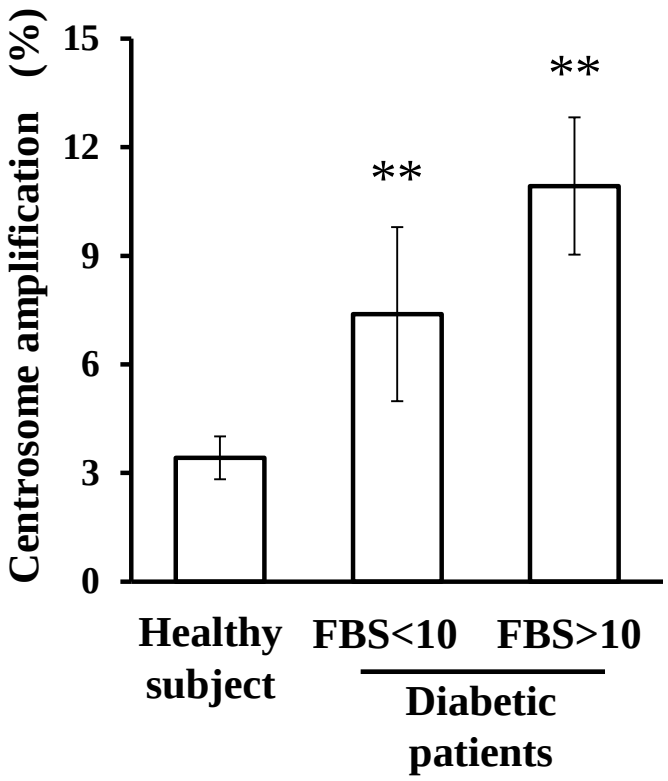
Centrosome amplification (%)
15
12
9
6
3
0
**
**
Healthy subject
FBS<10
FBS>10
Diabetic patients

Fig. 1D

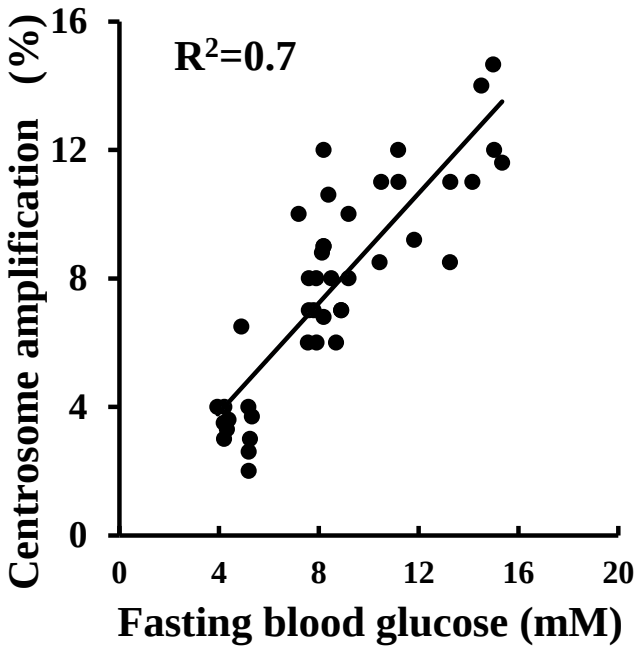
Centrosome amplification (%)
16
12
8
4
0
R2=0.7
0
4
8
12
16
20
Fasting blood glucose (mM)

Fig. 1E

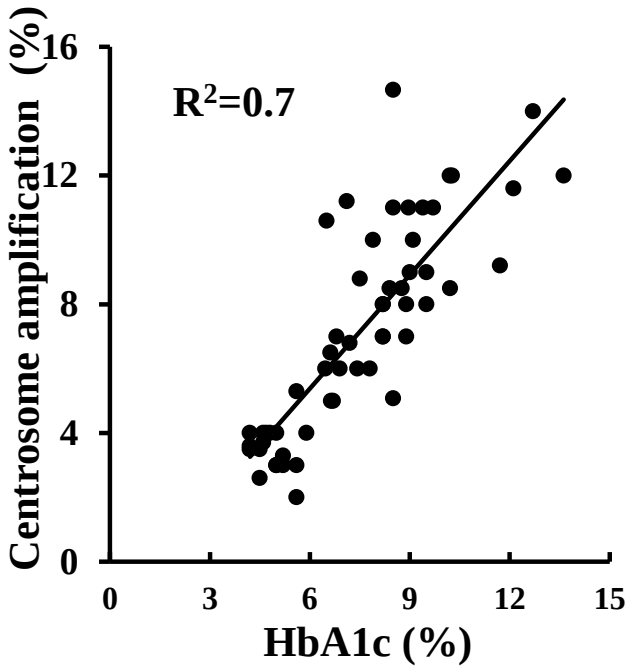

Fig. 1F

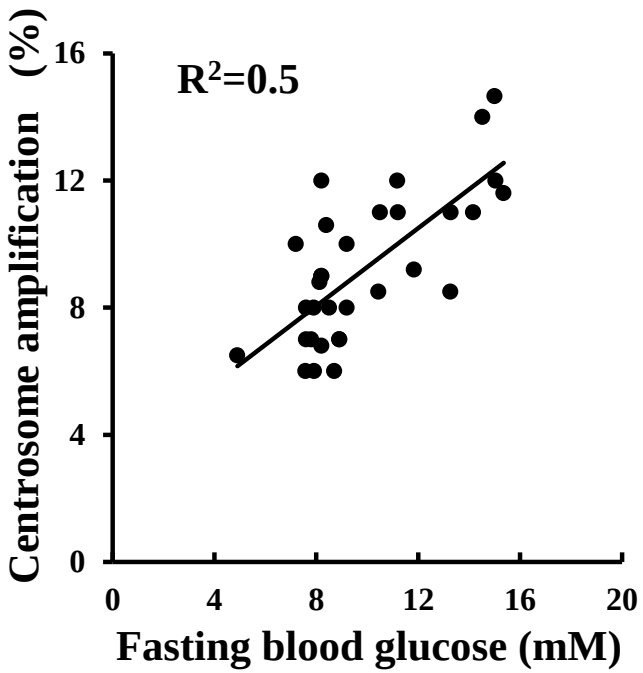
Centrosome amplification (%)
16
12
8
4
0
R2=0.5
0
4
8
12
16
20
Fasting blood glucose (mM)

Fig. 1G

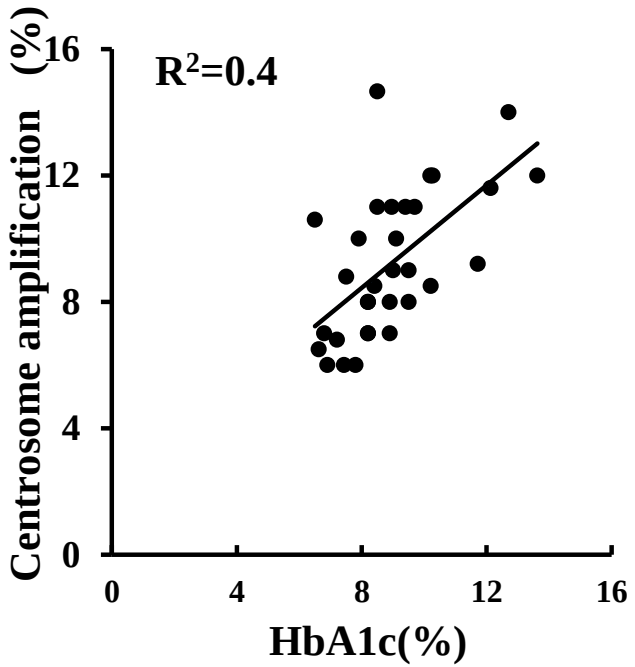

Fig. 2A

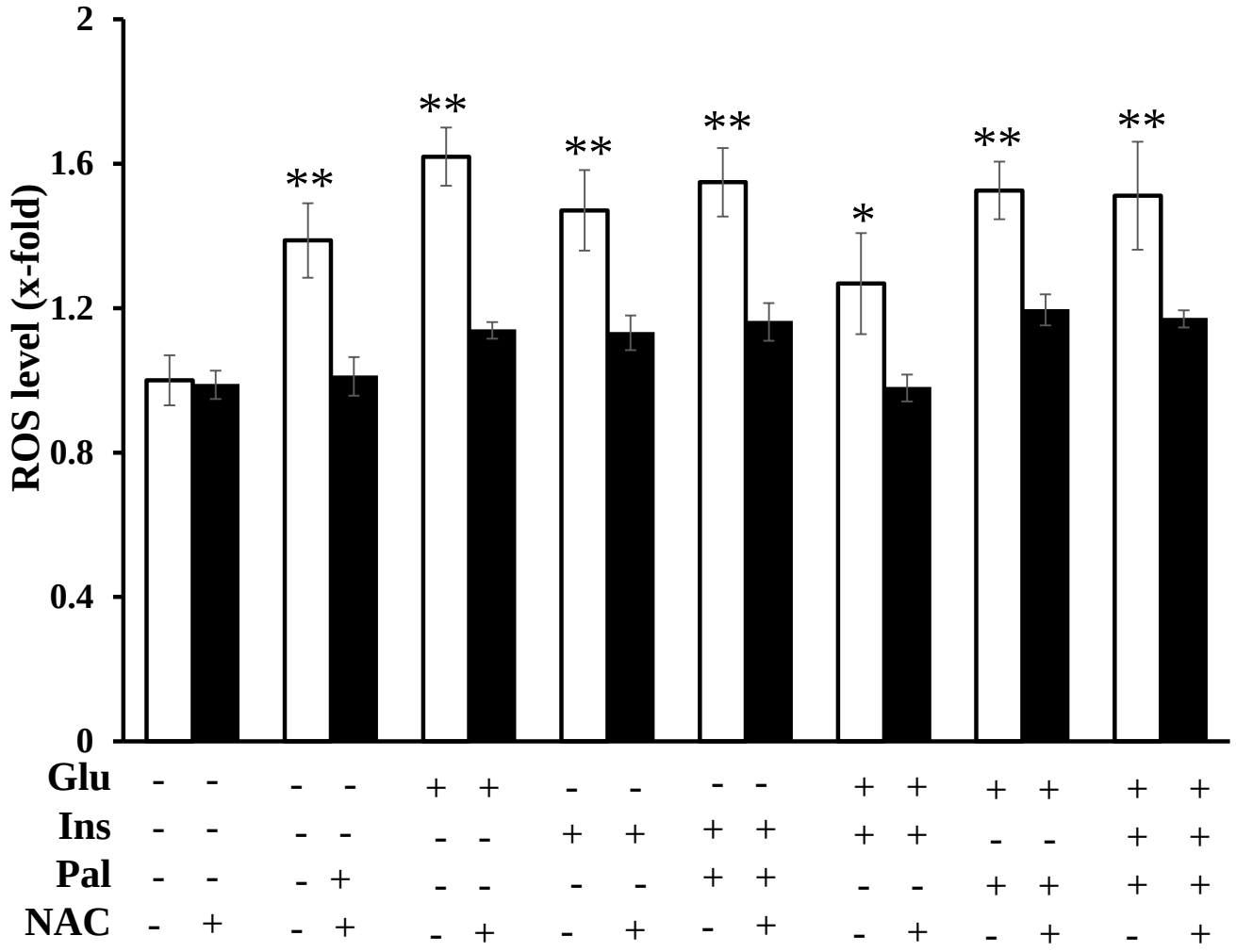

Fig. 2B

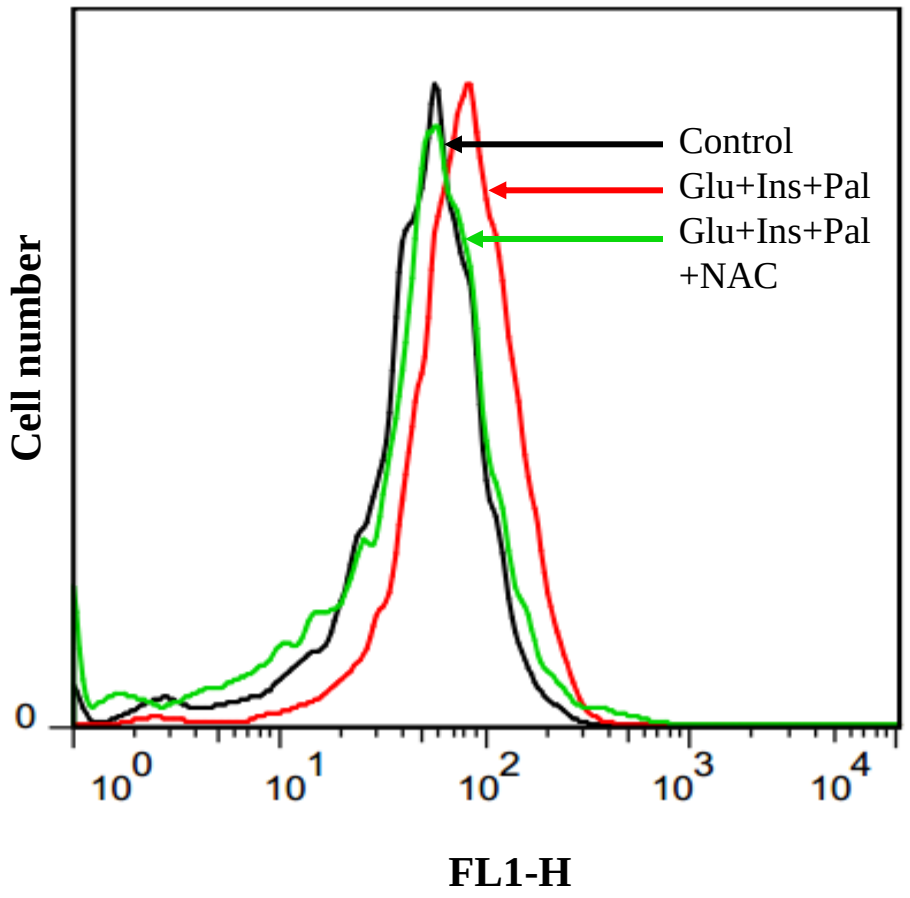
Control
Glu+Ins+Pal
Glu+Ins+Pal
+NAC
Cell number
0
10^0
10^1
10^2
10^3
10^4
FL1-H

Fig. 2C

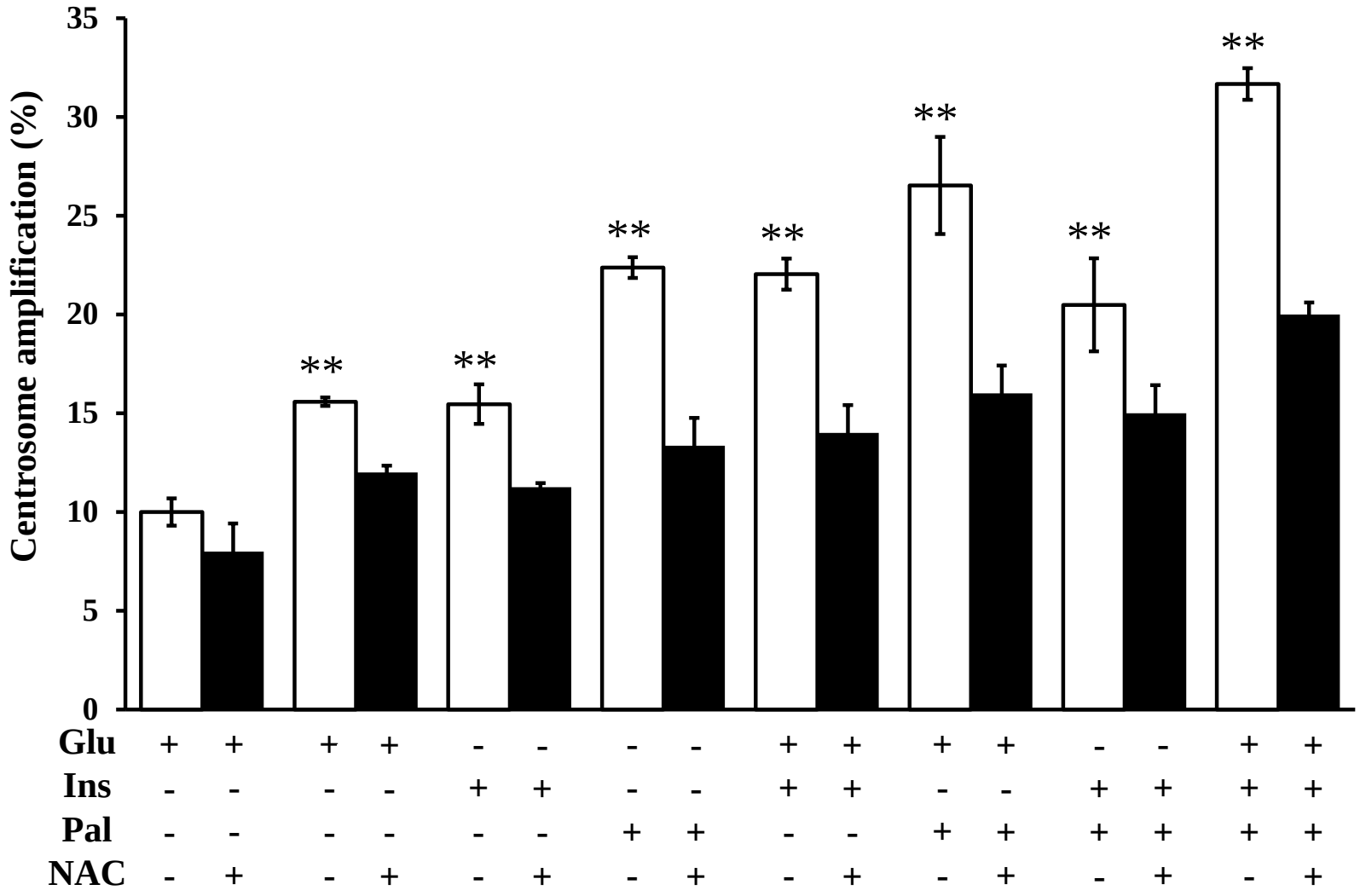

Fig. 2D

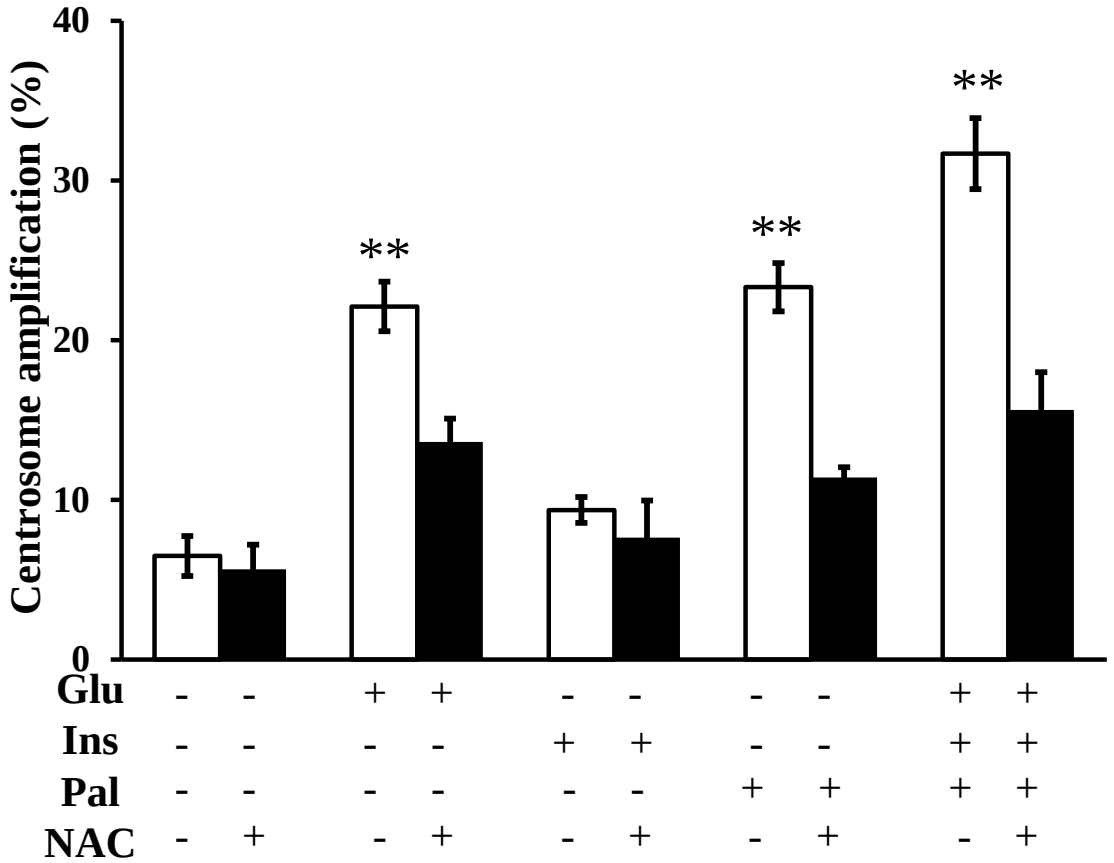

Fig. 3A

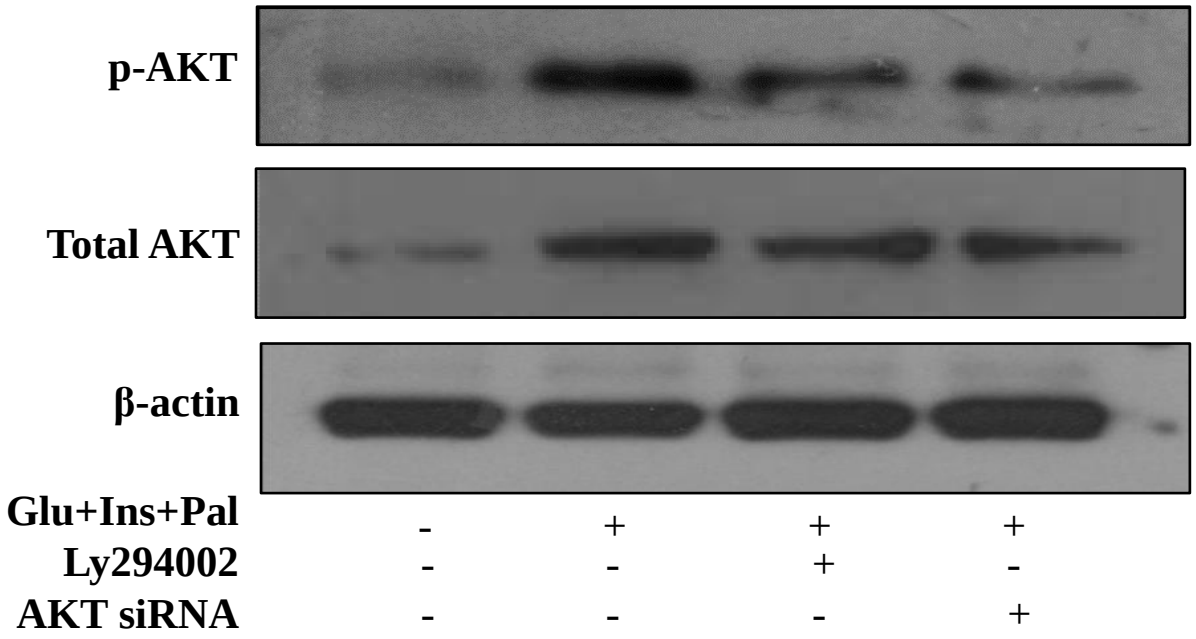

Fig. 3B

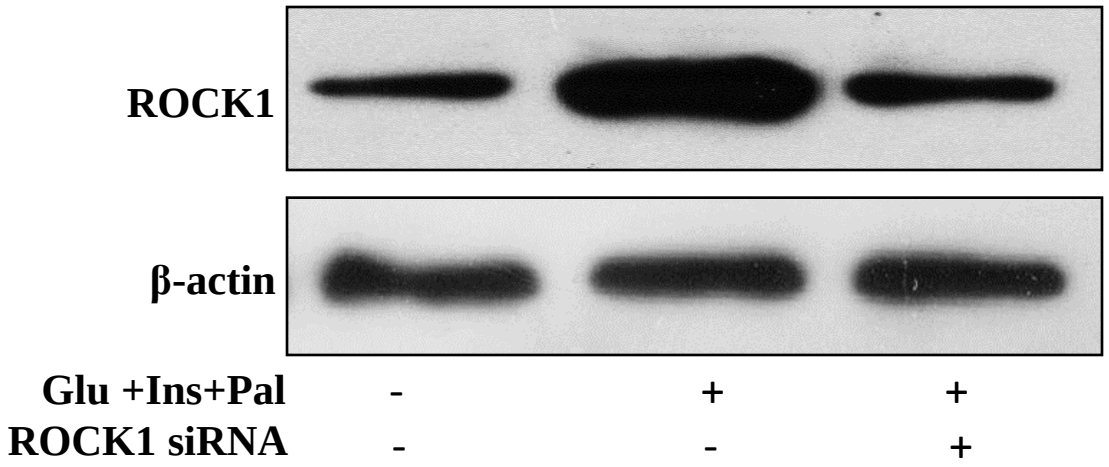

Fig. 3C

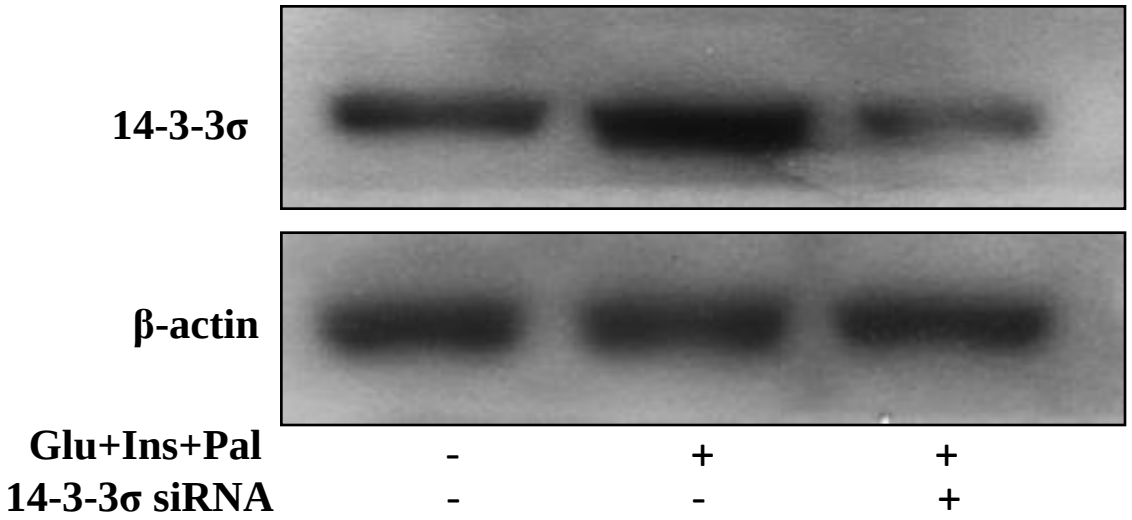

Fig. 3D

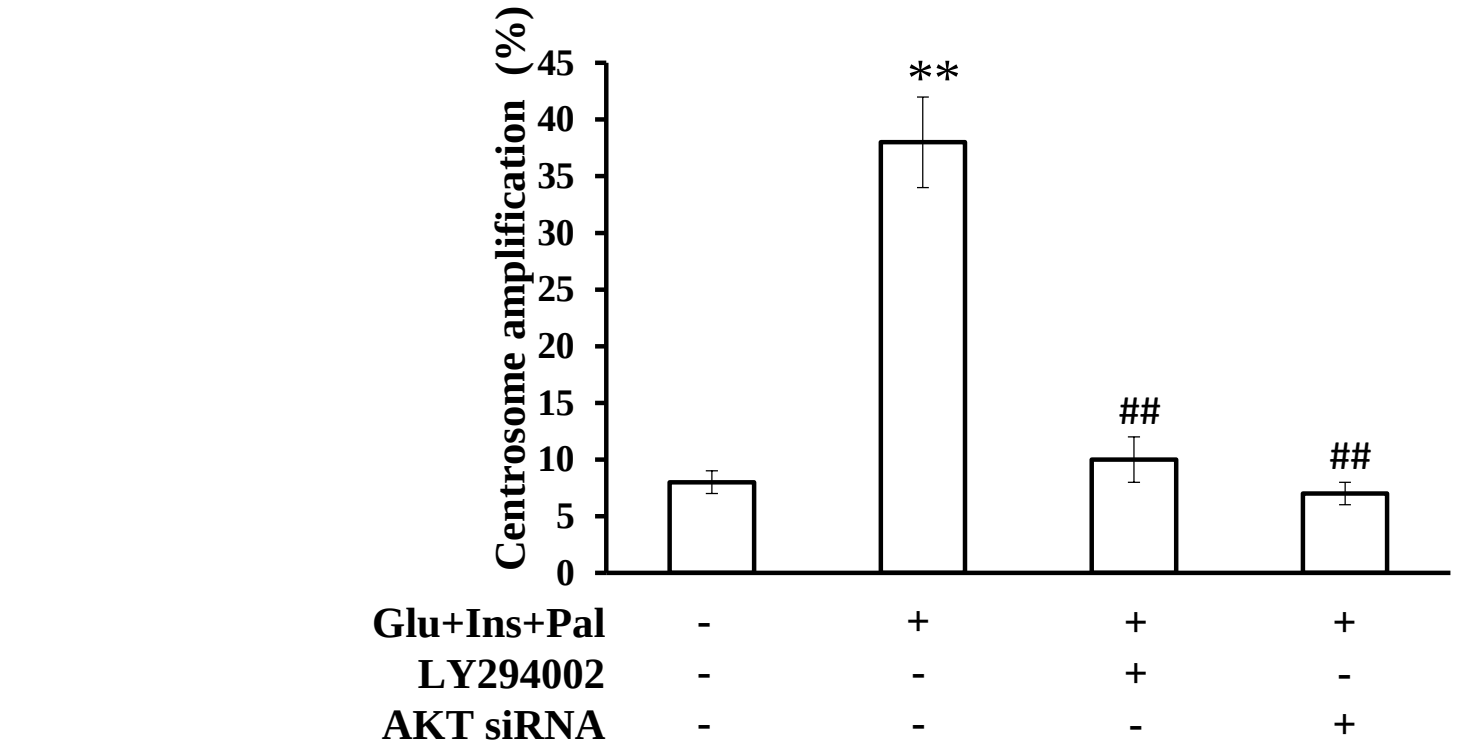
Centrosome amplification (%)
45
40
35
30
25
20
15
10
5
0
**
##
##
Glu+Ins+Pal - + + +
LY294002 - - + -
AKT siRNA - - - +

Fig. 3E

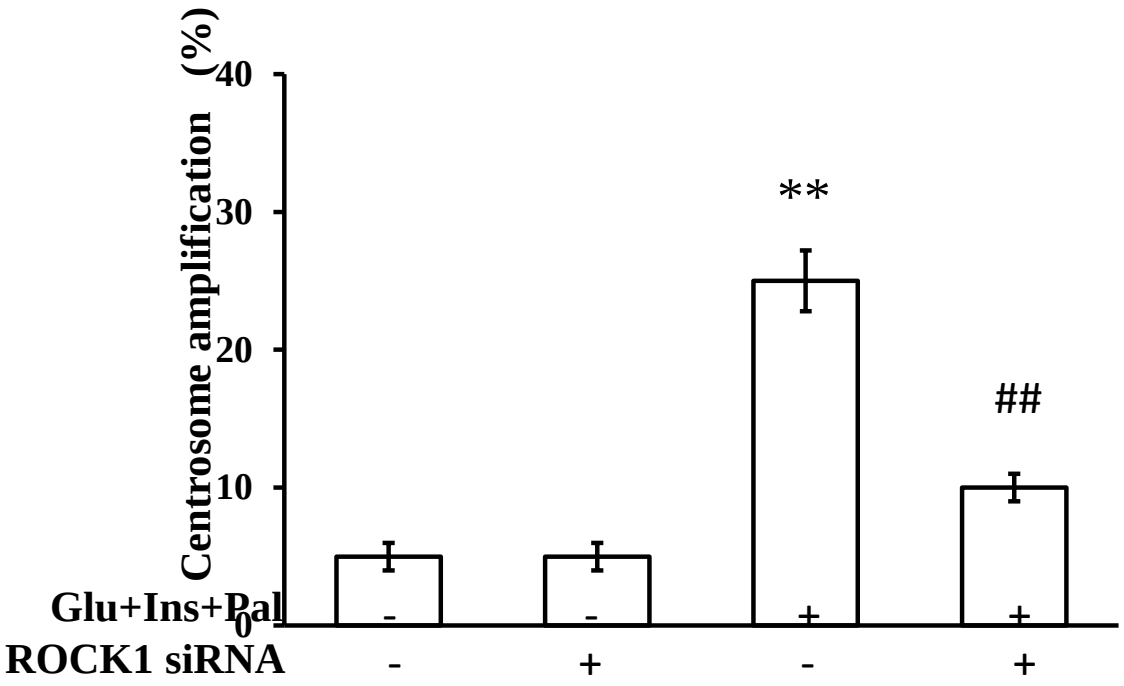
Centrosome amplification (%)
40
30
20
10
0
**
##
Glu+Ins+Pal
ROCK1 siRNA
-
+
-
+
-
-
+
+

Fig. 3F

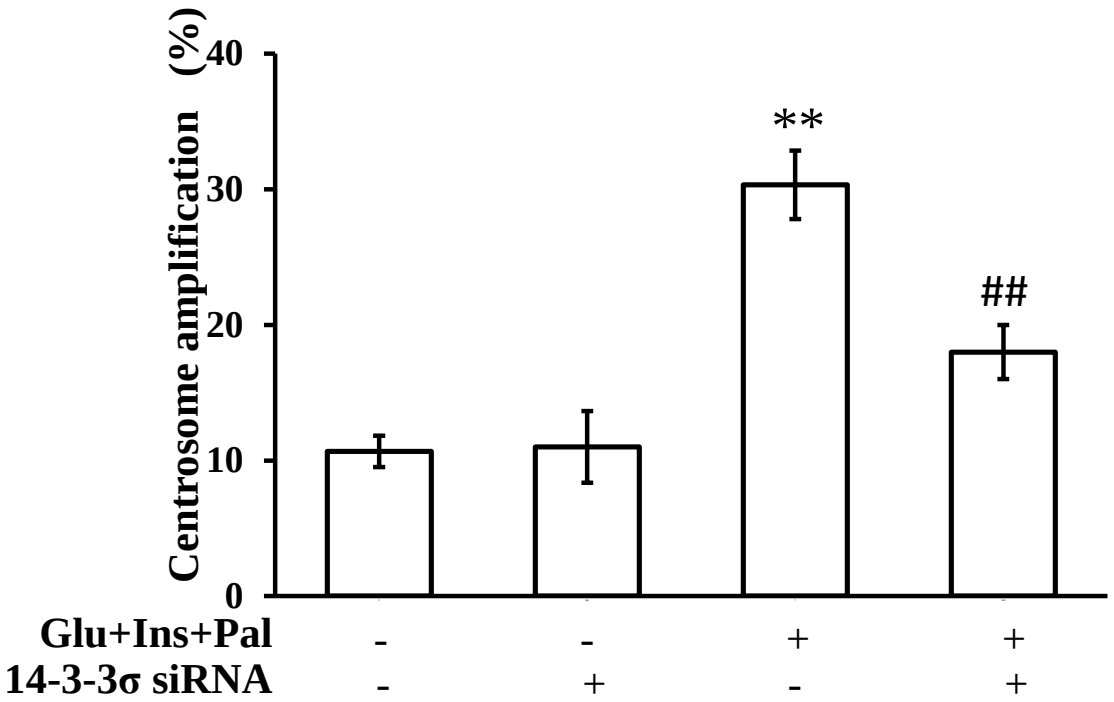
Centrosome amplification (%)
40
30
20
10
0
**
##
Glu+Ins+Pal
14-3-3σ siRNA
- - + +
- + - +

Fig. 3G

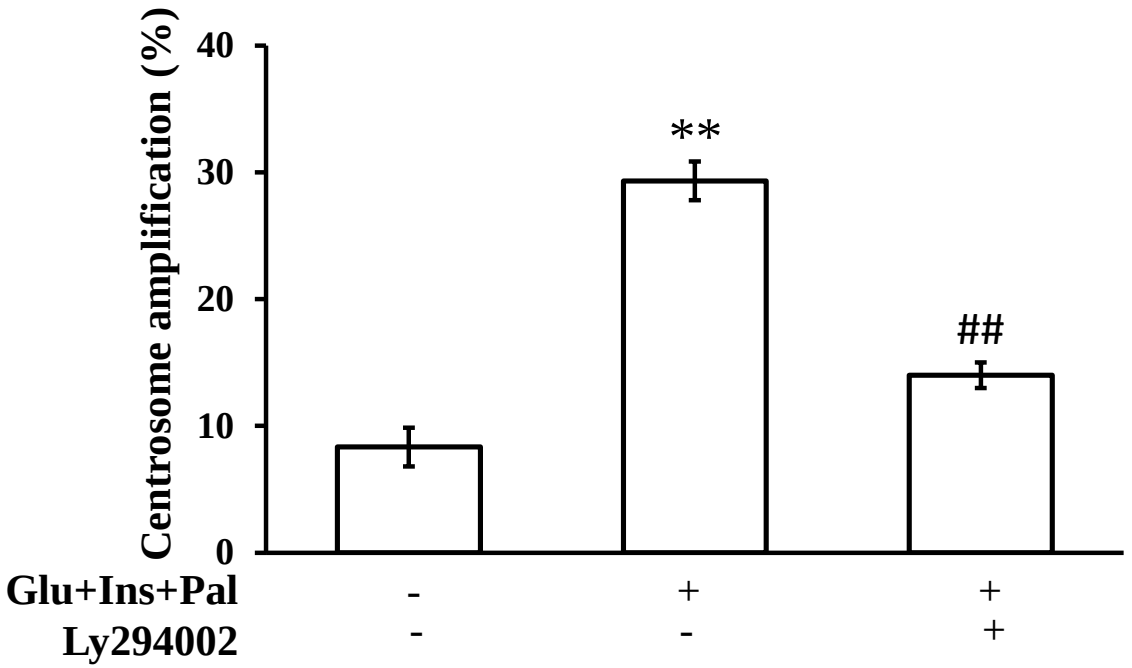

Fig. 3H

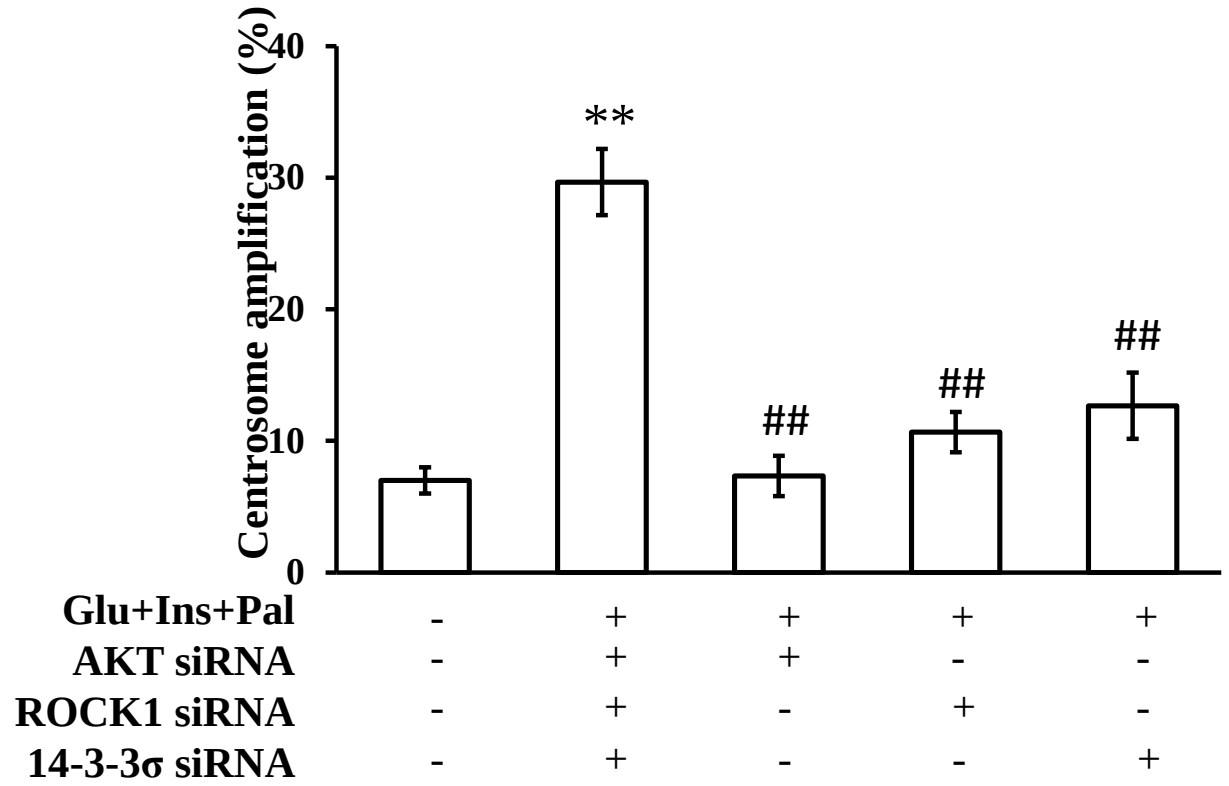
Centrosome amplification (%)
40
30
20
10
0
**
##
##
##
Glu+Ins+Pal - + + + +
AKT siRNA - + + - -
ROCK1 siRNA - + - + -
14-3-3σ siRNA - + - - +

Fig. 4A

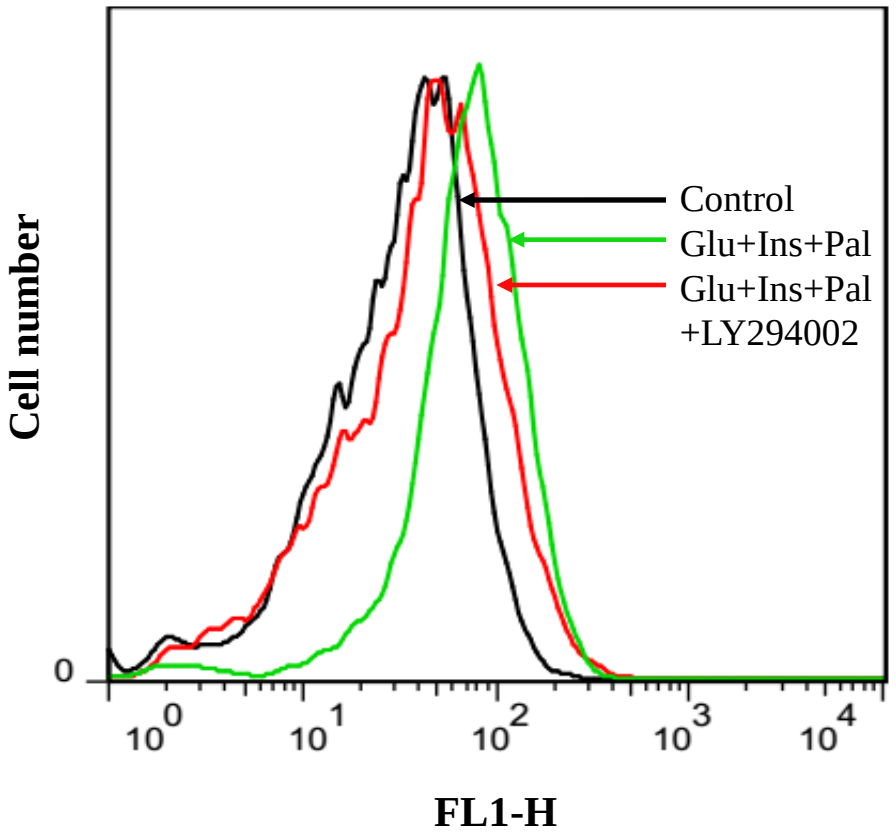
Cell number
0
10^0
10^1
10^2
10^3
10^4
FL1-H
Control
Glu+Ins+Pal
Glu+Ins+Pal
+LY294002

Fig. 4B

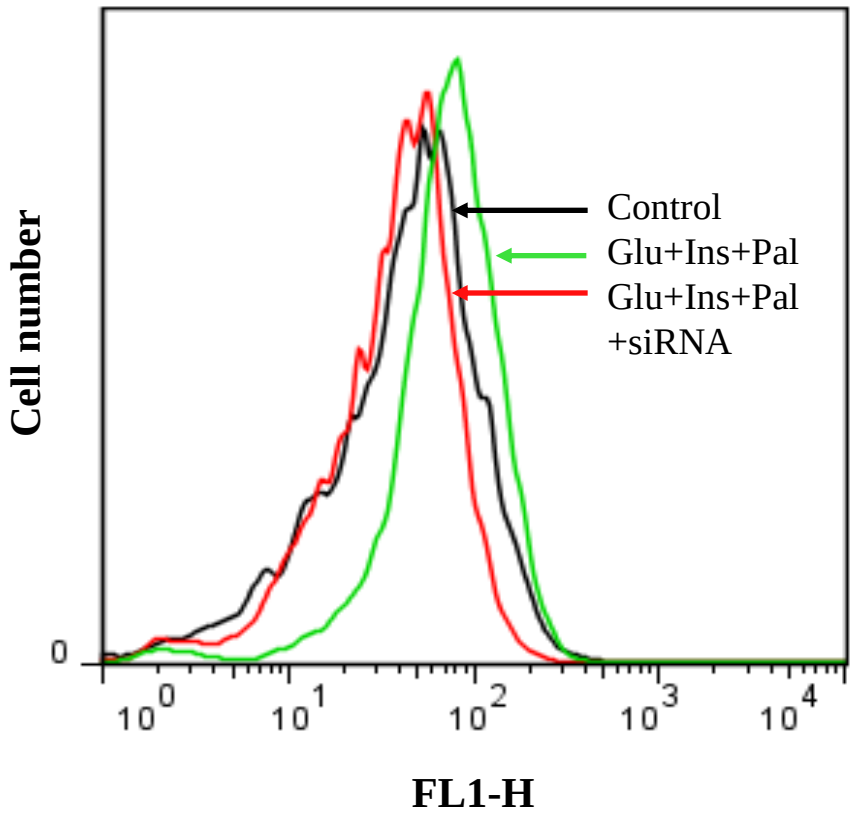
Cell number
0
10^0
10^1
10^2
10^3
10^4
FL1-H
Control
Glu+Ins+Pal
Glu+Ins+Pal
+siRNA

Fig. 4C

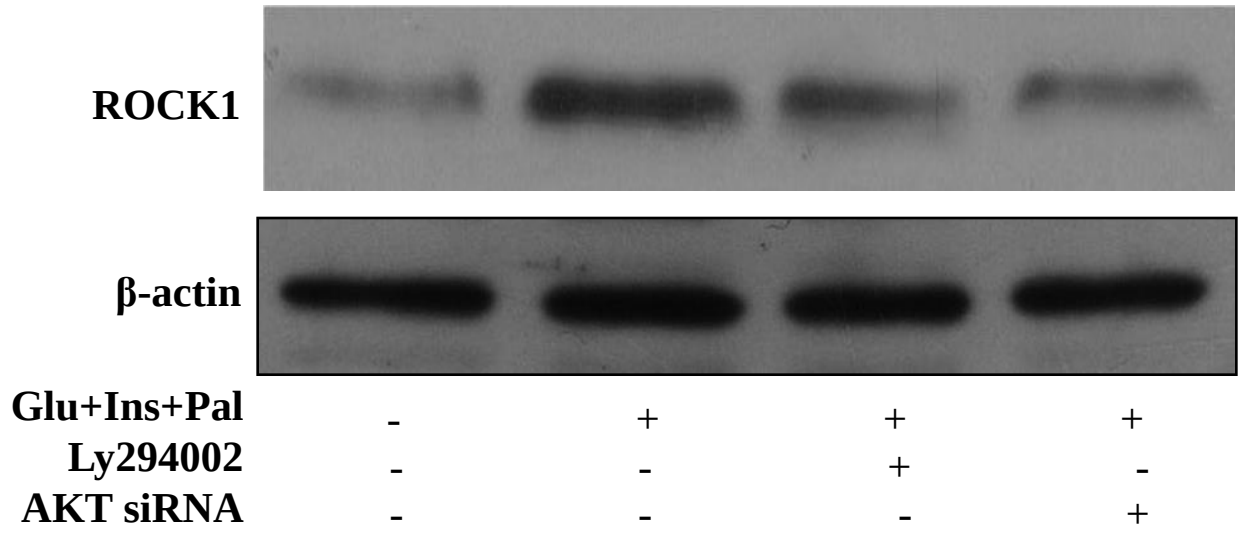

Fig. 4D

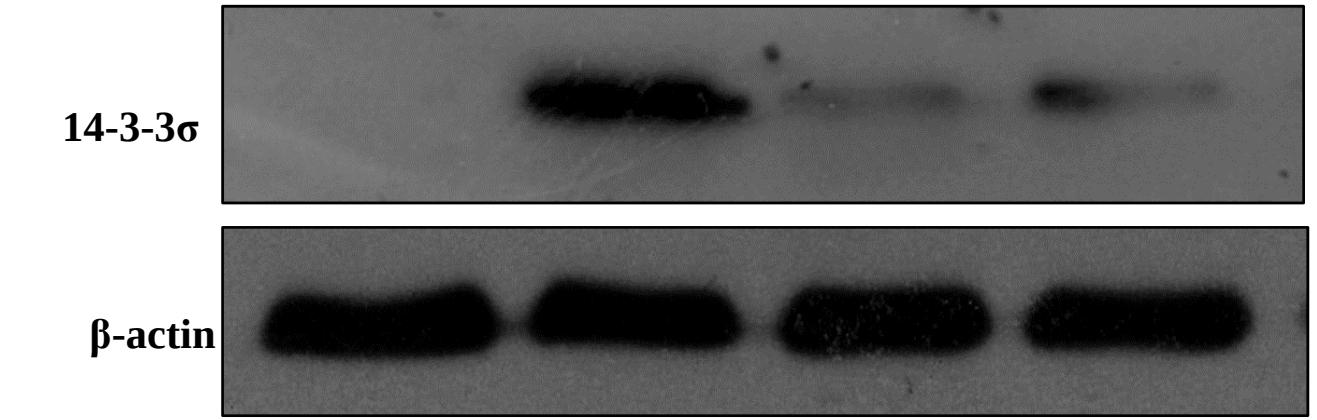

Fig. 4E

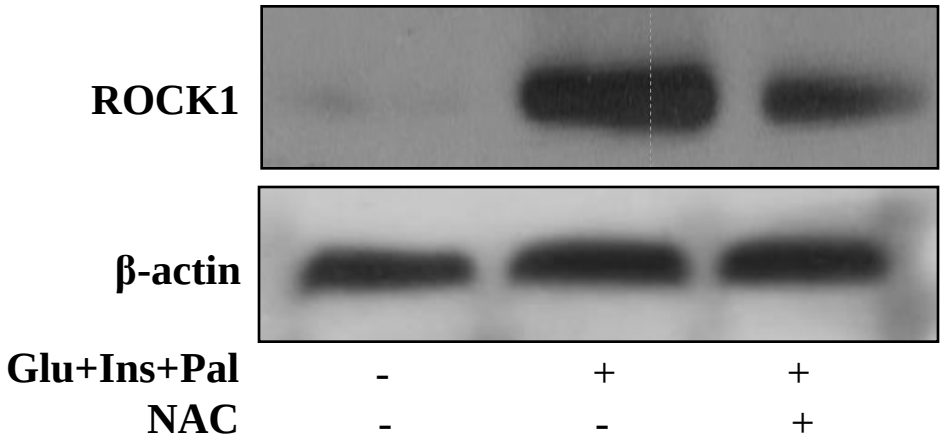

Fig. 4F

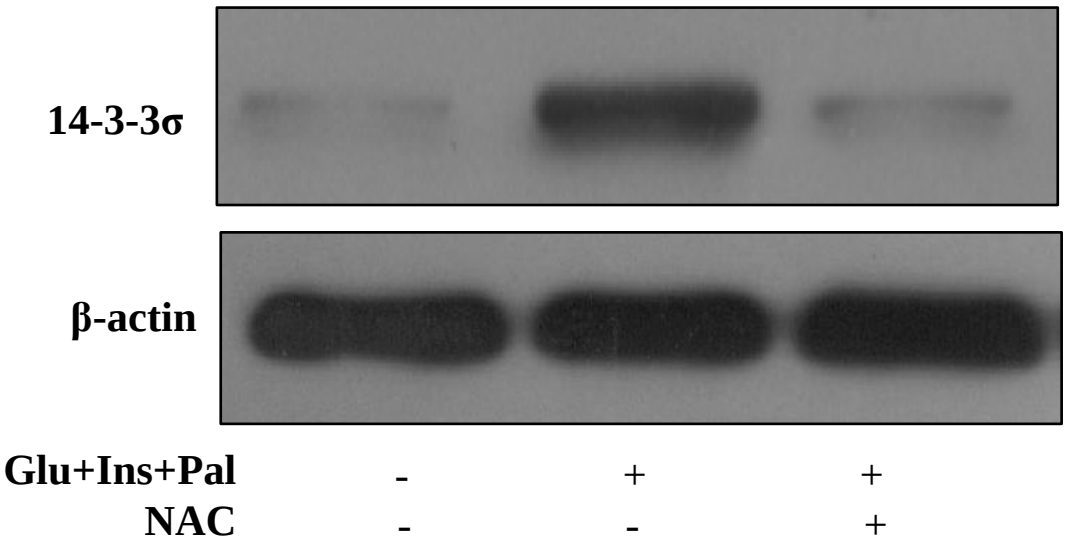

Fig. 5A

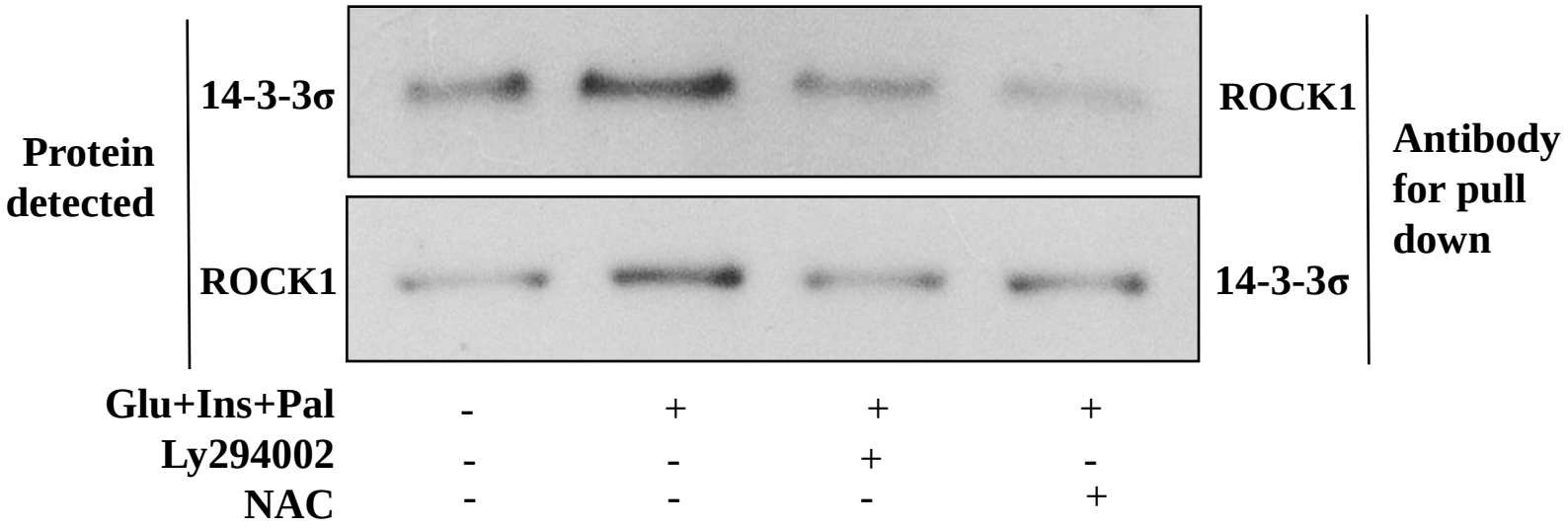
Protein detected
14-3-3σ
ROCK1
ROCK1
14-3-3σ
Antibody for pull down
Glu+Ins+Pal - + + +
Ly294002 - - + -
NAC - - - +

Fig. 5B

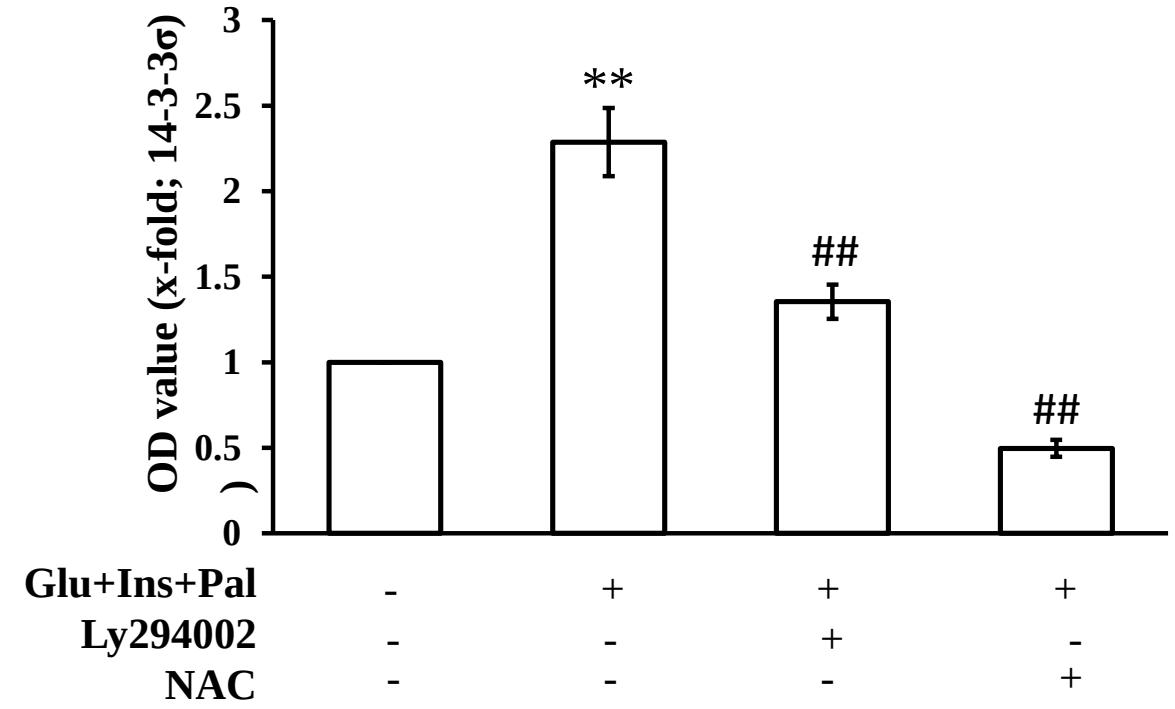

Fig. 5C

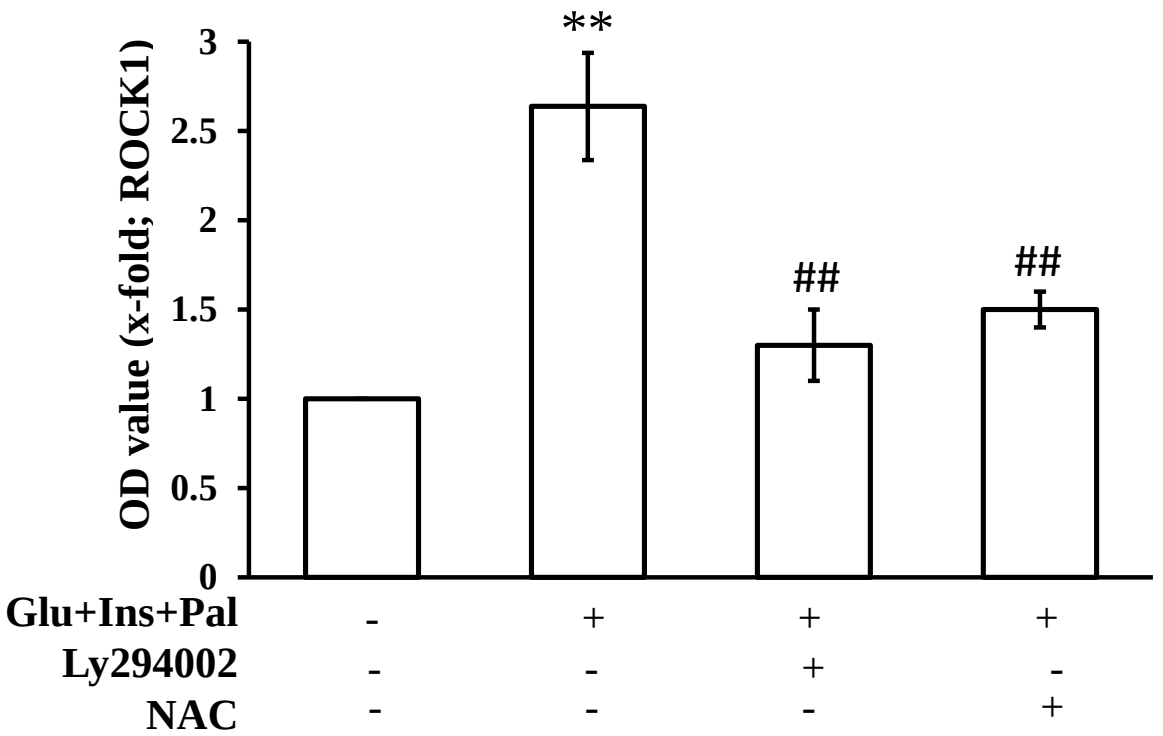

Fig. 5D

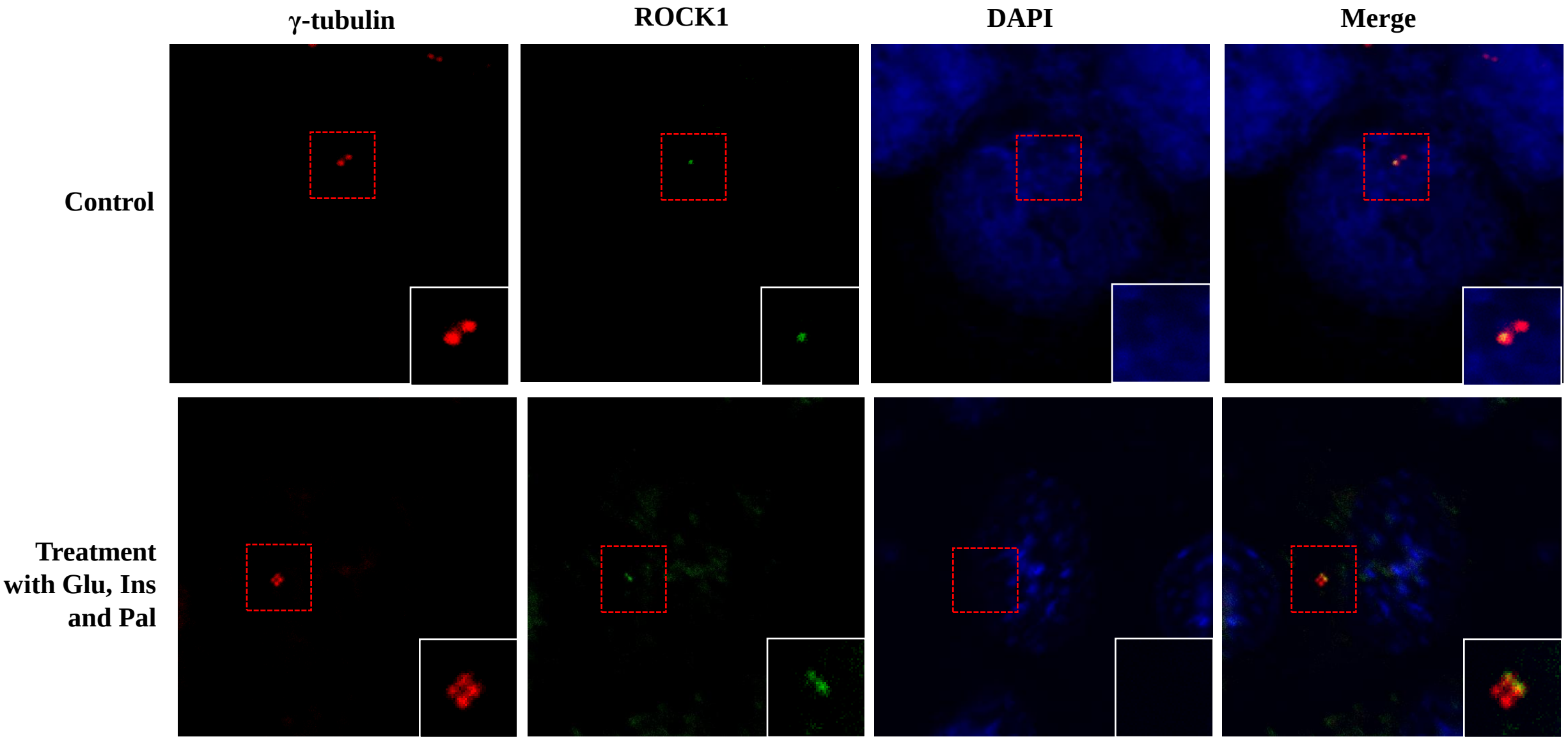
γ-tubulin
ROCK1
DAPI
Merge
Control
Treatment with Glu, Ins and Pal

Fig. 5E

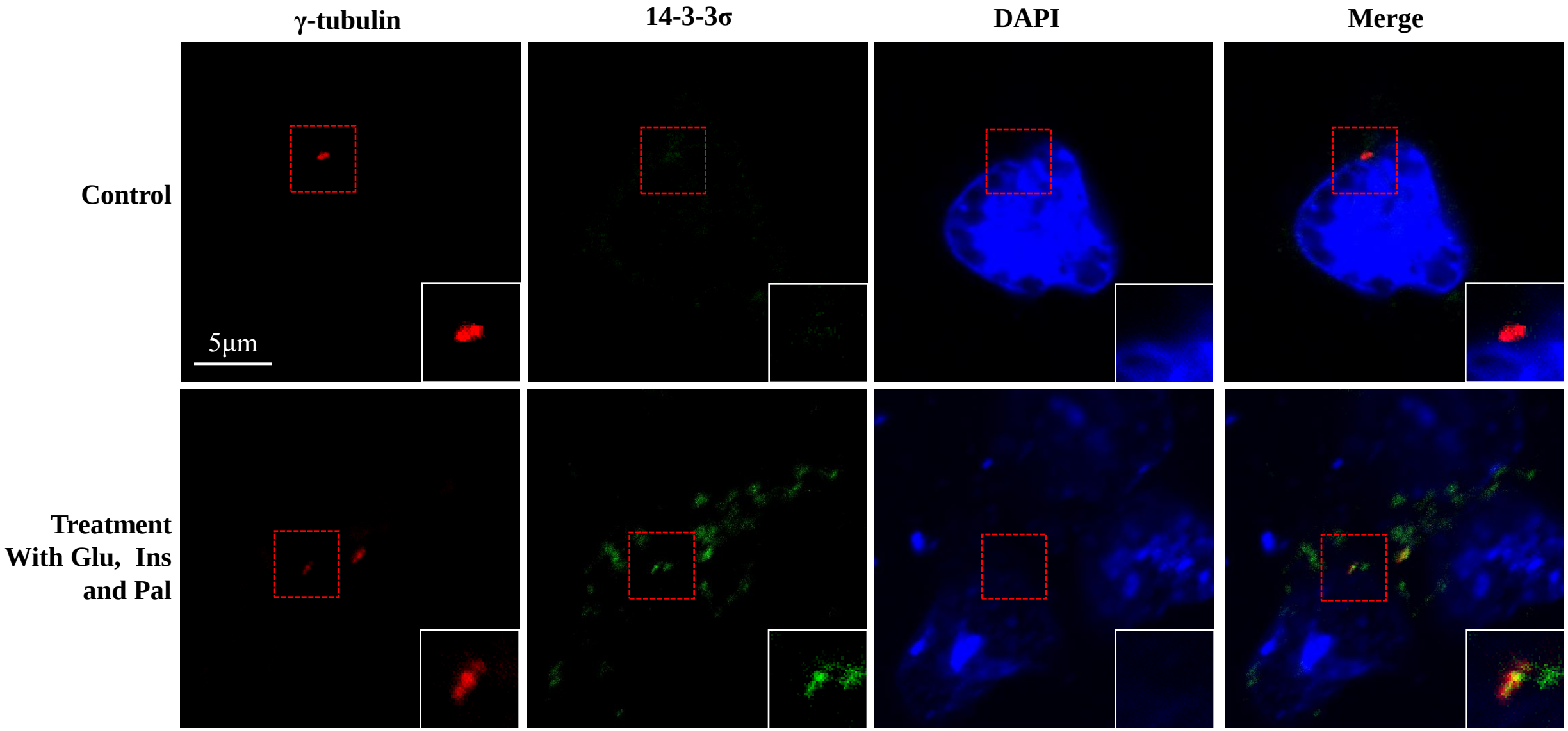
γ-tubulin
14-3-3σ
DAPI
Merge
Control
Treatment With Glu, Ins and Pal
5μm

Fig. 5F

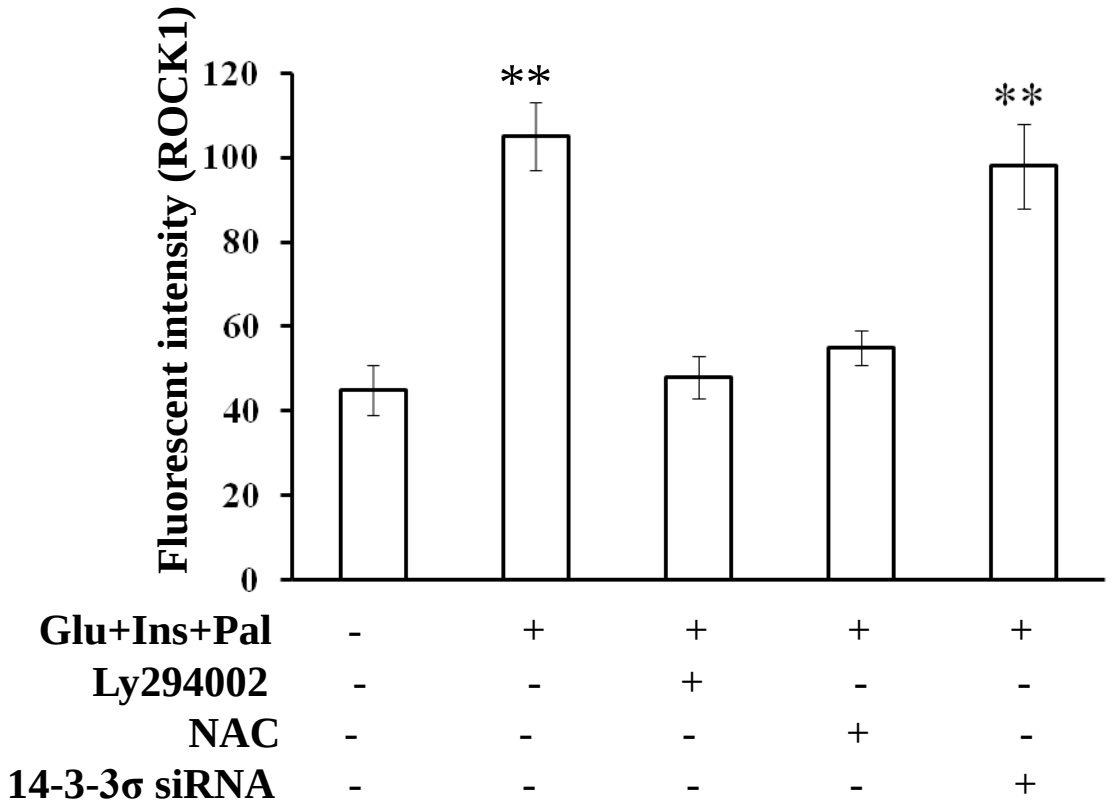
Fluorescent intensity (ROCK1)
120
100
80
60
40
20
0
**
**
Glu+Ins+Pal - + + + +
Ly294002 - - + - -
NAC - - - + -
14-3-3σ siRNA - - - - +

Fig. 5G

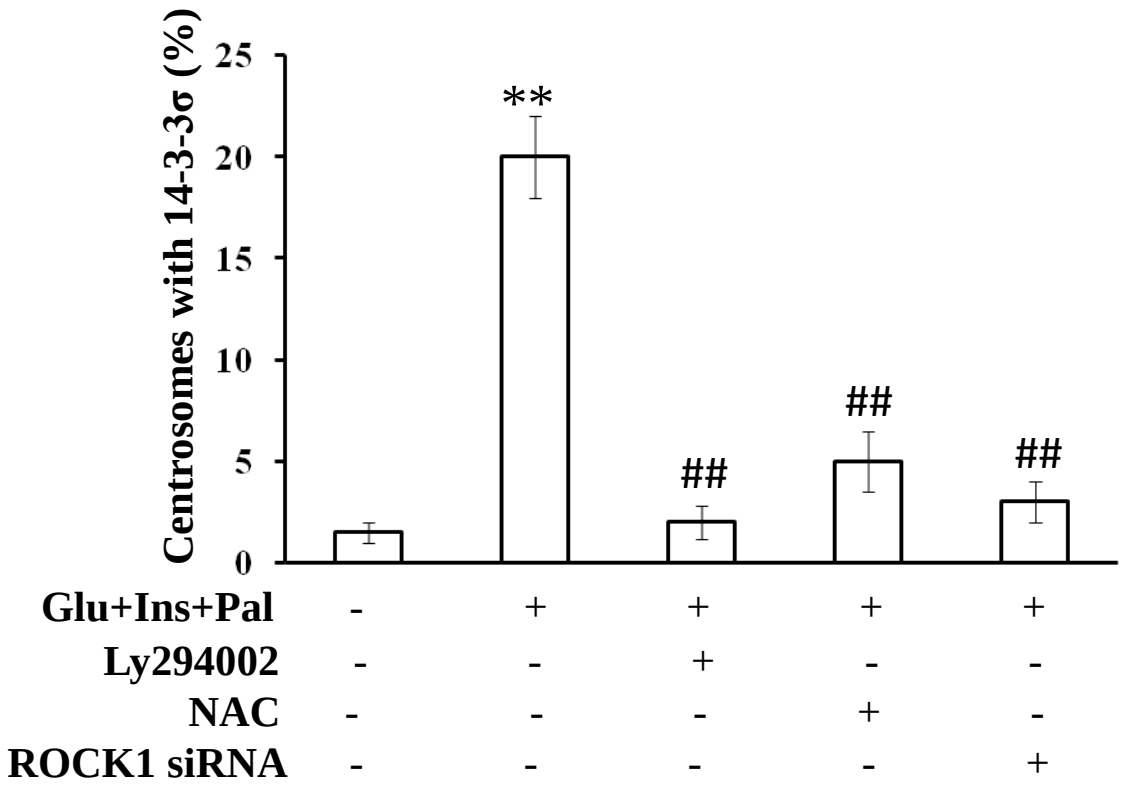
Centrosomes with 14-3-3σ (%)
25
20
15
10
5
0
**
##
##
##
Glu+Ins+Pal - + + + +
Ly294002 - - + - -
NAC - - - + -
ROCK1 siRNA - - - - +

Fig. 6A

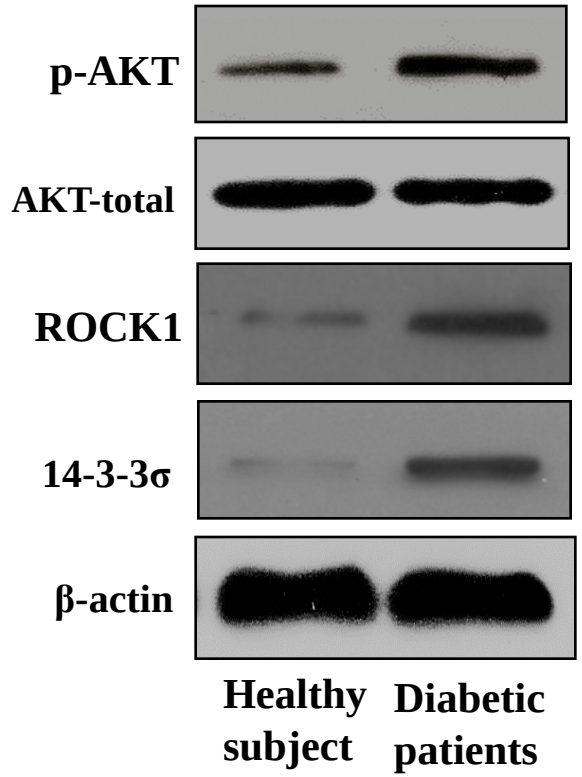
p-AKT
AKT-total
ROCK1
14-3-3σ
β-actin
Healthy subject
Diabetic patients

Fig. 6B

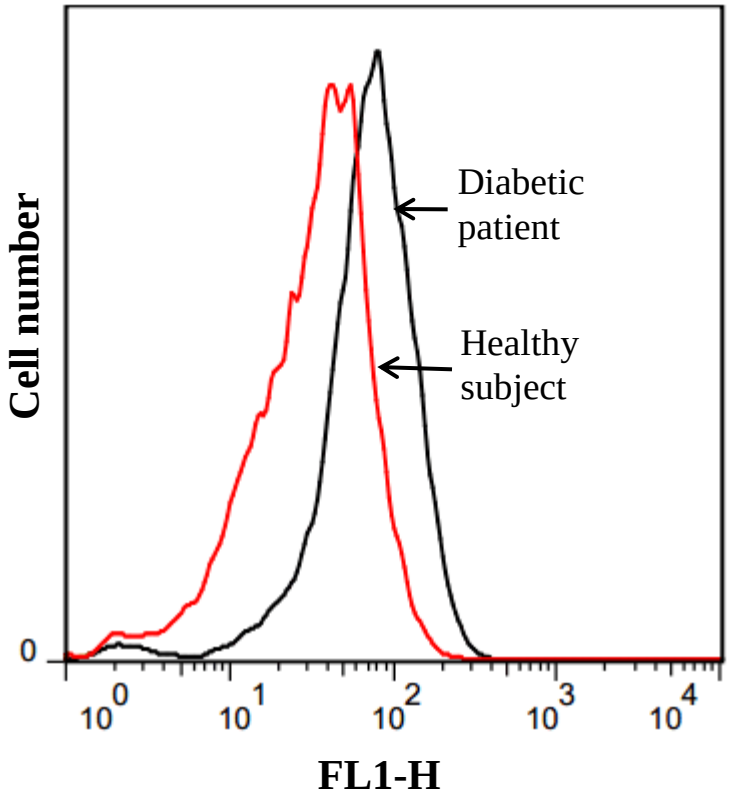
Cell number
0
Diabetic patient
Healthy subject
10^0
10^1
10^2
10^3
10^4
FL1-H

Fig. 6C

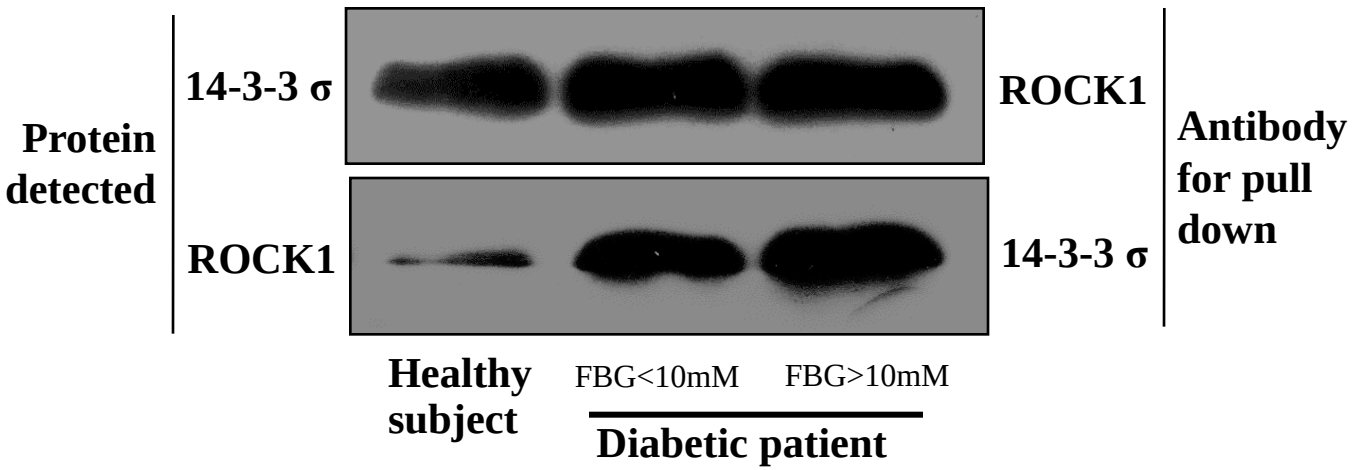
Protein detected
14-3-3 σ
ROCK1
ROCK1
14-3-3 σ
Antibody for pull down
Healthy subject
FBG<10mM
FBG>10mM
Diabetic patient

Fig. 6D

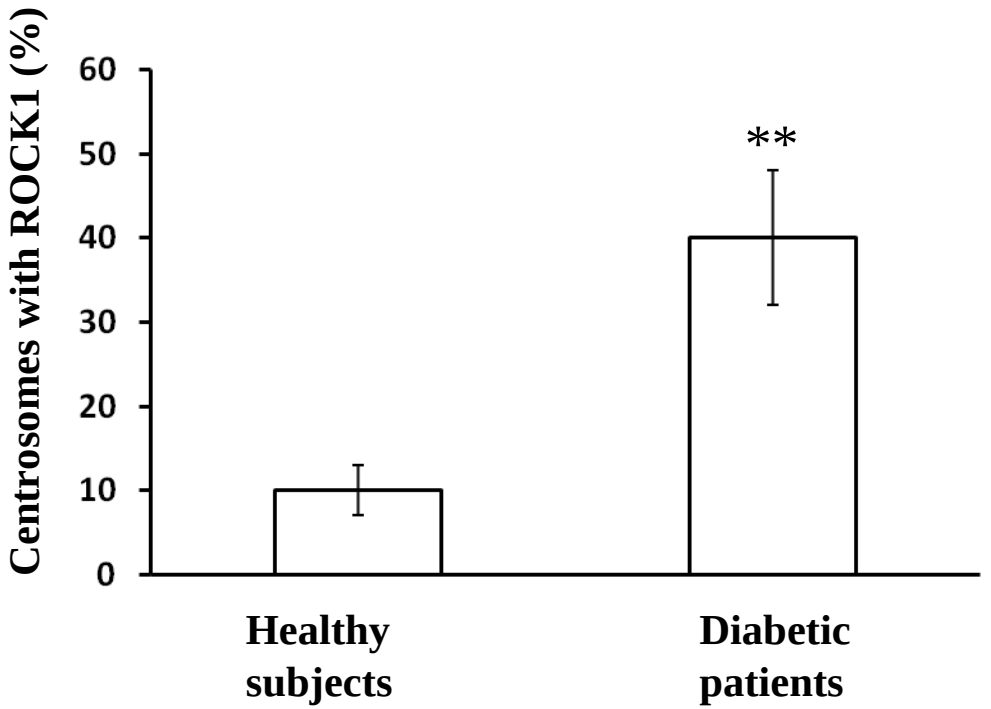
Centrosomes with ROCK1 (%)
60
50
40
30
20
10
0
**
Healthy subjects
Diabetic patients

Fig. 6E

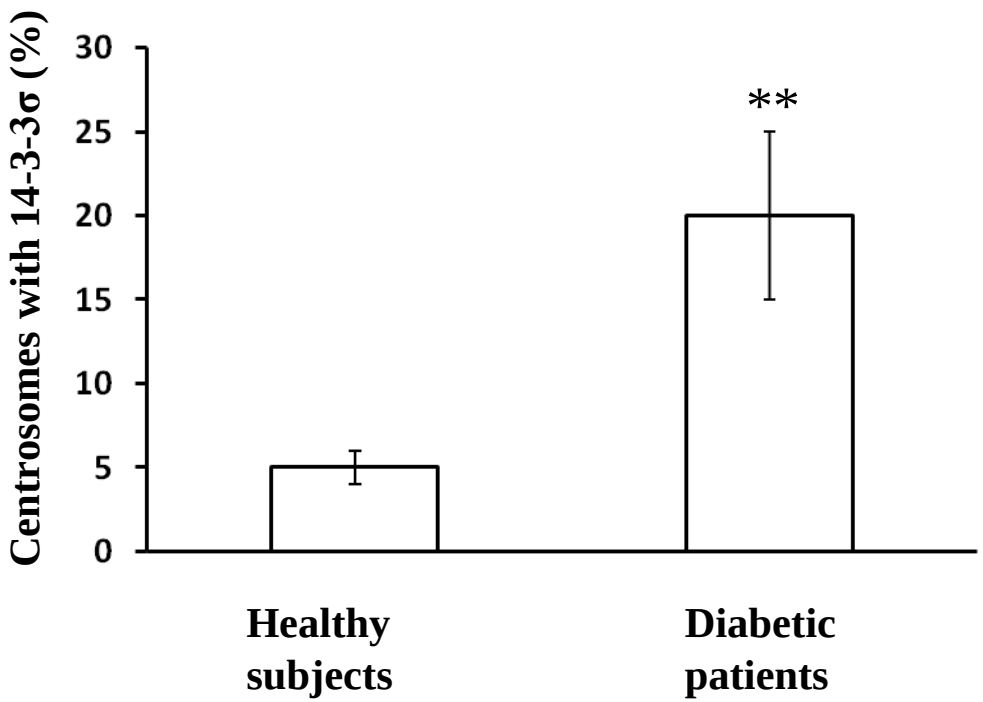
Centrosomes with 14-3-3σ (%)
30
25
20
15
10
5
0
**
Healthy subjects
Diabetic patients

Table S1. Differentially expressed genes and KEGG pathway analysis

Metabolism			
Overview			
ko01200	**Carbon metabolism**		
	ko:K00036	G6PD, zwf; glucose-6-phosphate 1-dehydrogenase	T up
ko01210	**2-Oxocarboxylic acid metabolism**		
ko01212	**Fatty acid metabolism**		
	ko:K08765	CPT1; carnitine O-palmitoyltransferase 1	T up
ko00030	**Pentose phosphate pathway**		
	ko:K00036	G6PD, zwf; glucose-6-phosphate 1-dehydrogenase	T up
ko00040	**Pentose and glucuronate interconversions**		
	ko:K00011	E1.1.1.21, AKR1; aldehyde reductase	T up
ko00051	**Fructose and mannose metabolism**		
	ko:K00846	KHK; ketohexokinase	T up
	ko:K00011	E1.1.1.21, AKR1; aldehyde reductase	T up
ko00052	**Galactose metabolism**		
	ko:K00011	E1.1.1.21, AKR1; aldehyde reductase	T up
ko00500	**Starch and sucrose metabolism**		
	ko:K01513	ENPP1_3; ectonucleotide pyrophosphatase/phosphodiesterase family member 1/3	T up
ko00520	**Amino sugar and nucleotide sugar metabolism**		
	ko:K00820	E2.6.1.16, glmS; glucosamine--fructose-6-phosphate aminotransferase	T up
ko00620	**Pyruvate metabolism**		
	ko:K00011	E1.1.1.21, AKR1; aldehyde reductase	T up
ko00630	**Glyoxylate and dicarboxylate metabolism**		
	ko:K15788	GLYCTK; glycerate kinase	C up
Energy metabolism			
ko00190	**Oxidative phosphorylation**		
	ko:K02148	ATPeV1C, ATP6C; V-type H+-transporting ATPase subunit C	T up
ko00910	**Nitrogen metabolism**		
	ko:K01672	E4.2.1.1; carbonic anhydrase	T up
ko00920	**Sulfur metabolism**		
	ko:K17218	sqr; sulfide:quinone oxidoreductase	T up
Lipid metabolism			
ko00061	**Fatty acid biosynthesis**		
ko00062	**Fatty acid elongation**		
	ko:K10248	ELOVL3; elongation of very long chain fatty acids protein 3	T up
ko00071	**Fatty acid degradation**		
	ko:K08765	CPT1; carnitine O-palmitoyltransferase 1	T up
ko00140	**Steroid hormone biosynthesis**		
	ko:K07408	CYP1A1; cytochrome P450, family 1, subfamily A, polypeptide 1	T up
	ko:K04119	AKR1C3; aldo-keto reductase family 1 member C3	T up
	ko:K01015	SULT2B1; alcohol sulfotransferase	T up

ko00561	**Glycerolipid metabolism**		
	ko:K01080	PPAP2; phosphatidate phosphatase	T up
	ko:K11160	DGAT2; diacylglycerol O-acyltransferase 2	T up
	ko:K00011	E1.1.1.21, AKR1; aldehyde reductase	T up
	ko:K15788	GLYCTK; glycerate kinase	C up
ko00564	**Glycerophospholipid metabolism**		
	ko:K01080	PPAP2; phosphatidate phosphatase	T up
	ko:K06124	PHOSPHO1; phosphoethanolamine/phosphocholine phosphatase	T up
	ko:K01049	ACHE; acetylcholinesterase	T up
ko00565	**Ether lipid metabolism**		
	ko:K01080	PPAP2; phosphatidate phosphatase	T up
ko00600	**Sphingolipid metabolism**		
	ko:K04718	SPHK; sphingosine kinase	T up
	ko:K12350	SMPD1, ASM; sphingomyelin phosphodiesterase	T up
	ko:K01080	PPAP2; phosphatidate phosphatase	T up
ko00590	**Arachidonic acid metabolism**		
	ko:K00509	PTGS1, COX1; prostaglandin-endoperoxide synthase 1	T up
	ko:K04119	AKR1C3; aldo-keto reductase family 1 member C3	T up
	ko:K07418	CYP2J; cytochrome P450, family 2, subfamily J	T up
	ko:K01832	TBXAS1, CYP5A; thromboxane-A synthase	T up
ko00591	**Linoleic acid metabolism**		
	ko:K07418	CYP2J; cytochrome P450, family 2, subfamily J	T up
Nucleotide metabolism			
ko00230	**Purine metabolism**		
	ko:K01513	ENPP1_3; ectonucleotide pyrophosphatase/phosphodiesterase family member 1/3	T up
	ko:K01509	E3.6.1.3; adenosinetriphosphatase	T up
	ko:K01487	E3.5.4.3, guaD; guanine deaminase	C up
	ko:K13762	PDE5; cGMP-specific 3',5'-cyclic phosphodiesterase	T up
	ko:K08045	ADCY5; adenylate cyclase 5	T up
ko00240	**Pyrimidine metabolism**		
Amino acid metabolism			
ko00250	**Alanine, aspartate and glutamate metabolism**		
	ko:K00820	E2.6.1.16, glmS; glucosamine--fructose-6-phosphate aminotransferase (isomerizing)	T up
ko00260	**Glycine, serine and threonine metabolism**		
	ko:K15788	GLYCTK; glycerate kinase	C up
	ko:K00314	SARDH; sarcosine dehydrogenase	T up
ko00330	**Arginine and proline metabolism**		
	ko:K00472	E1.14.11.2; prolyl 4-hydroxylase	T up
ko00380	**Tryptophan metabolism**		
	ko:K07408	CYP1A1; cytochrome P450, family 1, subfamily A, polypeptide 1	T up
Metabolism of other amino acids			

ko00480	**Glutathione metabolism**		
	ko:K00799	GST, gst; glutathione S-transferase	T up
	ko:K00036	G6PD, zwf; glucose-6-phosphate 1-dehydrogenase	T up
Glycan biosynthesis and metabolism			
ko00513	**Various types of N-glycan biosynthesis**		
	ko:K00781	SIAT6; N-acetyllactosaminide alpha-2,3-sialyltransferase (sialyltransferase 6)	C up
ko00512	**Mucin type O-glycan biosynthesis**		
	ko:K00727	GCNT1; beta-1,3-galactosyl-O-glycosyl-glycoprotein beta-1,6-N-acetylglucosaminyltransferase	T up
	ko:K00710	GALNT; polypeptide N-acetylgalactosaminyltransferase	T up
	ko:K00780	SIAT4A; beta-galactoside alpha-2,3-sialyltransferase (sialyltransferase 4A) [EC:2.4.99.4]	T up
ko00514	**Other types of O-glycan biosynthesis**		
	ko:K05948	FNG; fringe [EC:2.4.1.222]	T up
	ko:K00781	SIAT6; N-acetyllactosaminide alpha-2,3-sialyltransferase (sialyltransferase 6) [EC:2.4.99.6]	C up
ko00532	**Glycosaminoglycan biosynthesis - chondroitin sulfate / dermatan sulfate**		
	ko:K00771	XYLT; protein xylosyltransferase [EC:2.4.2.26]	T up
ko00534	**Glycosaminoglycan biosynthesis - heparan sulfate / heparin**		
	ko:K00771	XYLT; protein xylosyltransferase [EC:2.4.2.26]	T up
ko00533	**Glycosaminoglycan biosynthesis - keratan sulfate**		
	ko:K00780	SIAT4A; beta-galactoside alpha-2,3-sialyltransferase (sialyltransferase 4A) [EC:2.4.99.4]	T up
	ko:K00741	B3GNT1, B3GNT2; N-acetyllactosaminide beta-1,3-N-acetylglucosaminyltransferase [EC:2.4.1.149]	T up
	ko:K09664	B3GNT7; beta-1,3-N-acetylglucosaminyltransferase 7 [EC:2.4.1.-]	T up
	ko:K04745	CHST2; carbohydrate 6-sulfotransferase 2 [EC:2.8.2.-]	T up
	ko:K00781	SIAT6; N-acetyllactosaminide alpha-2,3-sialyltransferase (sialyltransferase 6) [EC:2.4.99.6]	C up
ko00601	**Glycosphingolipid biosynthesis - lacto and neolacto series**		
	ko:K00741	B3GNT1, B3GNT2; N-acetyllactosaminide beta-1,3-N-acetylglucosaminyltransferase [EC:2.4.1.149]	T up
	ko:K00781	SIAT6; N-acetyllactosaminide alpha-2,3-sialyltransferase (sialyltransferase 6) [EC:2.4.99.6]	C up
ko00603	**Glycosphingolipid biosynthesis - globo series**		
	ko:K00780	SIAT4A; beta-galactoside alpha-2,3-sialyltransferase (sialyltransferase 4A) [EC:2.4.99.4]	T up
	ko:K01988	A4GALT; lactosylceramide 4-alpha-galactosyltransferase [EC:2.4.1.228]	T up
ko00604	**Glycosphingolipid biosynthesis - ganglio series**		
	ko:K03373	SIAT7C, ST6GalNAc III; N-acetylgalactosaminide alpha-2,6-sialyltransferase (sialyltransferase 7C) [EC:2.4.99.-]	T up

	ko:K00780	SIAT4A; beta-galactoside alpha-2,3-sialyltransferase (sialyltransferase 4A) [EC:2.4.99.4]	T up
	ko:K00725	B4GALNT1, GALGT; (N-Acetylneuraminyl)-galactosylglucosylceramide N-acetylgalactosaminyltransferase [EC:2.4.1.92]	T up
Metabolism of cofactors and vitamins			
ko00730	**Thiamine metabolism**		
ko00740	**Riboflavin metabolism**		
	ko:K01513	ENPP1_3; ectonucleotide pyrophosphatase/phosphodiesterase family member 1/3 [EC:3.1.4.1 3.6.1.9]	T up
ko00750	**Vitamin B6 metabolism**		
ko00760	**Nicotinate and nicotinamide metabolism**		
	ko:K01513	ENPP1_3; ectonucleotide pyrophosphatase/phosphodiesterase family member 1/3 [EC:3.1.4.1 3.6.1.9]	T up
ko00770	**Pantothenate and CoA biosynthesis**		
	ko:K01513	ENPP1_3; ectonucleotide pyrophosphatase/phosphodiesterase family member 1/3 [EC:3.1.4.1 3.6.1.9]	T up
ko00830	**Retinol metabolism**		
	ko:K12664	CYP26B; cytochrome P450, family 26, subfamily B	T up
	ko:K07408	CYP1A1; cytochrome P450, family 1, subfamily A, polypeptide 1 [EC:1.14.14.1]	T up
Metabolism of terpenoids and polyketides			
ko00980	**Metabolism of xenobiotics by cytochrome P450**		
	ko:K07408	CYP1A1; cytochrome P450, family 1, subfamily A, polypeptide 1 [EC:1.14.14.1]	T up
	ko:K00799	GST, gst; glutathione S-transferase [EC:2.5.1.18]	T up
ko00982	**Drug metabolism - cytochrome P450**		
	ko:K00799	GST, gst; glutathione S-transferase [EC:2.5.1.18]	T up
Enzyme families			
Genetic Information Processing			
Transcription			
ko03040	**Spliceosome**		
	ko:K03283	HSPA1_8; heat shock 70kDa protein 1/8	T up
ko03041	**Spliceosome**		
Translation			
ko03010	**Ribosome**		
	ko:K02929	RP-L44e, RPL44; large subunit ribosomal protein L44e	C up
ko03011	**Ribosome**		
ko03016	**Transfer RNA biogenesis**		
ko00970	**Aminoacyl-tRNA biosynthesis**		
	ko:K01867	WARS, trpS; tryptophanyl-tRNA synthetase [EC:6.1.1.2]	C up
ko03013	**RNA transport**		

	ko:K03257	EIF4A; translation initiation factor 4A	C up
	ko:K03250	EIF3E, INT6; translation initiation factor 3 subunit E	C up
	ko:K00784	rnz; ribonuclease Z [EC:3.1.26.11]	C up
	ko:K03245	EIF3J; translation initiation factor 3 subunit J	C up
Folding, sorting and degradation			
ko03060	**Protein export**		
	ko:K09490	HSPA5, BIP; heat shock 70kDa protein 5	C up
ko04141	**Protein processing in endoplasmic reticulum**		
	ko:K09487	HSP90B, TRA1; heat shock protein 90kDa beta	C up
	ko:K04452	DDIT3, GADD153; DNA damage-inducible transcript 3	C up
	ko:K14019	PPP1R15A, GADD34; protein phosphatase 1 regulatory subunit 15A	C up
	ko:K09490	HSPA5, BIP; heat shock 70kDa protein 5	C up
	ko:K11863	ATXN3, MJD; Ataxin-3 [EC:3.4.22.-]	C up
	ko:K14027	HERPUD1, HERP; homocysteine-responsive endoplasmic reticulum-resident ubiquitin-like domain member 1 protein	C up
	ko:K03283	HSPA1_8; heat shock 70kDa protein 1/8	T up
ko04120	**Ubiquitin mediated proteolysis**		
	ko:K10605	BRCA1; breast cancer type 1 susceptibility protein	C up
ko03440	**Homologous recombination**		
	ko:K10865	MRE11; double-strand break repair protein MRE11	C up
	ko:K08775	BRCA2, FANCD1; breast cancer 2 susceptibility protein	C up
ko03450	**Non-homologous end-joining**		
	ko:K10865	MRE11; double-strand break repair protein MRE11	C up
	ko:K10886	XRCC4; DNA-repair protein XRCC4	C up
ko03460	**Fanconi anemia pathway**		
	ko:K10605	BRCA1; breast cancer type 1 susceptibility protein	C up
	ko:K08775	BRCA2, FANCD1; breast cancer 2 susceptibility protein	C up
Environmental Information Processing			
Membrane transport			
ko02000	**Transporters**		
ko02010	**ABC transporters**		
	ko:K05675	ABCD1, ALD; ATP-binding cassette, subfamily D (ALD), member 1	T up
	ko:K05679	ABCG1; ATP-binding cassette, subfamily G (WHITE), member 1	T up
	ko:K05680	ABCG4; ATP-binding cassette, subfamily G (WHITE), member 4	T up
Signal transduction			
ko04014	**Ras signaling pathway**		
	ko:K04543	GNG7; guanine nucleotide-binding protein G(I)/G(S)/G(O) subunit gamma-7	T up
	ko:K12361	RASGRP2; RAS guanyl-releasing protein 2	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K05466	ANGPT2; angiopoietin 2	C up

	ko:K17635	RGL1, RGL; ral guanine nucleotide dissociation stimulator-like 1	T up
	ko:K04349	RASGRF1; Ras-specific guanine nucleotide-releasing factor 1	C up
	ko:K16859	PGF; placenta growth factor	T up
	ko:K05453	CSF1, MCSF; macrophage colony-stimulating factor 1	T up
	ko:K05462	EFNA; ephrin-A	T up
	ko:K05462	EFNA; ephrin-A	T up
	ko:K02583	NGFR; nerve growth factor receptor (TNFR superfamily member 16)	T up
ko04015	**Rap1 signaling pathway**		
	ko:K05453	CSF1, MCSF; macrophage colony-stimulating factor 1	T up
	ko:K05462	EFNA; ephrin-A	T up
	ko:K05462	EFNA; ephrin-A	T up
	ko:K02583	NGFR; nerve growth factor receptor (TNFR superfamily member 16)	T up
	ko:K08045	ADCY5; adenylate cyclase 5 [EC:4.6.1.1]	T up
	ko:K12361	RASGRP2; RAS guanyl-releasing protein 2	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K05466	ANGPT2; angiopoietin 2	C up
	ko:K04266	ADORA2A, ADOR; adenosine receptor A2a	T up
	ko:K16859	PGF; placenta growth factor	T up
ko04010	**MAPK signaling pathway**		
	ko:K04434	MAPK8IP1, JIP1; mitogen-activated protein kinase 8 interacting protein 1	T up
	ko:K04859	CACNA2D2; voltage-dependent calcium channel alpha-2/delta-2	T up
	ko:K04415	MAP3K8, COT; mitogen-activated protein kinase kinase kinase 8 [EC:2.7.11.25]	T up
	ko:K04349	RASGRF1; Ras-specific guanine nucleotide-releasing factor 1	C up
	ko:K12361	RASGRP2; RAS guanyl-releasing protein 2	T up
	ko:K03283	HSPA1_8; heat shock 70kDa protein 1/8	T up
	ko:K04445	MSK1, RPS6KA5; ribosomal protein S6 kinase alpha-5 [EC:2.7.11.1]	C up
	ko:K04452	DDIT3, GADD153; DNA damage-inducible transcript 3	C up
	ko:K04854	CACNA1G; voltage-dependent calcium channel T type alpha-1G	T up
ko04012	**ErbB signaling pathway**		
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
ko04310	**Wnt signaling pathway**		
	ko:K00445	WNT6; wingless-type MMTV integration site family, member 6	T up
	ko:K01384	WNT11; wingless-type MMTV integration site family, member 11	T up
	ko:K00572	WNT7; wingless-type MMTV integration site family, member 7	T up
	ko:K03213	NKD; naked cuticle	T up
	ko:K02354	FZD4, fz4; frizzled 4	T up
	ko:K10162	BAMBI; BMP and activin membrane-bound inhibitor	T up
ko04330	**Notch signaling pathway**		
	ko:K06058	DTX; deltex	T up

	ko:K05948	FNG; fringe [EC:2.4.1.222]	T up
	ko:K06051	DLL; delta	T up
	ko:K02599	NOTCH; Notch	T up
ko04340	**Hedgehog signaling pathway**		
	ko:K00445	WNT6; wingless-type MMTV integration site family, member 6	T up
	ko:K16798	GLI2; zinc finger protein GLI2	T up
	ko:K01384	WNT11; wingless-type MMTV integration site family, member 11	T up
	ko:K00572	WNT7; wingless-type MMTV integration site family, member 7	T up
ko04350	**TGF-beta signaling pathway**		
	ko:K04657	CHRD; chordin	T up
	ko:K04514	Rock1; Rho-associated protein kinase 1 [EC:2.7.11.1]	T up
	ko:K04677	SMAD6_7; mothers against decapentaplegic homolog 6/7	T up
	ko:K10162	BAMBI; BMP and activin membrane-bound inhibitor	T up
ko04390	**Hippo signaling pathway**		
	ko:K16798	GLI2; zinc finger protein GLI2	T up
	ko:K02354	FZD4, fz4; frizzled 4	T up
	ko:K16819	AMOT; angiomotin	T up
	ko:K00445	WNT6; wingless-type MMTV integration site family, member 6	T up
	ko:K01384	WNT11; wingless-type MMTV integration site family, member 11	T up
	ko:K00572	WNT7; wingless-type MMTV integration site family, member 7	T up
ko04391	**Hippo signaling pathway -fly**		
	ko:K09851	RASSF2_4; Ras association domain-containing protein 2/4	T up
	ko:K16669	FAT4; protocadherin Fat 4	T up
ko04370	**VEGF signaling pathway**		
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K04718	SPHK; sphingosine kinase [EC:2.7.1.91]	T up
	ko:K08273	SH2D2A, VRAP; SH2 domain protein 2A	C up
ko04630	**Jak-STAT signaling pathway**		
	ko:K05134	IL10RA; interleukin 10 receptor alpha	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K11222	STAT4; signal transducer and activator of transcription 4	T up
	ko:K05138	IL22RA1; interleukin 22 receptor alpha 1	T up
	ko:K05433	IL15; interleukin 15	T up
ko04064	**NF-kappa B signaling pathway**		
	ko:K18052	PRKCQ; novel protein kinase C theta type [EC:2.7.11.13]	T up
	ko:K10030	IL8, CXCL8; interleukin 8	T up
ko04668	**TNF signaling pathway**		
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K05141	TNFRSF1B, TNFR2; tumor necrosis factor receptor superfamily member 1B	T up

	ko:K05453	CSF1, MCSF; macrophage colony-stimulating factor 1	T up
	ko:K04415	MAP3K8, COT; mitogen-activated protein kinase kinase kinase 8 [EC:2.7.11.25]	T up
	ko:K04445	MSK1, RPS6KA5; ribosomal protein S6 kinase alpha-5 [EC:2.7.11.1]	C up
	ko:K09048	CREB3; cyclic AMP-responsive element-binding protein 3	T up
	ko:K09048	CREB3; cyclic AMP-responsive element-binding protein 3	T up
	ko:K05433	IL15; interleukin 15	T up
ko04066	**HIF-1 signaling pathway**		
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K16451	TIMP1; metallopeptidase inhibitor 1	T up
	ko:K05466	ANGPT2; angiopoietin 2	C up
ko04068	**FoxO signaling pathway**		
	ko:K08861	PLK2; polo-like kinase 2 [EC:2.7.11.21]	C up
	ko:K08863	PLK4; polo-like kinase 4 [EC:2.7.11.21]	C up
	ko:K13302	SGK1; serum/glucocorticoid-regulated kinase 1 [EC:2.7.11.1]	T up
	ko:K17845	KLF2; krueppel-like factor 2	C up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K06623	CDKN2D, P19, INK4D; cyclin-dependent kinase inhibitor 2D	T up
	ko:K08336	ATG12; ubiquitin-like protein ATG12	C up
ko04020	**Calcium signaling pathway**		
	ko:K04633	GNAL; guanine nucleotide-binding protein G(olf) subunit alpha	T up
	ko:K04854	CACNA1G; voltage-dependent calcium channel T type alpha-1G	T up
	ko:K00907	MYLK; myosin-light-chain kinase [EC:2.7.11.18]	T up
	ko:K04718	SPHK; sphingosine kinase [EC:2.7.1.91]	T up
	ko:K04266	ADORA2A, ADOR; adenosine receptor A2a	T up
ko04070	**Phosphatidylinositol signaling system**		
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
ko04151	**PI3K-Akt signaling pathway**		
	ko:K06236	COL1AS; collagen, type I/II/III/V/XI/XXIV/XXVII, alpha	T up
	ko:K16859	PGF; placenta growth factor	T up
	ko:K06484	ITGA5; integrin alpha 5	T up
	ko:K05466	ANGPT2; angiopoietin 2	C up
	ko:K10605	BRCA1; breast cancer type 1 susceptibility protein	C up
	ko:K13302	SGK1; serum/glucocorticoid-regulated kinase 1 [EC:2.7.11.1]	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K04543	GNG7; guanine nucleotide-binding protein G(I)/G(S)/G(O) subunit gamma-7	T up
	ko:K06240	LAMA3_5; laminin, alpha 3/5	T up
	ko:K09487	HSP90B, TRA1; heat shock protein 90kDa beta	C up

	ko:K06250	SPP1, BNSP, OPN; secreted phosphoprotein 1	T up
	ko:K02583	NGFR; nerve growth factor receptor (TNFR superfamily member 16)	T up
	ko:K06237	COL4A; collagen, type IV, alpha	T up
	ko:K09048	CREB3; cyclic AMP-responsive element-binding protein 3	T up
	ko:K09048	CREB3; cyclic AMP-responsive element-binding protein 3	T up
	ko:K05462	EFNA; ephrin-A	T up
	ko:K05462	EFNA; ephrin-A	T up
	ko:K05717	FN1; fibronectin 1	T up
	ko:K05453	CSF1, MCSF; macrophage colony-stimulating factor 1	T up
	ko:K06591	ITGB8; integrin beta 8	C up
ko04150	**mTOR signaling pathway**		
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
ko04080	**Neuroactive ligand-receptor interaction**		
	ko:K04153	HTR1; 5-hydroxytryptamine receptor 1	T up
	ko:K04132	CHRM4; muscarinic acetylcholine receptor M4	T up
	ko:K04139	ADRA2B; adrenergic receptor alpha-2B	T up
	ko:K04309	LGR4, GPR48; leucine-rich repeat-containing G protein-coupled receptor 4	T up
	ko:K04266	ADORA2A, ADOR; adenosine receptor A2a	T up
	ko:K04295	S1PR5, EDG8; sphingosine 1-phosphate receptor 5	T up
	ko:K05205	GRIK5; glutamate receptor, ionotropic kainate 5	T up
	ko:K05206	GRID1; glutamate receptor delta-1 subunit	T up
	ko:K04607	GRM4; metabotropic glutamate receptor 4	T up
	ko:K05184	GABRD; gamma-aminobutyric acid receptor subunit delta	T up
	ko:K08362	NR1A2, THRB; thyroid hormone receptor beta	T up
	ko:K04265	ADORA1; adenosine A1 receptor	T up
ko04060	**Cytokine-cytokine receptor interaction**		
	ko:K10030	IL8, CXCL8; interleukin 8	T up
	ko:K05433	IL15; interleukin 15	T up
	ko:K05155	TNFRSF19, TROY; tumor necrosis factor receptor superfamily member 19	T up
	ko:K05141	TNFRSF1B, TNFR2; tumor necrosis factor receptor superfamily member 1B	T up
	ko:K05453	CSF1, MCSF; macrophage colony-stimulating factor 1	T up
	ko:K04175	IL8RA, CXCR1; interleukin 8 receptor alpha	T up
	ko:K04189	CXCR4; C-X-C chemokine receptor type 4	T up
	ko:K05134	IL10RA; interleukin 10 receptor alpha	T up
	ko:K05138	IL22RA1; interleukin 22 receptor alpha 1	T up
	ko:K02583	NGFR; nerve growth factor receptor (TNFR superfamily member 16)	T up
	ko:K05146	TNFRSF9, CD137; tumor necrosis factor receptor superfamily member 9	T up
	ko:K05480	EDA; ectodysplasin-A	T up

ko04052	**Cytokines**		
ko04512	**ECM-receptor interaction**		
	ko:K06250	SPP1, BNSP, OPN; secreted phosphoprotein 1	T up
	ko:K06236	COL1AS; collagen, type I/II/III/V/XI/XXIV/XXVII, alpha	T up
	ko:K06591	ITGB8; integrin beta 8	C up
	ko:K05717	FN1; fibronectin 1	T up
	ko:K06267	HMMR, RHAMM; hyaluronan-mediated motility receptor	C up
	ko:K06237	COL4A; collagen, type IV, alpha	T up
	ko:K06484	ITGA5; integrin alpha 5	T up
	ko:K06240	LAMA3_5; laminin, alpha 3/5	T up
ko04514	**Cell adhesion molecules (CAMs)**		
	ko:K06591	ITGB8; integrin beta 8	C up
	ko:K06759	CNTN1; contactin 1	T up
	ko:K16360	LRRC4B, NGL3; netrin-G3 ligand	T up
	ko:K06550	L1CAM; L1 cell adhesion molecule	T up
	ko:K16359	NTNG2; netrin-G2	T up
Cellular Processes			
Transport and catabolism			
ko04144	**Endocytosis**		
	ko:K13649	FOLR; folate receptor	T up
	ko:K04677	SMAD6_7; mothers against decapentaplegic homolog 6/7	T up
	ko:K03283	HSPA1_8; heat shock 70kDa protein 1/8	T up
	ko:K05126	RET; proto-oncogene tyrosine-protein kinase Ret [EC:2.7.10.1]	T up
	ko:K04175	IL8RA, CXCR1; interleukin 8 receptor alpha	T up
	ko:K12958	CAV2; caveolin 2	C up
	ko:K06278	CAV1; caveolin 1	C up
	ko:K04189	CXCR4; C-X-C chemokine receptor type 4	T up
ko04147	**Exosome**		
ko04145	**Phagosome**		
	ko:K02148	ATPeV1C, ATP6C; V-type H+-transporting ATPase subunit C	T up
	ko:K03990	C3; complement component 3	T up
	ko:K07375	TUBB; tubulin beta	T up
	ko:K07375	TUBB; tubulin beta	T up
	ko:K06484	ITGA5; integrin alpha 5	T up
	ko:K06560	MRC; mannose receptor, C type	T up
	ko:K07898	RAB7B; Ras-related protein Rab-7B	T up
ko04142	**Lysosome**		
	ko:K12350	SMPD1, ASM; sphingomyelin phosphodiesterase [EC:3.1.4.12]	T up
	ko:K12383	GM2A; ganglioside GM2 activator	T up
	ko:K12397	AP3B; AP-3 complex subunit beta	T up
	ko:K12394	AP1S1_2; AP-1 complex subunit sigma 1/2	C up
ko04146	**Peroxisome**		
	ko:K05675	ABCD1, ALD; ATP-binding cassette, subfamily D (ALD), member 1	T up

	ko:K13339	PEX6, PXAAA1; peroxin-6	T up
ko04140	**Regulation of autophagy**		
	ko:K08336	ATG12; ubiquitin-like protein ATG12	C up
Cell motility			
ko04810	**Regulation of actin cytoskeleton**		
	ko:K00907	MYLK; myosin-light-chain kinase [EC:2.7.11.18]	T up
	ko:K04132	CHRM4; muscarinic acetylcholine receptor M4	T up
	ko:K10351	MYL2; myosin regulatory light chain 2	C up
	ko:K06591	ITGB8; integrin beta 8	C up
	ko:K05717	FN1; fibronectin 1	T up
	ko:K06484	ITGA5; integrin alpha 5	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K04514	Rock1; Rho-associated protein kinase 1 [EC:2.7.11.1]	T up
Cell growth and death			
ko04110	**Cell cycle**		
	ko:K06671	STAG1_2, SCC3, IRR1; cohesin complex subunit SA-1/2	C up
	ko:K06623	CDKN2D, P19, INK4D; cyclin-dependent kinase inhibitor 2D	T up
	ko:K06622	CDKN2C, P18, INK4C; cyclin-dependent kinase inhibitor 2C	T up
	ko:K06669	SMC3, CSPG6; structural maintenance of chromosome 3 (chondroitin sulfate proteoglycan 6)	C up
	ko:K06644	SFN; stratifin	T up
ko04114	**Oocyte meiosis**		
	ko:K08045	ADCY5; adenylate cyclase 5 [EC:4.6.1.1]	T up
	ko:K06669	SMC3, CSPG6; structural maintenance of chromosome 3 (chondroitin sulfate proteoglycan 6)	C up
ko04210	**Apoptosis**		
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
ko04115	**p53 signaling pathway**		
	ko:K06509	KAI1, CD82, TSPAN27; CD82 antigen	T up
	ko:K10131	PMAIP1; phorbol-12-myristate-13-acetate-induced protein 1	C up
	ko:K10141	SESN; sestrin	T up
	ko:K06644	SFN; stratifin	T up
Cell communication			
ko04510	**Focal adhesion**		
	ko:K06250	SPP1, BNSP, OPN; secreted phosphoprotein 1	T up
	ko:K00907	MYLK; myosin-light-chain kinase [EC:2.7.11.18]	T up
	ko:K06237	COL4A; collagen, type IV, alpha	T up
	ko:K04514	Rock1; Rho-associated protein kinase 1 [EC:2.7.11.1]	T up
	ko:K12958	CAV2; caveolin 2	C up
	ko:K06278	CAV1; caveolin 1	C up
	ko:K10351	MYL2; myosin regulatory light chain 2	C up

	ko:K06591	ITGB8; integrin beta 8	C up
	ko:K05717	FN1; fibronectin 1	T up
	ko:K04349	RASGRF1; Ras-specific guanine nucleotide-releasing factor 1	C up
	ko:K16859	PGF; placenta growth factor	T up
	ko:K06236	COL1AS; collagen, type I/II/III/V/XI/XXIV/XXVII, alpha	T up
	ko:K06484	ITGA5; integrin alpha 5	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K06240	LAMA3_5; laminin, alpha 3/5	T up
ko04520	**Adherens junction**		
	ko:K06086	SORBS1, SH3D5, PONSIN, CAP; sorbin and SH3 domain containing 1	T up
ko04530	**Tight junction**		
	ko:K18052	PRKCQ; novel protein kinase C theta type [EC:2.7.11.13]	T up
	ko:K10351	MYL2; myosin regulatory light chain 2	C up
ko04540	**Gap junction**		
	ko:K08045	ADCY5; adenylate cyclase 5 [EC:4.6.1.1]	T up
	ko:K07375	TUBB; tubulin beta	T up
	ko:K07375	TUBB; tubulin beta	T up
Organismal Systems			
Immune system			
ko04640	**Hematopoietic cell lineage**		
	ko:K06484	ITGA5; integrin alpha 5	T up
	ko:K05453	CSF1, MCSF; macrophage colony-stimulating factor 1	T up
	ko:K04012	CR2, CD21; complement receptor type 2	T up
ko04610	**Complement and coagulation cascades**		
	ko:K03913	SERPINA5, PCI; protein C inhibitor	T up
	ko:K04012	CR2, CD21; complement receptor type 2	T up
	ko:K03909	TFPI; tissue factor pathway inhibitor	C up
	ko:K03990	C3; complement component 3	T up
	ko:K01314	F10; coagulation factor X [EC:3.4.21.6]	T up
	ko:K03984	SERPINA1, AAT; alpha-1-antitrypsin	T up
ko04611	**Platelet activation**		
	ko:K00907	MYLK; myosin-light-chain kinase [EC:2.7.11.18]	T up
	ko:K06236	COL1AS; collagen, type I/II/III/V/XI/XXIV/XXVII, alpha	T up
	ko:K01832	TBXAS1, CYP5A; thromboxane-A synthase [EC:5.3.99.5]	T up
	ko:K00509	PTGS1, COX1; prostaglandin-endoperoxide synthase 1 [EC:1.14.99.1]	T up
	ko:K12361	RASGRP2; RAS guanyl-releasing protein 2	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K08045	ADCY5; adenylate cyclase 5 [EC:4.6.1.1]	T up

	ko:K04514	Rock1; Rho-associated protein kinase 1 [EC:2.7.11.1]	T up
ko04620	**Toll-like receptor signaling pathway**		
	ko:K10030	IL8, CXCL8; interleukin 8	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K04415	MAP3K8, COT; mitogen-activated protein kinase kinase kinase 8 [EC:2.7.11.25]	T up
	ko:K06250	SPP1, BNSP, OPN; secreted phosphoprotein 1	T up
ko04621	**NOD-like receptor signaling pathway**		
	ko:K09487	HSP90B, TRA1; heat shock protein 90kDa beta	C up
	ko:K10030	IL8, CXCL8; interleukin 8	T up
ko04622	**RIG-I-like receptor signaling pathway**		
	ko:K10030	IL8, CXCL8; interleukin 8	T up
	ko:K08336	ATG12; ubiquitin-like protein ATG12	C up
ko04623	**Cytosolic DNA-sensing pathway**		
ko04650	**Natural killer cell mediated cytotoxicity**		
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K07987	RAET1; retinoic acid early transcript 1	T up
ko04612	**Antigen processing and presentation**		
	ko:K03283	HSPA1_8; heat shock 70kDa protein 1/8	T up
ko04660	**T cell receptor signaling pathway**		
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K18052	PRKCQ; novel protein kinase C theta type [EC:2.7.11.13]	T up
	ko:K04415	MAP3K8, COT; mitogen-activated protein kinase kinase kinase 8 [EC:2.7.11.25]	T up
ko04662	**B cell receptor signaling pathway**		
	ko:K04012	CR2, CD21; complement receptor type 2	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
ko04664	**Fc epsilon RI signaling pathway**		
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
ko04666	**Fc gamma R-mediated phagocytosis**		
	ko:K01080	PPAP2; phosphatidate phosphatase [EC:3.1.3.4]	T up
	ko:K04718	SPHK; sphingosine kinase [EC:2.7.1.91]	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
ko04670	**Leukocyte transendothelial migration**		
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K04189	CXCR4; C-X-C chemokine receptor type 4	T up

	ko:K04514	Rock1; Rho-associated protein kinase 1 [EC:2.7.11.1]	T up
	ko:K10351	MYL2; myosin regulatory light chain 2	C up
ko04672	**Intestinal immune network for IgA production**		
	ko:K04189	CXCR4; C-X-C chemokine receptor type 4	T up
	ko:K05433	IL15; interleukin 15	T up
ko04062	**Chemokine signaling pathway**		
	ko:K04543	GNG7; guanine nucleotide-binding protein G(I)/G(S)/G(O) subunit gamma-7	T up
	ko:K08045	ADCY5; adenylate cyclase 5 [EC:4.6.1.1]	T up
	ko:K10030	IL8, CXCL8; interleukin 8	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K12361	RASGRP2; RAS guanyl-releasing protein 2	T up
	ko:K12365	PREX1; phosphatidylinositol-3,4,5-trisphosphate-dependent Rac exchanger 1 protein	T up
	ko:K04175	IL8RA, CXCR1; interleukin 8 receptor alpha	T up
	ko:K04189	CXCR4; C-X-C chemokine receptor type 4	T up
	ko:K04514	Rock1; Rho-associated protein kinase 1 [EC:2.7.11.1]	T up
Endocrine system			
ko04911	**Insulin secretion**		
	ko:K09048	CREB3; cyclic AMP-responsive element-binding protein 3	T up
	ko:K09048	CREB3; cyclic AMP-responsive element-binding protein 3	T up
	ko:K04944	KCNN3; potassium intermediate/small conductance calcium-activated channel subfamily N member 3	T up
	ko:K08045	ADCY5; adenylate cyclase 5 [EC:4.6.1.1]	T up
	ko:K16882	PCLO; protein piccolo	T up
ko04910	**Insulin signaling pathway**		
	ko:K07192	FLOT; flotillin	C up
	ko:K06086	SORBS1, SH3D5, PONSIN, CAP; sorbin and SH3 domain containing 1	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
ko04920	**Adipocytokine signaling pathway**		
	ko:K18052	PRKCQ; novel protein kinase C theta type [EC:2.7.11.13]	T up
	ko:K08765	CPT1; carnitine O-palmitoyltransferase 1 [EC:2.3.1.21]	T up
	ko:K05141	TNFRSF1B, TNFR2; tumor necrosis factor receptor superfamily member 1B	T up
ko03320	**PPAR signaling pathway**		
	ko:K06086	SORBS1, SH3D5, PONSIN, CAP; sorbin and SH3 domain containing 1	T up
	ko:K08765	CPT1; carnitine O-palmitoyltransferase 1 [EC:2.3.1.21]	T up
	ko:K08755	FABP6; fatty acid-binding protein 6, ileal (gastrotropin)	T up
ko04912	**GnRH signaling pathway**		

	ko:K08045	ADCY5; adenylate cyclase 5 [EC:4.6.1.1]	T up
ko04913	**Ovarian Steroidogenesis**		
	ko:K07418	CYP2J; cytochrome P450, family 2, subfamily J [EC:1.14.14.1]	T up
	ko:K07408	CYP1A1; cytochrome P450, family 1, subfamily A, polypeptide 1 [EC:1.14.14.1]	T up
	ko:K04119	AKR1C3; aldo-keto reductase family 1 member C3 [EC:1.1.1.64 1.1.1.188 1.1.1.213]	T up
	ko:K08045	ADCY5; adenylate cyclase 5 [EC:4.6.1.1]	T up
ko04915	**Estrogen signaling pathway**		
	ko:K08045	ADCY5; adenylate cyclase 5 [EC:4.6.1.1]	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K03283	HSPA1_8; heat shock 70kDa protein 1/8	T up
	ko:K09048	CREB3; cyclic AMP-responsive element-binding protein 3	T up
	ko:K09048	CREB3; cyclic AMP-responsive element-binding protein 3	T up
	ko:K09487	HSP90B, TRA1; heat shock protein 90kDa beta	C up
ko04914	**Progesterone-mediated oocyte maturation**		
	ko:K08045	ADCY5; adenylate cyclase 5 [EC:4.6.1.1]	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
ko04917	**Prolactin signaling pathway**		
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
ko04921	**Oxytocin signaling pathway**		
	ko:K04859	CACNA2D2; voltage-dependent calcium channel alpha-2/delta-2	T up
	ko:K00907	MYLK; myosin-light-chain kinase [EC:2.7.11.18]	T up
	ko:K08045	ADCY5; adenylate cyclase 5 [EC:4.6.1.1]	T up
	ko:K04514	Rock1; Rho-associated protein kinase 1 [EC:2.7.11.1]	T up
	ko:K05005	KCNJ12; potassium inwardly-rectifying channel subfamily J member 12	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
ko04918	**Thyroid hormone synthesis**		
	ko:K09487	HSP90B, TRA1; heat shock protein 90kDa beta	C up
	ko:K08045	ADCY5; adenylate cyclase 5 [EC:4.6.1.1]	T up
	ko:K09490	HSPA5, BIP; heat shock 70kDa protein 5	C up
	ko:K09048	CREB3; cyclic AMP-responsive element-binding protein 3	T up
	ko:K09048	CREB3; cyclic AMP-responsive element-binding protein 3	T up
ko04919	**Thyroid hormone signaling pathway**		
	ko:K08362	NR1A2, THRB; thyroid hormone receptor beta	T up
	ko:K02599	NOTCH; Notch	T up
	ko:K17903	RCAN2, ZAKI4; calcipressin-2	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up

	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
ko04916	**Melanogenesis**		
	ko:K02354	FZD4, fz4; frizzled 4	T up
	ko:K09048	CREB3; cyclic AMP-responsive element-binding protein 3	T up
	ko:K09048	CREB3; cyclic AMP-responsive element-binding protein 3	T up
	ko:K01384	WNT11; wingless-type MMTV integration site family, member 11	T up
	ko:K00445	WNT6; wingless-type MMTV integration site family, member 6	T up
	ko:K08045	ADCY5; adenylate cyclase 5 [EC:4.6.1.1]	T up
	ko:K00572	WNT7; wingless-type MMTV integration site family, member 7	T up
ko04614	**Renin-angiotensin system**		
Circulatory system			
ko04260	**Cardiac muscle contraction**		
	ko:K04859	CACNA2D2; voltage-dependent calcium channel alpha-2/delta-2	T up
	ko:K10351	MYL2; myosin regulatory light chain 2	C up
ko04261	**Adrenergic signaling in cardiomyocytes**		
	ko:K04859	CACNA2D2; voltage-dependent calcium channel alpha-2/delta-2	T up
	ko:K09048	CREB3; cyclic AMP-responsive element-binding protein 3	T up
	ko:K09048	CREB3; cyclic AMP-responsive element-binding protein 3	T up
	ko:K04445	MSK1, RPS6KA5; ribosomal protein S6 kinase alpha-5 [EC:2.7.11.1]	C up
	ko:K10351	MYL2; myosin regulatory light chain 2	C up
	ko:K04845	SCN1B; voltage-gated sodium channel type I beta	T up
	ko:K08045	ADCY5; adenylate cyclase 5 [EC:4.6.1.1]	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
ko04270	**Vascular smooth muscle contraction**		
	ko:K00907	MYLK; myosin-light-chain kinase [EC:2.7.11.18]	T up
	ko:K04266	ADORA2A, ADOR; adenosine receptor A2a	T up
	ko:K18052	PRKCQ; novel protein kinase C theta type [EC:2.7.11.13]	T up
	ko:K08045	ADCY5; adenylate cyclase 5 [EC:4.6.1.1]	T up
Digestive system			
ko04970	**Salivary secretion**		
	ko:K08045	ADCY5; adenylate cyclase 5 [EC:4.6.1.1]	T up
ko04971	**Gastric acid secretion**		
	ko:K00907	MYLK; myosin-light-chain kinase [EC:2.7.11.18]	T up
	ko:K08045	ADCY5; adenylate cyclase 5 [EC:4.6.1.1]	T up
ko04972	**Pancreatic secretion**		
	ko:K08045	ADCY5; adenylate cyclase 5 [EC:4.6.1.1]	T up
	ko:K07884	RAB3D; Ras-related protein Rab-3D	T up
ko04976	**Bile secretion**		
	ko:K08045	ADCY5; adenylate cyclase 5 [EC:4.6.1.1]	T up
ko04973	**Carbohydrate digestion and absorption**		
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up

ko04974	**Protein digestion and absorption**		
	ko:K13781	SLC7A8, LAT2; solute carrier family 7 (L-type amino acid transporter), member 8	T up
	ko:K06236	COL1AS; collagen, type I/II/III/V/XI/XXIV/XXVII, alpha	T up
	ko:K14207	SLC38A2, SNAT2; solute carrier family 38 (sodium-coupled neutral amino acid transporter), member 2	C up
	ko:K06237	COL4A; collagen, type IV, alpha	T up
ko04975	**Fat digestion and absorption**		
	ko:K11160	DGAT2; diacylglycerol O-acyltransferase 2 [EC:2.3.1.20 2.3.1.75]	T up
	ko:K01080	PPAP2; phosphatidate phosphatase [EC:3.1.3.4]	T up
ko04977	**Vitamin digestion and absorption**		
ko04978	**Mineral absorption**		
Excretory system			
ko04962	**Vasopressin-regulated water reabsorption**		
	ko:K09048	CREB3; cyclic AMP-responsive element-binding protein 3	T up
	ko:K09048	CREB3; cyclic AMP-responsive element-binding protein 3	T up
ko04960	**Aldosterone-regulated sodium reabsorption**		
	ko:K13302	SGK1; serum/glucocorticoid-regulated kinase 1 [EC:2.7.11.1]	T up
	ko:K08555	NR3C2, MR; mineralocorticoid receptor	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
ko04961	**Endocrine and other factor-regulated calcium reabsorption**		
ko04964	**Proximal tubule bicarbonate reclamation**		
ko04966	**Collecting duct acid secretion**		
	ko:K02148	ATPeV1C, ATP6C; V-type H+-transporting ATPase subunit C	T up
Nervous system			
ko04724	**Glutamatergic synapse**		
	ko:K14207	SLC38A2, SNAT2; solute carrier family 38 (sodium-coupled neutral amino acid transporter), member 2	C up
	ko:K04543	GNG7; guanine nucleotide-binding protein G(I)/G(S)/G(O) subunit gamma-7	T up
	ko:K08045	ADCY5; adenylate cyclase 5 [EC:4.6.1.1]	T up
	ko:K15009	SHANK; SH3 and multiple ankyrin repeat domains protein	T up
	ko:K05205	GRIK5; glutamate receptor, ionotropic kainate 5	T up
	ko:K04607	GRM4; metabotropic glutamate receptor 4	T up
ko04727	**GABAergic synapse**		
	ko:K04543	GNG7; guanine nucleotide-binding protein G(I)/G(S)/G(O) subunit gamma-7	T up
	ko:K08045	ADCY5; adenylate cyclase 5 [EC:4.6.1.1]	T up
	ko:K05184	GABRD; gamma-aminobutyric acid receptor subunit delta	T up
	ko:K04647	HAP1; huntingtin-associated protein 1	T up
	ko:K14207	SLC38A2, SNAT2; solute carrier family 38 (sodium-coupled neutral amino acid transporter), member 2	C up

ko04725	**Cholinergic synapse**		
	ko:K01049	ACHE; acetylcholinesterase [EC:3.1.1.7]	T up
	ko:K09048	CREB3; cyclic AMP-responsive element-binding protein 3	T up
	ko:K09048	CREB3; cyclic AMP-responsive element-binding protein 3	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K05005	KCNJ12; potassium inwardly-rectifying channel subfamily J member 12	T up
	ko:K04132	CHRM4; muscarinic acetylcholine receptor M4	T up
	ko:K08045	ADCY5; adenylate cyclase 5 [EC:4.6.1.1]	T up
	ko:K04543	GNG7; guanine nucleotide-binding protein G(I)/G(S)/G(O) subunit gamma-7	T up
ko04728	**Dopaminergic synapse**		
	ko:K04543	GNG7; guanine nucleotide-binding protein G(I)/G(S)/G(O) subunit gamma-7	T up
	ko:K08045	ADCY5; adenylate cyclase 5 [EC:4.6.1.1]	T up
	ko:K04633	GNAL; guanine nucleotide-binding protein G(olf) subunit alpha	T up
	ko:K09048	CREB3; cyclic AMP-responsive element-binding protein 3	T up
	ko:K09048	CREB3; cyclic AMP-responsive element-binding protein 3	T up
ko04726	**Serotonergic synapse**		
	ko:K07418	CYP2J; cytochrome P450, family 2, subfamily J [EC:1.14.14.1]	T up
	ko:K00509	PTGS1, COX1; prostaglandin-endoperoxide synthase 1 [EC:1.14.99.1]	T up
	ko:K04543	GNG7; guanine nucleotide-binding protein G(I)/G(S)/G(O) subunit gamma-7	T up
	ko:K08045	ADCY5; adenylate cyclase 5 [EC:4.6.1.1]	T up
	ko:K04153	HTR1; 5-hydroxytryptamine receptor 1	T up
ko04720	**Long-term potentiation**		
ko04730	**Long-term depression**		
ko04723	**Retrograde endocannabinoid signaling**		
	ko:K04543	GNG7; guanine nucleotide-binding protein G(I)/G(S)/G(O) subunit gamma-7	T up
	ko:K08045	ADCY5; adenylate cyclase 5 [EC:4.6.1.1]	T up
	ko:K05184	GABRD; gamma-aminobutyric acid receptor subunit delta	T up
	ko:K13700	ABHD6; abhydrolase domain-containing protein 6 [EC:3.1.1.23]	T up
ko04721	**Synaptic vesicle cycle**		
	ko:K02148	ATPeV1C, ATP6C; V-type H+-transporting ATPase subunit C	T up
	ko:K15294	CPLX1_2; complexin-1/2	T up
ko04722	**Neurotrophin signaling pathway**		
	ko:K02583	NGFR; nerve growth factor receptor (TNFR superfamily member 16)	T up
	ko:K04445	MSK1, RPS6KA5; ribosomal protein S6 kinase alpha-5 [EC:2.7.11.1]	C up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up

Sensory system			
ko04744	**Phototransduction**		
	ko:K13765	RGS9; regulator of G-protein signaling 9	T up
ko04740	**Olfactory transduction**		
	ko:K04633	GNAL; guanine nucleotide-binding protein G(olf) subunit alpha	T up
ko04742	**Taste transduction**		
	ko:K04607	GRM4; metabotropic glutamate receptor 4	T up
ko04750	**Inflammatory mediator regulation of TRP channels**		
	ko:K04971	TRPV2; transient receptor potential cation channel subfamily V member 2	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K08045	ADCY5; adenylate cyclase 5 [EC:4.6.1.1]	T up
	ko:K07418	CYP2J; cytochrome P450, family 2, subfamily J [EC:1.14.14.1]	T up
	ko:K18052	PRKCQ; novel protein kinase C theta type [EC:2.7.11.13]	T up
Development			
ko04320	**Dorso-ventral axis formation**		
	ko:K02599	NOTCH; Notch	T up
ko04360	**Axon guidance**		
	ko:K06820	PLXNA; plexin A	T up
	ko:K16359	NTNG2; netrin-G2	T up
	ko:K06838	SLIT1; slit 1	T up
	ko:K06842	SEMA6; semaphorin 6	T up
	ko:K06842	SEMA6; semaphorin 6	T up
	ko:K06550	L1CAM; L1 cell adhesion molecule	T up
	ko:K05114	EPHB6; Eph receptor B6 [EC:2.7.10.1]	T up
	ko:K06521	SEMA4; semaphorin 4	T up
	ko:K06843	NTN1; netrin 1	T up
	ko:K05462	EFNA; ephrin-A	T up
	ko:K05462	EFNA; ephrin-A	T up
	ko:K04189	CXCR4; C-X-C chemokine receptor type 4	T up
	ko:K07529	DPYSL5, CRAM; dihydropyrimidinase-like 5	T up
	ko:K06840	SEMA3; semaphorin 3	T up
	ko:K06840	SEMA3; semaphorin 3	T up
	ko:K05112	EPHB3, HEK2, ETK2; Eph receptor B3 [EC:2.7.10.1]	T up
ko04380	**Osteoclast differentiation**		
	ko:K05453	CSF1, MCSF; macrophage colony-stimulating factor 1	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
ko04713	**Circadian entrainment**		
	ko:K04543	GNG7; guanine nucleotide-binding protein G(I)/G(S)/G(O) subunit gamma-7	T up
	ko:K08045	ADCY5; adenylate cyclase 5 [EC:4.6.1.1]	T up

	ko:K04854	CACNA1G; voltage-dependent calcium channel T type alpha-1G	T up
	ko:K04445	MSK1, RPS6KA5; ribosomal protein S6 kinase alpha-5 [EC:2.7.11.1]	C up
ko04626	**Plant-pathogen interaction**		
	ko:K09487	HSP90B, TRA1; heat shock protein 90kDa beta	C up
Human Diseases			
Cancers			
ko05200	**Pathways in cancer**		
	ko:K00572	WNT7; wingless-type MMTV integration site family, member 7	T up
	ko:K10030	IL8, CXCL8; interleukin 8	T up
	ko:K06240	LAMA3_5; laminin, alpha 3/5	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K08775	BRCA2, FANCD1; breast cancer 2 susceptibility protein	C up
	ko:K00445	WNT6; wingless-type MMTV integration site family, member 6	T up
	ko:K01384	WNT11; wingless-type MMTV integration site family, member 11	T up
	ko:K16859	PGF; placenta growth factor	T up
	ko:K05126	RET; proto-oncogene tyrosine-protein kinase Ret [EC:2.7.10.1]	T up
	ko:K09348	NKX3-1; homeobox protein Nkx-3.1	T up
	ko:K05717	FN1; fibronectin 1	T up
	ko:K06237	COL4A; collagen, type IV, alpha	T up
	ko:K02354	FZD4, fz4; frizzled 4	T up
	ko:K16798	GLI2; zinc finger protein GLI2	T up
	ko:K04514	Rock1; Rho-associated protein kinase 1 [EC:2.7.11.1]	T up
	ko:K09487	HSP90B, TRA1; heat shock protein 90kDa beta	C up
ko05202	**Transcriptional misregulation in cancers**		
	ko:K09355	PBX1; pre-B-cell leukemia transcription factor 1	T up
	ko:K15187	MLLT1_3, ENL, AF9; YEATS domain-containing protein 1/3	T up
	ko:K04452	DDIT3, GADD153; DNA damage-inducible transcript 3	C up
	ko:K02583	NGFR; nerve growth factor receptor (TNFR superfamily member 16)	T up
	ko:K06622	CDKN2C, P18, INK4C; cyclin-dependent kinase inhibitor 2C	T up
	ko:K10030	IL8, CXCL8; interleukin 8	T up
ko05206	**MicroRNAs in cancer**		
	ko:K16866	TIMP3; metalloproteinase inhibitor 3	T up
	ko:K17460	BMF; Bcl-2-modifying factor	T up
	ko:K16865	PDCD4; programmed cell death protein 4	C up
	ko:K04445	MSK1, RPS6KA5; ribosomal protein S6 kinase alpha-5 [EC:2.7.11.1]	C up
	ko:K10605	BRCA1; breast cancer type 1 susceptibility protein	C up
	ko:K06484	ITGA5; integrin alpha 5	T up
	ko:K02599	NOTCH; Notch	T up
ko05205	**Proteoglycans in cancer**		
	ko:K01384	WNT11; wingless-type MMTV integration site family, member 11	T up
	ko:K00445	WNT6; wingless-type MMTV integration site family, member 6	T up

	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K00572	WNT7; wingless-type MMTV integration site family, member 7	T up
	ko:K06484	ITGA5; integrin alpha 5	T up
	ko:K16865	PDCD4; programmed cell death protein 4	C up
	ko:K06278	CAV1; caveolin 1	C up
	ko:K12958	CAV2; caveolin 2	C up
	ko:K05717	FN1; fibronectin 1	T up
	ko:K16866	TIMP3; metalloproteinase inhibitor 3	T up
	ko:K02354	FZD4, fz4; frizzled 4	T up
ko05204	**Chemical carcinogenesis**		
	ko:K00799	GST, gst; glutathione S-transferase [EC:2.5.1.18]	T up
	ko:K07408	CYP1A1; cytochrome P450, family 1, subfamily A, polypeptide 1 [EC:1.14.14.1]	T up
ko05203	**Viral carcinogenesis**		
	ko:K09048	CREB3; cyclic AMP-responsive element-binding protein 3	T up
	ko:K09048	CREB3; cyclic AMP-responsive element-binding protein 3	T up
	ko:K03990	C3; complement component 3	T up
	ko:K10131	PMAIP1; phorbol-12-myristate-13-acetate-induced protein 1	C up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
ko05210	**Colorectal cancer**		
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
ko05212	**Pancreatic cancer**		
	ko:K08775	BRCA2, FANCD1; breast cancer 2 susceptibility protein	C up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
ko05214	**Glioma**		
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
ko05216	**Thyroid cancer**		
	ko:K05126	RET; proto-oncogene tyrosine-protein kinase Ret [EC:2.7.10.1]	T up
ko05221	**Acute myeloid leukemia**		
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
ko05220	**Chronic myeloid leukemia**		
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
ko05217	**Basal cell carcinoma**		
	ko:K00572	WNT7; wingless-type MMTV integration site family, member 7	T up
	ko:K02354	FZD4, fz4; frizzled 4	T up
	ko:K16798	GLI2; zinc finger protein GLI2	T up

	ko:K00445	WNT6; wingless-type MMTV integration site family, member 6	T up
	ko:K01384	WNT11; wingless-type MMTV integration site family, member 11	T up
ko05218	**Melanoma**		
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
ko05211	**Renal cell carcinoma**		
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
ko05219	**Bladder cancer**		
	ko:K10030	IL8, CXCL8; interleukin 8	T up
	ko:K04445	MSK1, RPS6KA5; ribosomal protein S6 kinase alpha-5 [EC:2.7.11.1]	C up
ko05215	**Prostate cancer**		
	ko:K09487	HSP90B, TRA1; heat shock protein 90kDa beta	C up
	ko:K09048	CREB3; cyclic AMP-responsive element-binding protein 3	T up
	ko:K09048	CREB3; cyclic AMP-responsive element-binding protein 3	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K09348	NKX3-1; homeobox protein Nkx-3.1	T up
ko05213	**Endometrial cancer**		
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
ko05222	**Small cell lung cancer**		
	ko:K05717	FN1; fibronectin 1	T up
	ko:K06240	LAMA3_5; laminin, alpha 3/5	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K06237	COL4A; collagen, type IV, alpha	T up
ko05223	**Non-small cell lung cancer**		
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
Immune diseases			
ko05322	**Systemic lupus erythematosus**		
	ko:K03990	C3; complement component 3	T up
ko05323	**Rheumatoid arthritis**		
	ko:K10030	IL8, CXCL8; interleukin 8	T up
	ko:K05453	CSF1, MCSF; macrophage colony-stimulating factor 1	T up
	ko:K02148	ATPeV1C, ATP6C; V-type H+-transporting ATPase subunit C	T up
	ko:K05433	IL15; interleukin 15	T up
ko05320	**Autoimmune thyroid disease**		
ko05321	**Inflammatiory bowel disease (IBD)**		
	ko:K11222	STAT4; signal transducer and activator of transcription 4	T up
Neurodegenerative diseases			
ko05010	**Alzheimer's disease**		

	ko:K04550	LRP1, CD91; low-density lipoprotein receptor-related protein 1 (alpha-2-macroglobulin receptor)	T up
ko05012	**Parkinson's disease**		
	ko:K04266	ADORA2A, ADOR; adenosine receptor A2a	T up
	ko:K04633	GNAL; guanine nucleotide-binding protein G(olf) subunit alpha	T up
	ko:K08045	ADCY5; adenylate cyclase 5 [EC:4.6.1.1]	T up
ko05014	**Amyotrophic lateral sclerosis (ALS)**		
	ko:K05141	TNFRSF1B, TNFR2; tumor necrosis factor receptor superfamily member 1B	T up
ko05016	**Huntington's disease**		
	ko:K04647	HAP1; huntingtin-associated protein 1	T up
	ko:K09048	CREB3; cyclic AMP-responsive element-binding protein 3	T up
	ko:K09048	CREB3; cyclic AMP-responsive element-binding protein 3	T up
	ko:K10408	DNAH; dynein heavy chain, axonemal	C up
ko05020	**Prion diseases**		
	ko:K09490	HSPA5, BIP; heat shock 70kDa protein 5	C up
Substance dependence			
ko05030	**Cocaine addiction**		
	ko:K13765	RGS9; regulator of G-protein signaling 9	T up
	ko:K08045	ADCY5; adenylate cyclase 5 [EC:4.6.1.1]	T up
	ko:K09048	CREB3; cyclic AMP-responsive element-binding protein 3	T up
	ko:K09048	CREB3; cyclic AMP-responsive element-binding protein 3	T up
ko05031	**Amphetamine addiction**		
	ko:K09048	CREB3; cyclic AMP-responsive element-binding protein 3	T up
	ko:K09048	CREB3; cyclic AMP-responsive element-binding protein 3	T up
	ko:K08045	ADCY5; adenylate cyclase 5 [EC:4.6.1.1]	T up
ko05032	**Morphine addiction**		
	ko:K08045	ADCY5; adenylate cyclase 5 [EC:4.6.1.1]	T up
	ko:K04543	GNG7; guanine nucleotide-binding protein G(I)/G(S)/G(O) subunit gamma-7	T up
	ko:K04265	ADORA1; adenosine A1 receptor	T up
	ko:K05184	GABRD; gamma-aminobutyric acid receptor subunit delta	T up
ko05033	**Nicotine addiction**		
	ko:K05184	GABRD; gamma-aminobutyric acid receptor subunit delta	T up
ko05034	**Alcoholism**		
	ko:K04266	ADORA2A, ADOR; adenosine receptor A2a	T up
	ko:K09048	CREB3; cyclic AMP-responsive element-binding protein 3	T up
	ko:K09048	CREB3; cyclic AMP-responsive element-binding protein 3	T up
	ko:K04543	GNG7; guanine nucleotide-binding protein G(I)/G(S)/G(O) subunit gamma-7	T up
	ko:K08045	ADCY5; adenylate cyclase 5 [EC:4.6.1.1]	T up
Cardiovascular diseases			
ko05410	**Hypertrophic cardiomyopathy (HCM)**		

	ko:K06591	ITGB8; integrin beta 8	C up
	ko:K10351	MYL2; myosin regulatory light chain 2	C up
	ko:K06484	ITGA5; integrin alpha 5	T up
	ko:K07610	DES; desmin	T up
	ko:K04859	CACNA2D2; voltage-dependent calcium channel alpha-2/delta-2	T up
ko05412	**Arrhythmogenic right ventricular cardiomyopathy (ARVC)**		
	ko:K06591	ITGB8; integrin beta 8	C up
	ko:K06484	ITGA5; integrin alpha 5	T up
	ko:K07610	DES; desmin	T up
	ko:K04859	CACNA2D2; voltage-dependent calcium channel alpha-2/delta-2	T up
ko05414	**Dilated cardiomyopathy (DCM)**		
	ko:K06484	ITGA5; integrin alpha 5	T up
	ko:K07610	DES; desmin	T up
	ko:K04859	CACNA2D2; voltage-dependent calcium channel alpha-2/delta-2	T up
	ko:K08045	ADCY5; adenylate cyclase 5 [EC:4.6.1.1]	T up
	ko:K10351	MYL2; myosin regulatory light chain 2	C up
	ko:K06591	ITGB8; integrin beta 8	C up
ko05416	**Viral myocarditis**		
	ko:K06278	CAV1; caveolin 1	C up
Endocrine and metabolic diseases			
ko04930	**Type II diabetes mellitus**		
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K04854	CACNA1G; voltage-dependent calcium channel T type alpha-1G	T up
ko04950	**Maturity onset diabetes of the young**		
	ko:K08027	NR5A2, FTF; nuclear receptor subfamily 5 group A member 2	T up
ko04932	**Non-alcoholic fatty liver disease (NAFLD)**		
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K10030	IL8, CXCL8; interleukin 8	T up
	ko:K04452	DDIT3, GADD153; DNA damage-inducible transcript 3	C up
Infectious diseases			
ko05110	**Vibrio cholerae infection**		
	ko:K02148	ATPeV1C, ATP6C; V-type H+-transporting ATPase subunit C	T up
ko05120	**Epithelial cell signaling in Helicobacter pylori infection**		
	ko:K02148	ATPeV1C, ATP6C; V-type H+-transporting ATPase subunit C	T up
	ko:K04175	IL8RA, CXCR1; interleukin 8 receptor alpha	T up
	ko:K10030	IL8, CXCL8; interleukin 8	T up
ko05130	**Pathogenic Escherichia coli infection**		
	ko:K07375	TUBB; tubulin beta	T up
	ko:K07375	TUBB; tubulin beta	T up
ko05132	**Salmonella infection**		
	ko:K07898	RAB7B; Ras-related protein Rab-7B	T up

	ko:K10030	IL8, CXCL8; interleukin 8	T up
ko05131	**Shigellosis**		
	ko:K10030	IL8, CXCL8; interleukin 8	T up
	ko:K06484	ITGA5; integrin alpha 5	T up
ko05133	**Pertussis**		
	ko:K06484	ITGA5; integrin alpha 5	T up
	ko:K03990	C3; complement component 3	T up
	ko:K10030	IL8, CXCL8; interleukin 8	T up
ko05134	**Legionellosis**		
	ko:K10030	IL8, CXCL8; interleukin 8	T up
	ko:K03283	HSPA1_8; heat shock 70kDa protein 1/8	T up
	ko:K03990	C3; complement component 3	T up
ko05150	**Staphylococcus aureus infection**		
	ko:K03990	C3; complement component 3	T up
ko05152	**Tuberculosis**		
	ko:K04718	SPHK; sphingosine kinase [EC:2.7.1.91]	T up
	ko:K03990	C3; complement component 3	T up
	ko:K06560	MRC; mannose receptor, C type	T up
	ko:K05134	IL10RA; interleukin 10 receptor alpha	T up
	ko:K10049	CEBPG; CCAAT/enhancer binding protein (C/EBP), gamma	C up
ko05100	**Bacterial invasion of epithelial cells**		
	ko:K06484	ITGA5; integrin alpha 5	T up
	ko:K16938	SEPT3_9_12; septin 3/9/12	T up
	ko:K05717	FN1; fibronectin 1	T up
	ko:K06278	CAV1; caveolin 1	C up
	ko:K12958	CAV2; caveolin 2	C up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
ko05166	**HTLV-I infection**		
	ko:K09341	MSX; homeobox protein MSX	T up
	ko:K09341	MSX; homeobox protein MSX	T up
	ko:K05433	IL15; interleukin 15	T up
	ko:K08045	ADCY5; adenylate cyclase 5 [EC:4.6.1.1]	T up
	ko:K00572	WNT7; wingless-type MMTV integration site family, member 7	T up
	ko:K00445	WNT6; wingless-type MMTV integration site family, member 6	T up
	ko:K01384	WNT11; wingless-type MMTV integration site family, member 11	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02354	FZD4, fz4; frizzled 4	T up
	ko:K06622	CDKN2C, P18, INK4C; cyclin-dependent kinase inhibitor 2C	T up
ko05162	**Measles**		
	ko:K18052	PRKCQ; novel protein kinase C theta type [EC:2.7.11.13]	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up

	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K03283	HSPA1_8; heat shock 70kDa protein 1/8	T up
ko05164	**Influenza A**		
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K03283	HSPA1_8; heat shock 70kDa protein 1/8	T up
	ko:K10030	IL8, CXCL8; interleukin 8	T up
	ko:K01349	FURIN, PCSK3; furin [EC:3.4.21.75]	T up
	ko:K15046	NS1BP; influenza virus NS1A-binding protein	C up
ko05161	**Hepatitis B**		
	ko:K09048	CREB3; cyclic AMP-responsive element-binding protein 3	T up
	ko:K09048	CREB3; cyclic AMP-responsive element-binding protein 3	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K11222	STAT4; signal transducer and activator of transcription 4	T up
	ko:K10030	IL8, CXCL8; interleukin 8	T up
ko05160	**Hepatitis C**		
	ko:K10030	IL8, CXCL8; interleukin 8	T up
	ko:K03250	EIF3E, INT6; translation initiation factor 3 subunit E	C up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K14217	IFIT1; interferon-induced protein with tetratricopeptide repeats 1	T up
ko05168	**Herpes simplex infection**		
	ko:K05433	IL15; interleukin 15	T up
	ko:K14217	IFIT1; interferon-induced protein with tetratricopeptide repeats 1	T up
	ko:K03990	C3; complement component 3	T up
ko05169	**Epstein-Barr virus infection**		
	ko:K05134	IL10RA; interleukin 10 receptor alpha	T up
	ko:K04012	CR2, CD21; complement receptor type 2	T up
	ko:K03283	HSPA1_8; heat shock 70kDa protein 1/8	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
ko05146	**Amoebiasis**		
	ko:K04633	GNAL; guanine nucleotide-binding protein G(olf) subunit alpha	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K05717	FN1; fibronectin 1	T up
	ko:K06240	LAMA3_5; laminin, alpha 3/5	T up
	ko:K10030	IL8, CXCL8; interleukin 8	T up
	ko:K06236	COL1AS; collagen, type I/II/III/V/XI/XXIV/XXVII, alpha	T up
	ko:K07898	RAB7B; Ras-related protein Rab-7B	T up
	ko:K06237	COL4A; collagen, type IV, alpha	T up
ko05144	**Malaria**		

	ko:K10030	IL8, CXCL8; interleukin 8	T up
	ko:K04550	LRP1, CD91; low-density lipoprotein receptor-related protein 1 (alpha-2-macroglobulin receptor)	T up
ko05145	**Toxoplasmosis**		
	ko:K06240	LAMA3_5; laminin, alpha 3/5	T up
	ko:K05134	IL10RA; interleukin 10 receptor alpha	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K03283	HSPA1_8; heat shock 70kDa protein 1/8	T up
ko05140	**Leishmaniasis**		
	ko:K03990	C3; complement component 3	T up
ko05142	**Chagas disease (American trypanosomiasis)**		
	ko:K03990	C3; complement component 3	T up
	ko:K04633	GNAL; guanine nucleotide-binding protein G(olf) subunit alpha	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K02649	PIK3R; phosphoinositide-3-kinase, regulatory subunit	T up
	ko:K10030	IL8, CXCL8; interleukin 8	T up

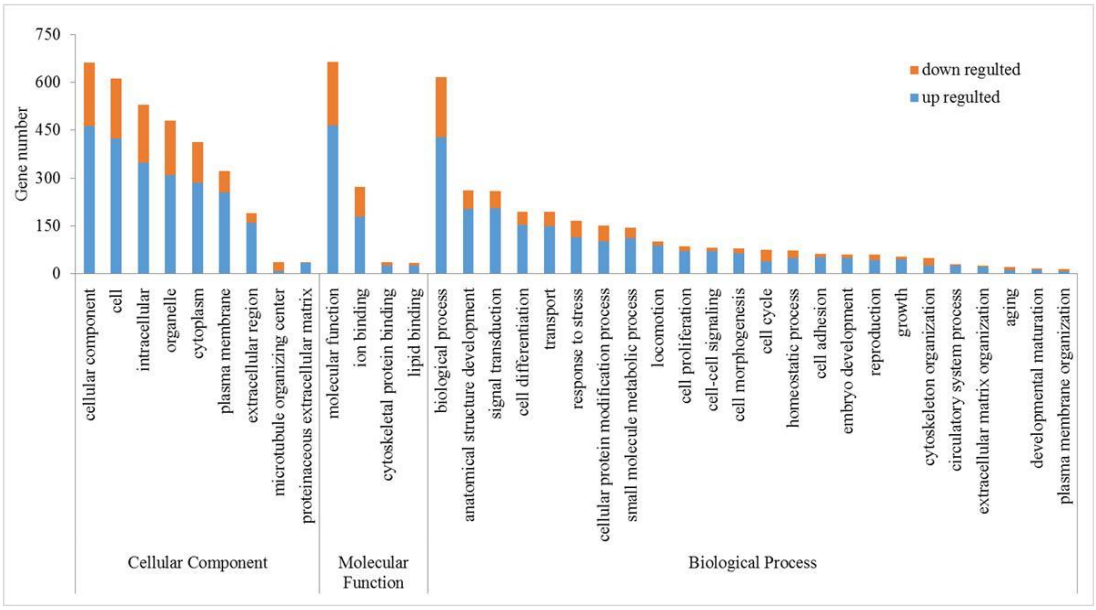

Fig. S1. GO annotation of the differentially expressed genes. The genes are enriched in different terms in three functional categories.

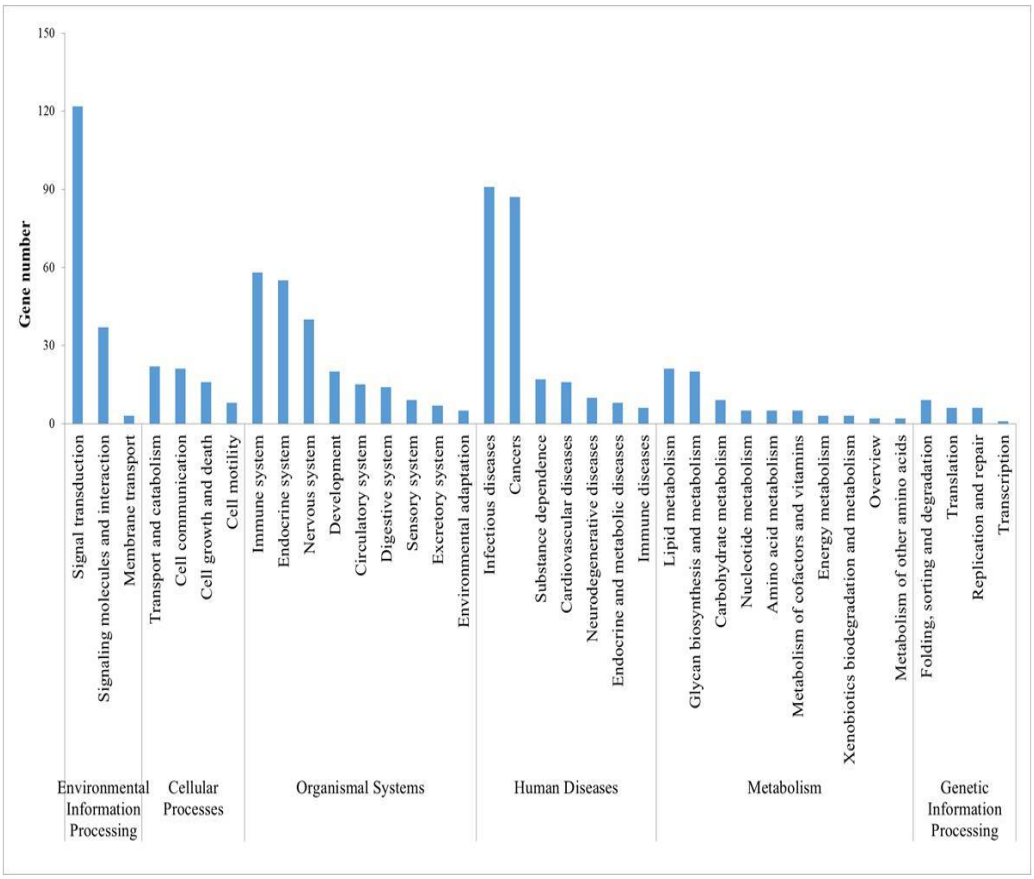

Fig. S2. KEGG annotation of the differentially expressed genes. The genes are enriched in different pathways in different functional groups.

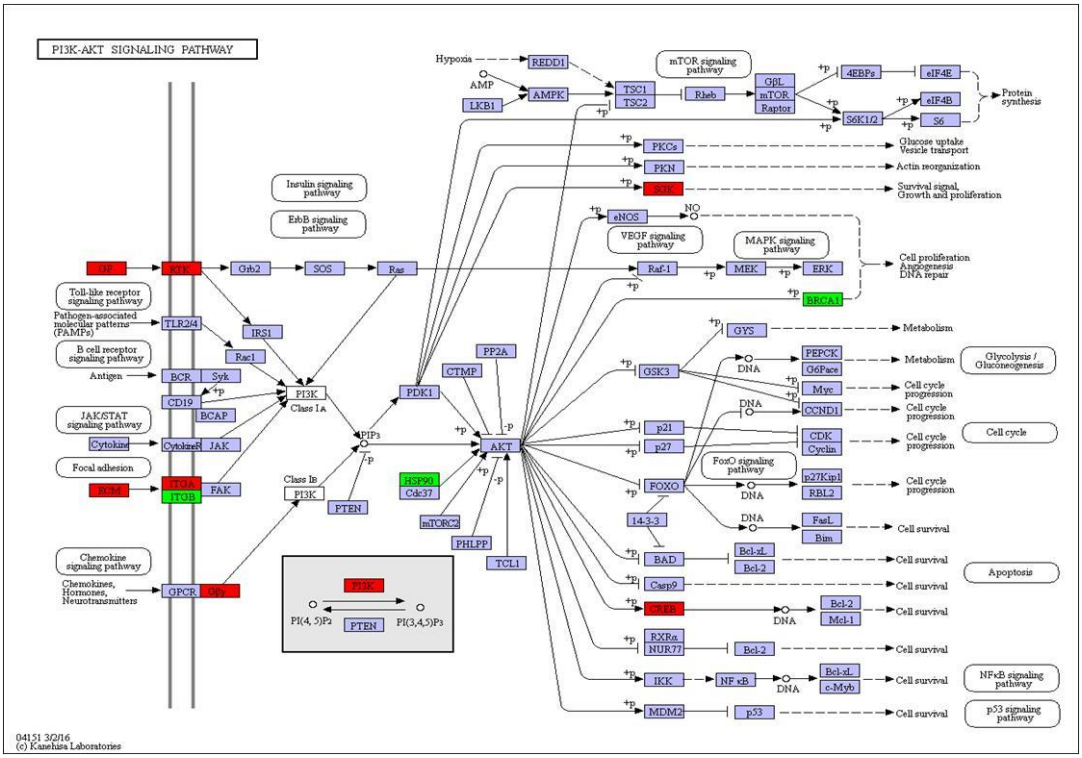

Fig. S3. KEGG analysis reveals that AKT pathway is activated by high glucose, insulin and palmitic acid.

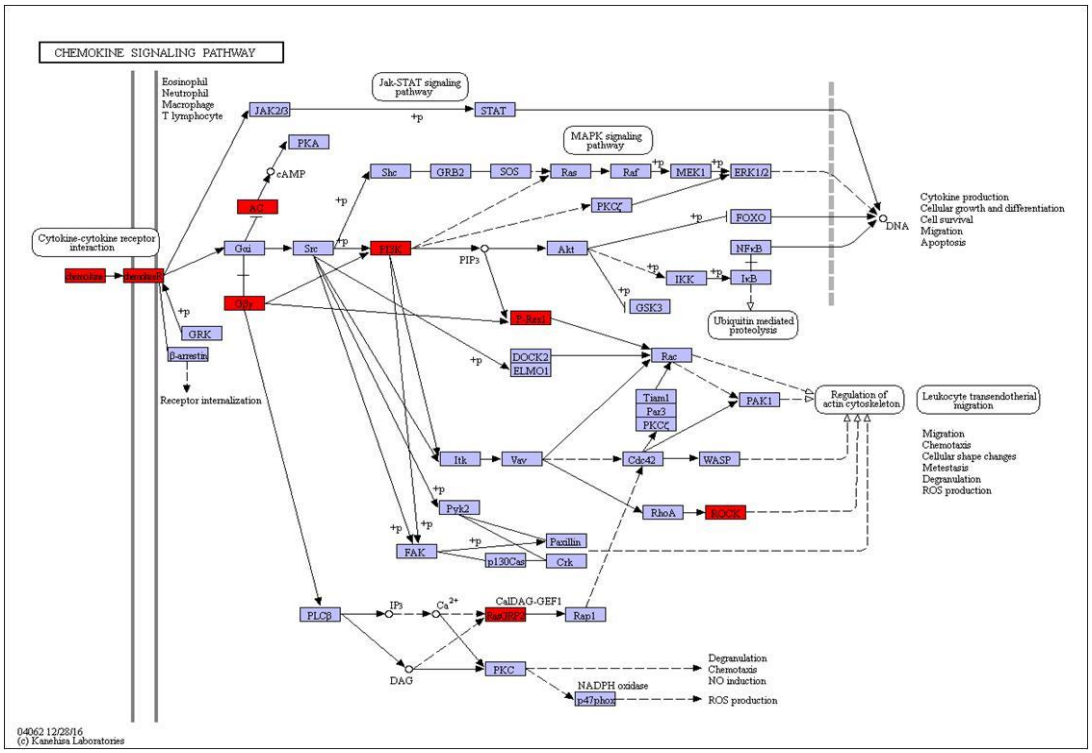

Fig. S4. KEGG analysis reveals that ROCK pathway is activated by high glucose, insulin and palmitic acid.

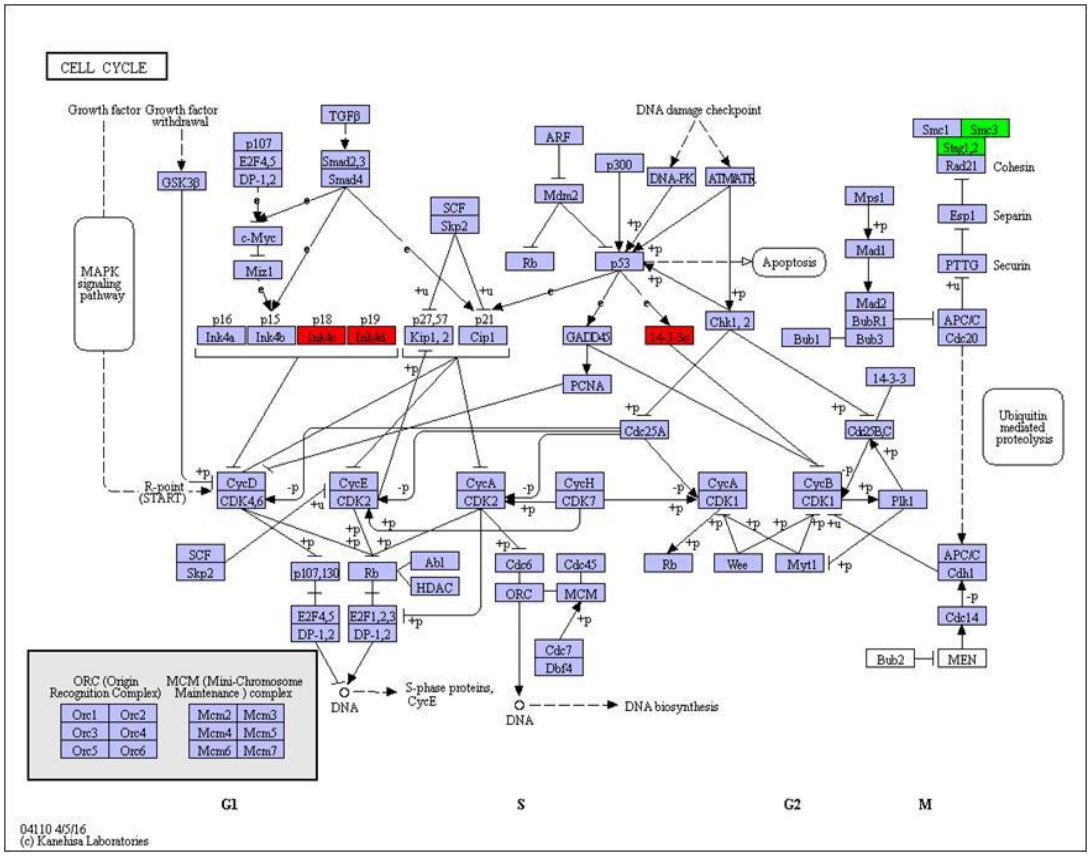

Fig. S5. KEGG analysis reveals that 14-3-3σ pathway is activated by high glucose, insulin and palmitic acid.