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# B-cell translocation gene-2 increases hepatic gluconeogenesis via induction of CREB

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ABSTRACT

Hepatic gluconeogenesis is mediated by the network of transcriptional factors and cofactors. Here, we show that B-cell translocation gene-2 (BTG2) plays a crucial cofactor in hepatic gluconeogenesis via upregulation of the cyclic AMP (cAMP) response element binding (CREB) in hepatocytes. cAMP/dexamethasone (Dex) significantly increased BTG2 and other gluconeogenic genes such as Nur77, phosphoenolpyruvate carboxykinase (PEPCK), and glucose-6-phosphatase (G6Pase) in hepatocytes. In contrast, insulin treatment completely blocks their expressions. Interestingly, overexpression of BTG2 using adenoviral system (Ad-BTG2) significantly elevated hepatic glucose production via the increase of transcriptional activity and gene expression of CREB, PEPCK, and G6Pase in hepatocytes, suggesting that BTG2 is the key player on hepatic glucose production. Physiological interaction studies demonstrated that BTG2 correlated CREB recruitment on the PEPCK gene promoter via a direct interaction. Finally, knockdown of endogenous BTG2 expression markedly inhibits the cAMP/Dex-induced transcriptional activity of gluconeogenic genes and glucose production in hepatocytes. Overall, the present study provides us with a novel molecular mechanism of BTG2-mediated induction of hepatic gluconeogenesis and suggests that BTG2 plays an important role in hepatic glucose metabolism.



## 1. Introduction

Hepatic gluconeogenesis is commonly regulated by the activities of key enzymes, such as phosphoenolpyruvate carboxykinase (PEPCK), fructose bisphosphatase (Fbp1) and glucose-6-phosphatase (G6Pase) [1]. The expression of the key hepatic gluconeogenic genes are regulated by key hormones, including insulin, glucagon, and glucocorticoids [1,2]. Hepatic gluconeogenic gene expression is mediated by the network of transcriptional factors and cofactors, such as cAMP response element-binding protein (CREB), hepatocyte nuclear factor (HNF)-4α, FoxA2 (also known of HNF-3β), and peroxisome proliferators-activated receptor γ coativator-1α (PGC-1α), transducer of regulated CREB activity 2 (TORC2), CREB-binding protein [3–6]. Especially, the basic leucine zipper protein CREB binds to DNA sequences called cAMP-response element (CRE) that contains consensus motif (TGACGTCA) and induces the transcription of CRE-harboring gluconeogenic genes [7]. The transcriptional regulation of CREB is known to be mediated by a variety of signaling and physiological events, including cAMP-dependent protein kinase A, $Ca^{2+}$, and fasting conditions [3,7].

BTG2 (B-cell translocation gene 2), also has known as pheochromocytoma cell 3 (PC3) in the rat and tetradecanoyl phorbol acetate-inducible sequence 21 (TIS21) in the mouse, belongs to the BTG/Tob gene family containing two homology domains (Box A and B), which are highly conserved among various species [8]. This family has been known to display anti-proliferative properties and comprises an emerging gene family that is involved in cell growth, death, differentiation and survival [9–12]. BTG2 gene is induced upon cellular stress by p53-dependent and p53-independent mechanisms and indicates reduced expression in a number of tumor tissues [13]. Moreover, the involvement of BTG2, known as a transcriptional co-regulator, is supported by results indicated that BTG2 acts as transcriptional cofactors via the physical interaction of HOXB9, CCR4, and CAF1 [14,15]. A recent report suggest that growth hormone, known as stimulator of hepatic gluconeogenesis, significantly increases a set of early response genes, such as c-Fos, cystein-rich 61, BTG2, and suppressor of cytokine signaling 3 (Socs3) in adipocytes [16]. However, no study has been known whether how a strong relevance between BTG2 and CREB are involved in hepatic gluconeogenesis.

In the current study, we demonstrate that BTG2 acts a novel co-activator of CREB to positively regulate hepatic gluconeogenesis

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and these results strongly suggest that BTG2 may be the key target for developing novel therapeutic agents to treat hepatic diseases.

## 2. Materials and methods

### 2.1. Chemicals

8-Bromoadenosine 3,5-cyclic monophosphate (cAMP, Sigma, St. Louis, Mo, USA), dexamethasone (Dex, Sigma, St. Louis, MO, USA), and insulin (Norvolin R, Green Cross, Republic of Korea) were purchased from the indicated companies, and dissolved in the recommended solvents.

### 2.2. Cloning of rat BTG2 and CREB

The cDNA encompassing the entire BTG2 and CREB open reading frame was cloned by reverse transcriptase-PCR. Primers containing EcoRI and XhoI were used for cloning of rat BTG2 and CREB. The PCR product was digested by EcoRI and XhoI and ligated into pcDNA3 (Invitrogen, CA, USA). The sequence of the resultant plasmid was confirmed by restriction mapping and sequencing.

### 2.3. Plasmids and DNA constructions

The reporter plasmids human G6Pase promoter (−1227/+57)-Luc, rat PEPCK-Luc (−2000/+73), and human CRE-Luc were previously described [7,17]. The pcDNA3-BTG2 was constructed into pcDNA3 vector using EcoRI and XhoI sites. BTG2 was subcloned into GST vector using EcoRI and XhoI. The pcDNA3-CREB was previously described [7]. All plasmids were confirmed by sequencing analysis.

### 2.4. Cell culture and transient transfection assays

HepG2 (human hepatoma) cells were cultured in Dulbecco's modified Eagle's medium (DMEM; Gibco-BRL, NY, USA) supplemented with 10% fetal bovine serum (FBS; Hyclone, UT, USA) and antibiotics in a humidified atmosphere containing 5% $CO_2$ at 37 °C, and AML-12 cells (immortalized mouse hepatocytes) were cultured in DMEM/F-12 medium (Invitrogen) supplemented with 10% FBS, ITS (insulin–transferrin–selenium; Gibco-BRL), Dex (40 ng/ml), and antibiotics in a humidified atmosphere containing 5% $CO_2$ at 37 °C. Transient transfections were carried out as previously described [17,18].

### 2.5. Preparation of recombinant adenovirus and siRNA experiments

Adenovirus encoding rat BTG2 (Ad-BTG2) has been performed according to the method described previously [17]. The siRNAs for BTG2 (si Scram and si BTG2) were chemically synthesized (Bioneer Research, Republic of Korea), and transfected according to the manufacturer's instructions. HepG2 cells were transfected with siRNA using Oligofectamine™ reagent (invitrogen). The siRNAs for BTG2 were chemically synthesized, deprotected, annealed, and transfected according to the manufacturer's instructions. The sequences of siRNA are as follows: siRNA scramble 5′-ATGAGCCACGGGAAGAGAACC-3′; siRNA BTG2 5′-CTATCGCTGTATCCGCATCAA-3′.

### 2.6. Northern blot analysis

Total RNA was isolated from each of the samples, and then utilized for Northern blot analysis as previously described [17]. The expression of all transcripts was normalized to GAPDH levels.

### 2.7. GST Pull-down and in vivo interaction assay

GST pull down assay and *in vivo* interaction assay were performed according to the method described previously [7].

### 2.8. Chromatin immunoprecipitation (ChIP) assay

The ChIP assay was performed as described previously [18,19]. Briefly, after 24 h transfection with BTG2 in HepG2 cells, cells were treated with cAMP (500 μM)/Dex (1 μM). The cells were subsequently harvested, and ChIP assay was performed with anti-CREB. The final DNA extractions were quantified by PCR with two pairs of primers for the proximal (−200/+10 bp) and distal (−1700/−1500 bp) region of the PEPCK promoter, as described previously [7].

### 2.9. Glucose production assay

Glucose production assay from AML12 cells was measured according to the manufacturer's protocol, using a colorimetric glucose oxidase assay (Sigma). Briefly, after the experimental time period as observed, the cells were washed three times with phosphate-buffered saline, and then cells were incubated for 3 h at 37 °C, 5% $CO_2$ in glucose production buffer (glucose-free DMEM (pH 7.4) containing sodium lactate (20 mM), sodium pyruvate (1 mM), and HEPES (15 mM), without phenol red). The glucose assays were carried out in triplicate, and the intra-assay coefficient of variation was 5% as described previously [7,19].

### 2.10. Statistical analysis

Results are expressed as means (±S.E.M.). Analysis of variance was employed to determine significant differences as detected by Student's *t* tests and/or one-way ANOVA methods using prism program. Statistical significance was considered at $P < 0.05$.

## 3. Results

### 3.1. BTG2 gene expression is induced by glucagon signaling in hepatocytes

Previous studies have shown that glucagon stimulates cAMP concentration and activates cAMP-dependent pathway, conversely insulin inhibits hepatic gluconeogenesis via AKT activation [1–3,20,21]. Based on these findings, we examined whether BTG2 involves in gluconeogenesis pathway in hepatocytes. As shown in

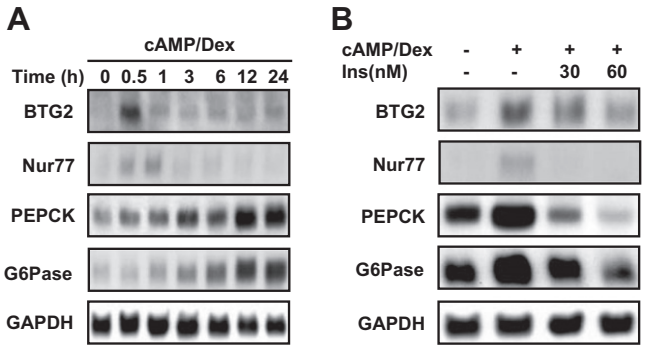


**Fig. 1.** Glucagon signaling induces BTG2 gene expression. (A) AML-12 cells were treated with cAMP (500 μM)/Dex (1 μM) for various time periods up to 24 h. (B) AML12 cells were treated with cAMP/Dex and then treated with insulin (Ins) at the various concentrations. The levels of BTG2, Nur77, PEPCK, and G6Pase mRNA were measured by Northern blot analysis, and then normalized to GAPDH.

Fig. 1A, treatment of immortalized mouse liver (AML-12) cells with cAMP/Dex significantly increased expression of BTG2 gene as well as Nur77, PEPCK, and G6Pase in a time-dependent manner. However, this stimulatory effect of cAMP/Dex was markedly decreased by insulin treatment (Fig. 1B). Overall, these observations strongly suggest a novel potential role of the BTG2 in the regulation of glucagon-mediated hepatic gluconeogenic gene expression.

### 3.2. BTG2 increases hepatic gluconeogenesis via induction of CREB

Since CREB plays a key role in hepatic gluconeogenesis, we have attempted to identify the potential correlation between BTG2 and CREB in hepatocytes. Overexpression of BTG2 using adenoviral system (Ad-BTG2) significantly increased CREB gene expression, and subsequently increased PEPCK and G6Pase gene expression in a dose-dependent manner (Fig. 2A). Glucose production in hepatocytes was effectively increased by Ad-BTG2 when compared with that of the control group (Fig. 2B). Next, we confirmed whether BTG2 also regulates transcriptional activity of CREB and gluconeogenic genes following these promoters. As expected, BTG2 significantly increased the transcriptional activity of the CREB, PEPCK, and G6Pase in a dose-dependent manner (Fig. 2C and D). Together, these results strongly demonstrate that BTG2 positively regulates hepatic gluconeogenesis through CREB in hepatocytes.

### 3.3. BTG2 physically interacts with CREB and mediates CREB occupancy on the gluconeogenic gene promoter

Many transcriptional co-regulators can function through binding to the specific transcription factors [22]. To confirm the physical interaction between BTG2 and CREB, we performed GST-pull down assays. Our *in vitro* GST-pull down assay displayed that

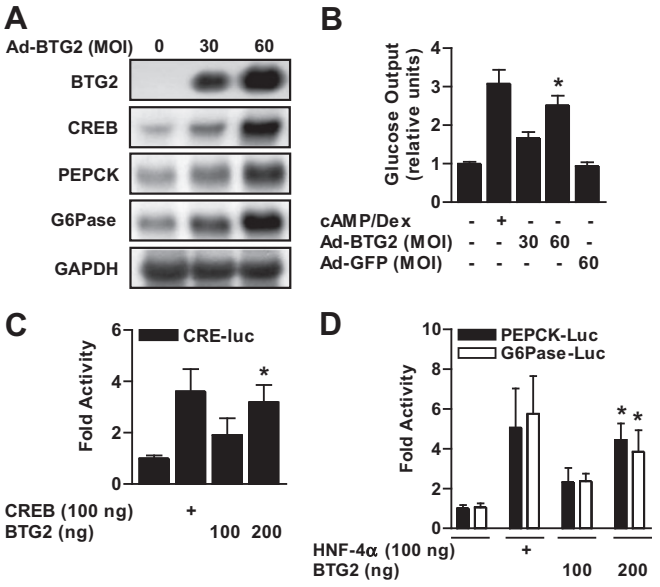


**Fig. 2.** BTG2 induces hepatic gluconeogenesis. (A) AML-12 cells were infected with Ad-BTG2 at a multiplicity of infection (MOI) of 30 or 60 for 24 h. Total RNAs were extracted from hepatocytes and utilized for Northern blot analysis. BTG2, CREB, PEPCK, and G6Pase mRNA level were normalized to GAPDH. (B) A glucose output assay was performed from AML-12 cells infected with Ad-GFP and Ad-BTG2 for 24 h at the various concentrations, using glucose-free media supplemented with gluconeogenic substrate sodium lactate (20 mM) and sodium pyruvate (1 mM). (C and D) HepG2 cells were transfected with BTG2 in the indicated reporter genes. cAMP/Dex and HNF-4α were used as a positive control, respectively. Luciferase activity was measured after 36 h and normalized to β-galactosidase activity. All data are representative of at least three independent experiments. $^{*}P < 0.05$ compared with untreated control.

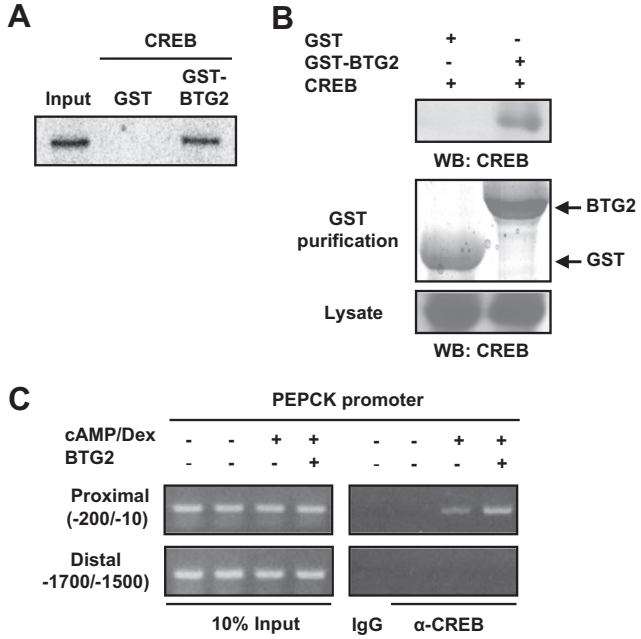


**Fig. 3.** Interaction of between BTG2 and CREB. (A) *In vitro* GST-pull down assay. CREB protein was labeled with [$^{35}$S] methionine by *in vitro* translation and incubated with bacterially expressed GST alone and GST–BTG2 fusion protein. (B) *In vivo* interaction between BTG2 and CREB. HepG2 cells were cotransfected with expression vectors for CREB together with pEBG-BTG2 (GST–BTG2), and pEBG (GST alone) as a control. The complex formation (*top panel*) and the amount of CREB used for the *in vivo* binding assay (*bottom panel*, lysate) were analyzed by Western blot analysis using anti-CREB antibody. The same blot was stripped and re-probed with an anti-GST antibody (*middle panel*) to confirm the expression levels of the GST–BTG2 and the GST control. (C) Chromatin immunoprecipitation (ChIP) assay shows the recruitment of CREB on the PEPCK gene promoter. HepG2 cells were transfected with BTG2 for 24 h, and then treated with cAMP/Dex, respectively. Soluble chromatin was immunoprecipitated with anti-CREB antibody or IgG as indicated. Purified DNA samples were employed for PCR with primers binding to the specific proximal (*top panel*) and nonspecific distal (*bottom panel*) regions on the PEPCK gene promoter. 10% of the soluble chromatin was used as an input.

labeled CREB was bound to bacterially expressed GST–BTG2 (Fig. 3A). As shown in Fig. 3B, CREB strongly interacted with GST–BTG2 but not with the negative control GST alone in HepG2 cells. Collectively, these results demonstrate that BTG2 physically interacts with CREB *in vivo* and *in vitro*. To further confirm whether BTG2 and CREB interaction affects DNA binding of CREB protein on its target gene promoter, we performed chromatin immunoprecipitation (ChIP) assay in hepatocytes. The endogenous binding activity of CREB to its proximal region by cAMP/Dex treatment was significantly increased by BTG2 overexpression compared to that of control (Fig. 3C, *top panel*). Moreover, the nonspecific distal region of the PEPCK promoter was unable to recruit CREB under all conditions (Fig. 3C, *bottom panel*). Taken together, these results strongly suggest that BTG2 plays a key role in CREB occupancy on the PEPCK gene promoter via a physical interaction.

### 3.4. cAMP/Dex-induced hepatic gluconeogenesis is altered by BTG2

To further confirm whether cAMP/Dex-mediated hepatic gluconeogenesis is mediated by BTG2, we introduced knock-down system of BTG2 in hepatocytes. First, our Northern blot analysis demonstrated that endogenous knockdown of BTG2 were successfully transduced in hepatocytes (Fig. 4A). As shown in Fig. 4B, cAMP/Dex significantly increased glucose production, whereas this phenomenon was abolished by endogenous BTG2 knockdown (Fig. 4B). Finally, we investigated the biological correlation between the cAMP/Dex-induced transcriptional activity of hepatic

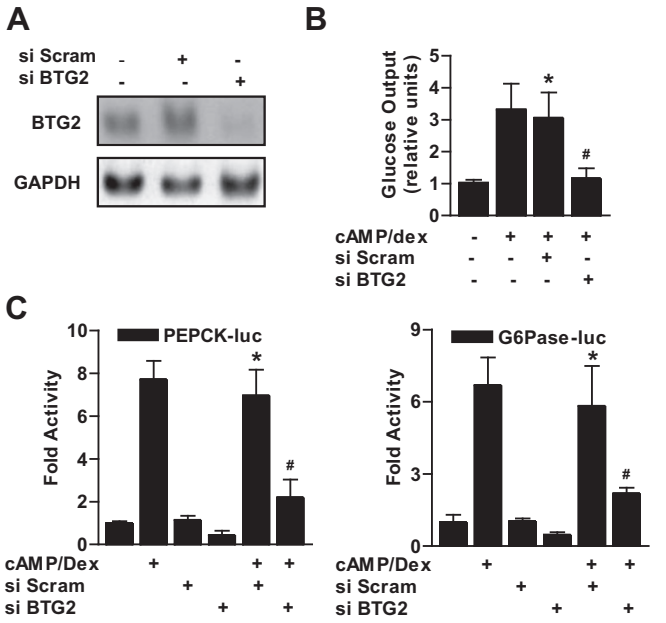


**Fig. 4.** Induction of hepatic gluconeogenesis by glucagon signaling is BTG2 dependent. (A) AML-12 cells were transfected with the oligonucleotide siRNA BTG2 (si BTG2) and siRNA Scramble (si Scram) for 36 h. Total RNAs were extracted from hepatocytes and utilized for Northern blot analysis. BTG2 mRNA level was normalized to GAPDH. (B) A glucose output assay was performed from AML-12 cells transfected with si Scram and si BTG2 for 36 h and then treated with cAMP/Dex, using glucose-free media supplemented with the gluconeogenic substrate sodium lactate (20 mM) and sodium pyruvate (1 mM). (C) HepG2 cells were transfected with the si BTG2 and si Scram. After transfection for 36 h, cells were transfected with the indicated reporter gene, and then treated with cAMP/Dex. Luciferase activity was normalized to β-galactosidase activity. All data are representative of at least three independent experiments. $^{*}P < 0.05$ and $^{\#}P < 0.05$ compared with untreated control and cAMP/Dex-treated cells.

gluconeogenic genes and BTG2 using knock-down experiments. Strikingly, the activity of PEPCK and G6Pase gene promoter was significantly increased by cAMP/Dex in a pattern similar to that indicated by hepatic gluconeogenic gene expression (Fig. 1), whereas this stimulatory effect of cAMP/Dex was markedly decreased by BTG2 knockdown (Fig. 4C). Overall, these findings strongly demonstrate that BTG2 has a crucial role in the positive regulation of cAMP/Dex-mediated hepatic gluconeogenesis.

## 4. Discussion

In this study, we have demonstrated that glucagon signaling increased BTG2 gene expression, and BTG2 positively regulated hepatic gluconeogenesis via CREB induction using gain-of-function and/or loss-of-function. On this basic of those findings, we propose that the glucagon-BTG2-CREB network may provide a novel molecular mechanism in controlling hepatic glucose homeostasis, as well as a key regulator for regulating hepatic gluconeogenesis.

A previous report suggests that growth hormone, known as stimulator of hepatic gluconeogenesis, significantly increases BTG2 in adipocytes, suggesting that BTG2 might involve in hepatic gluconeogenesis [16]. However, there is no evidence a biological relationship between the cAMP/PKA-mediated regulation of BTG2 gene expression and its subsequent role in hepatic gluconeogenesis. Herein, we demonstrate that induction of BTG2 by glucagon signaling might increase cAMP/Dex-mediated hepatic gluconeogenesis by inducing CREB. First, we have revealed a potential effect of BTG2 on the cAMP/Dex-dependent pathway in hepatocytes. As expected, cAMP/Dex significantly increased BTG2, Nur77, and gluconeogenic genes in hepatocytes (Fig. 1), whereas this stimulatory effect of cAMP/Dex was abolished by endogenous BTG2 knockdown (Fig. 4). Second, overexpression of BTG2 significantly increased hepatic gluconeogenesis through CREB induction in hepatocytes, which is consistent with cAMP/Dex treatment in a pattern similar to that indicated by hepatic gluconeogenic gene expression (Fig. 1). Overall, these results strongly suggest that BTG2 plays a key role in the regulation of cAMP/Dex-stimulated hepatic gluconeogenesis by CREB induction.

As previously described, CREB recruits transcriptional cofactors such as PGC-1, TORC2, CREB-binding protein to CRE-harboring target genes and subsequently facilitates hepatic gluconeogenesis [3,5–7]. Indeed, BTG2, known as a transcriptional co-activator, is supported by results demonstrated that BTG2 induces HOXB9-mediated transcription and can affect ERα-mediated transcription through its interaction with CCR4 and hCAF1 [14,15]. Based on these findings, CREB co-activators have a cooperative effect in regulating hepatic gluconeogenesis; however, the potential relevance between CREB and unknown transcriptional cofactors on hepatic glucose homeostasis remain largely unclear. In the current study, we identified that a novel transcriptional cofactor upon hepatic glucose homeostasis under glucagon-BTG2-CREB axis, such as gain-of-function and/or loss-of-function, physical interaction, CREB occupancy on its target promoter (Figs. 1–4). Our current findings suggest that BTG2 is a crucial co-activator in regulating hepatic glucose metabolism. However, we cannot exclude the possibility that the detailed molecular mechanism of a link between BTG2/CREB-dependent pathway and hepatic glucose homeostasis may depend on unknown mechanism of protein stability, co-regulator interaction, co-activator recruitment, and other signal pathway to regulate the induction pattern of hepatic gluconeogenesis. Therefore, a further detailed explanation is required to elucidate the detail molecular network of glucagon-BTG2-CREB axis and other transcriptional co-regulator in the future.

In conclusion, our current study demonstrates that BTG2 acts as a novel co-activator to regulate hepatic gluconeogenesis. These results suggest that the increase of BTG2 by glucagon signaling positively regulates hepatic gluconeogenesis via CREB induction in hepatocytes. We speculate that the glucagon-BTG2-CREB network may provide a key player on the regulation of hepatic gluconeogenesis. Therefore, a novel molecular mechanism involved in CREB induction by BTG2 may provide new insights into the beneficial effects of hepatic metabolic dysfunctions and development of novel therapeutic agents to treat hepatic diseases.

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