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Down-regulation of ATBF1 activates STAT3 signaling via PIAS3 in pacing-induced HL-1 atrial myocytes

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ABSTRACT

Atrial fibrillation (AF) is progressive and is the most common clinical arrhythmia. It is associated with inflammatory changes characterized by signal transducer and activator of transcription 3 (STAT3) signaling. A zinc finger homeobox 3 (ZFHX3, also named AT-motif binding factor 1, ATBF1) gene variant has been found in patients with AF. However, the mechanism by which the ATBF1 leads to inflammation in AF remains unknown. The aim of this study was to investigate whether tachypacing induces a decrease in ATBF1 expression and then activates STAT3 signaling via protein inhibitor of activated STAT3 (PIAS3). Atrial (HL-1 myocytes) cells were cultured in the presence of rapid electrical stimulations. In tachypaced HL-1 cells, we found that ATBF1 and PIAS3 protein levels were decreased, while the level of phosphorylated STAT3 (p-STAT3) was highly up-regulated compared with that of total STAT3. Knockdown of ATBF1 enhanced this trend, while the overexpression of ATBF1 had the opposite effect. A binary complex of ATBF1 and PIAS3 was formed and then the DNA-binding ability of activated STAT3 was enhanced in tachypaced HL-1 cells. These data indicate that tachypacing decreased ATBF1, leading to enhanced STAT3 DNA-binding activity due to the reduced formation of a binary complex of ATBF1 and PIAS3.

1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia encountered in clinical practice, and it is associated with cardiovascular morbidity and mortality [1,2]. According to the Framingham Heart Study, lifetime risks of developing AF are approximately 1 in 4 for men and women at age 40 years or older [3]. The age-standardized prevalence of AF in both genders in the Chinese population ($\geqslant$30 years of age) is 0.65% (0.66% for males and 0.63% for females) in the age composition data from all previous investigations. The age-specific prevalence increases substantially with age, rising from 0.51% among adults younger than 55 years to 12.16% in persons aged 85 years or older in the Chinese population of mainland China [4]. Important changes in AF include electrical, contractile and structural remodeling [5], which promote the occurrence and maintenance of AF.

ATBF1, a 404-kDa homeotic transcription factor that contains 4 homeodomains and 23 zinc fingers, was identified as a transcriptional repressor of the human alpha-fetoprotein (AFP) and protein–protein interactions [6,7]. Recently, genome-wide association studies identified a single-nucleotide polymorphism (SNP), rs2106261, in ZFHX3 as highly significantly associated with AF in a large Chinese Gene ID population of Han ethnic descent [8]. However, the molecular mechanism by which ZFHX3 leads to AF pathogenesis remains unknown. The activation of the local renin-angiotensin system (angiotensin II/Rac1/STAT) in atrial tissue may play important roles in atrial structural remodeling and inflammatory changes [9]. STATs are the major downstream mediators of inflammatory signaling, which increase the expression of chemotactic factor IL-8 with the activation of the c-src/STAT3 pathway in endothelial cells [10] and up-regulate monocyte chemoattractant protein-1 in macrophages [11]. STATs likely mediate inflammatory changes and play a crucial role in the progress of AF.

At present, there is no information concerning the expression of ATBF1 protein, and the involvement of ATBF1 in AF pathogenesis remains unknown. Thus, we hypothesized that the expression of ZFHX3 protein may decrease in atrial tissues of AF patients. The down-regulation of ATBF1 then attenuates the suppression of the STAT3 pathway by interacting with PIAS3, and this effect induces the activity of STAT3 and promotes inflammation in the AF atrium. In other words, the down-regulation of ATBF1 activates STAT3 signaling via PIAS3, and this may contribute to AF generation.

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In the present study, we investigated the mechanisms by which STAT3-mediated signaling is induced by a decrease in ATBF1. Our in vitro data show that electrical stimulation decreases ATBF1 expression in HL-1 cardiomyocytes. This decrease in turn may increase the STAT3 transcriptional activity responsible for inflammatory changes, by reducing the amount of ATBF1 available to bind to the STAT3 inhibitor PIAS3.

2. Materials and methods

2.1. HL-1 cell culture and tachypacing

HL-1 cells, derived from the AT-1 mouse atrial cardiomyocyte tumor lineage [12], were kindly provided by Dr. William Claycomb (Louisiana State University Health Science Center, New Orleans, LA, USA). The cells were cultured and maintained in supplemented Claycomb Medium (Sigma–Aldrich, St. Louis, Mo) as previously described [12]. The cells were serum-starved for 24 h on the third day after passaging and then used for electrical stimulation. The spontaneous rate of confluent HL-1 cells is 0.5–1 Hz. After serum starvation for 24 h, the HL-1 atrial cells were subjected to field stimulation or cultured in parallel in the absence of stimulation (control group). Stimulated myocytes were paced as previously described [6,7,13–15] with a C-Pace100TM-culture pacer and C-Dish100TM culture dishes (IonOptix Corporation, Netherlands) with a 5-ms duration and 25 Hz square-wave pulses (45 ± 3 V pulse-voltage, 7 V/cm) for 24 h. Capture efficiency >90% was confirmed by microscopic examination and by shortening of action potential duration as described previously (Supplementary material online, Fig. S1) [16]. In some experiments, HL-1 cells were treated with si-m-ATBF1 (100 nmol), si-m-PIAS3 (100 nmol) or pKUXal-HA-ATBF1 (2 μg) 24 h prior to tachypacing to achieve complete silencing or overexpression of the gene, respectively.

2.2. Small interfering (si) RNA and plasmid transfection

ATBF1 was silenced using a siRNA targeting mouse ATBF1 (ATBF1 siRNA) with the sequence 5′-GGACCUGUCCAAAUUCGAU-3′. PIAS3 was silenced using a siRNA targeting mouse PIAS3 (PIAS3 siRNA) with the sequence 5′-CCAACACCAUCGUAGUUAA-3′. These two siRNAs and a negative-control siRNA (control siRNA that has limited similarity to sequences in the mouse genome) were synthesized and purified by the Reibo siRNA Company (Guangzhou, China). ATBF1 siRNA (100 nM), PIAS3 siRNA (100 nM) and the control siRNA (100 nM) were transferred into HL-1 cells using Lipofectamine™ 2000 (Life Technologies, Carlsbad, CA) according to the manufacturer's instructions. The plasmid of pKXUa1-HA-ATBF1 (AddGene plasmid 40926) was obtained from the AddGene Plasmid Repository, and the empty control vector pKXUa1-HA was purchased from Invitrogen. Plasmid transfection assays were performed with Lipofectamine™ 2000 following the manufacturer's protocol.

2.3. Western blotting and co-immunoprecipitation (co-IP)

Protein was extracted from lysed HL-1 cells as previously described [17,18]. Total protein concentration was determined with a BCA Protein Assay Kit (Pierce, Rockford, IL, USA). Equal amounts of protein in SDS–polyacrylamide gel electrophoresis (PAGE) sample buffer were subjected to electrophoresis in 4–10% or 8% SDS–polyacrylamide (Life Technologies, Carlsbad, CA) and then blotted onto nitrocellulose membranes. Afterwards, the membranes were incubated with specific antibodies against ATBF1 (AT-6, MBL), PIAS3 (#4164, Cell Signaling Technology, Beverly, MA), p-Stat3 (#9145, Cell Signaling Technology, Beverly, MA), STAT3 (#4940, Cell Signaling Technology, Beverly, MA), Caspase 3 (ab115183, Abcam LNC, MA, USA) (Supplementary material online, Fig. S2) and β-actin (#4970, Cell Signaling Technology, Beverly, MA). After the addition of chemiluminescent reagents (Thermo Scientific, Rockford, IL, USA), bands were detected using a Molecular imager ChemiDoc™ XRS + (Bio-Rad) and quantified by Image Lab™ Software. Co-immunoprecipitation analysis was performed using Dynabeads® Protein G (Life Technologies) following the manufacturer's instructions. Briefly, anti-ATBF1 antibody was pre-absorbed with Dynabeads Protein G for 2 h at 4 °C. Antibody-bead complexes were used to immunoprecipitate ATBF1 protein. Western blots were revealed using anti-ATBF1, anti-PIAS3, anti-p-SIAT3 and anti-STAT3 antibodies, followed by goat anti-rabbit IgG antibody conjugated to horseradish peroxidase (1:2000, #4412, Cell Signaling Technology, Beverly, MA).

2.4. Electrophoretic mobility shift assay (EMSA)

The DNA-binding activity of STAT3 was evaluated by EMSA according to the manufacturer's protocol (LightShift chemiluminescent EMSA kit; Thermo Scientific, Rockford, IL, USA). HL-1 cellular nuclear extracts were prepared using the NE-PER extraction kit (Thermo Scientific, Rockford, IL, USA). The protein concentration was measured with BCA Protein Assay Kit (Thermo Scientific, Rockford, IL, USA). A biotin-labeled double-stranded oligonucleotide probe with Bax promoter (5′-GAT CCT TCT GGG AAT TCC TAG ATC-3′) (Beyotime, Nanjing, China) was used in this study. One microgram of nuclear protein extracts and primary antibody or normal rabbit IgG (control group) were incubated with biotin-labeled DNA probes (10 fmol) for 20 min at room temperature. To confirm the specificity of the primary antibody, normal rabbit IgG was used as a control for binding the protein-DNA complex. For the supershift assay, p-STAT3 antibody was added to the mixture before the biotin-labeled probe. Protein-DNA complexes were separated on nondenaturing polyacrylamide gels, and Image Lab™ software was used to analyze the band intensities.

2.5. Statistical analysis

All values are expressed as the means ± SEM. Statistical analyses between groups were performed using one-way ANOVA followed by a two-tailed unpaired Student's *t*-test. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Tachypacing decreases ATBF1 expression, and ATBF1 siRNA augments the pacing-induced STAT3 signaling activation

We examined whether ATBF1 activates STAT3 signaling after treatment with rapid electrical stimulation. For this purpose, we first reduced the ATBF1 expression level in HL-1 cells by ATBF1 siRNA transfection and then tachypaced these cells at a constant frequency for 24 h [18,19]. The cells were transfected with ATBF1 siRNA or control siRNA. After 72 h of transfection and 24 h of stimulation, the ATBF1 protein expression was probed by Western blot analysis using anti-ATBF1 antibody. Tachypacing significantly reduced cellular ATBF1 expression (Fig. 1A and B). Additionally, transfection of ATBF1 siRNA down-regulated ATBF1 protein by approximately 70% in HL-1 cells compared with control siRNA transfection. This finding suggests that endogenous ATBF1 can be efficiently knocked down by the transfection of ATBF1 siRNA. Next, we determined the effect of ATBF1 knockdown on HL-1 cells in the presence of tachypacing. ATBF1 was more significantly down-regulated by ATBF1 siRNA plus tachypacing than by either alone.

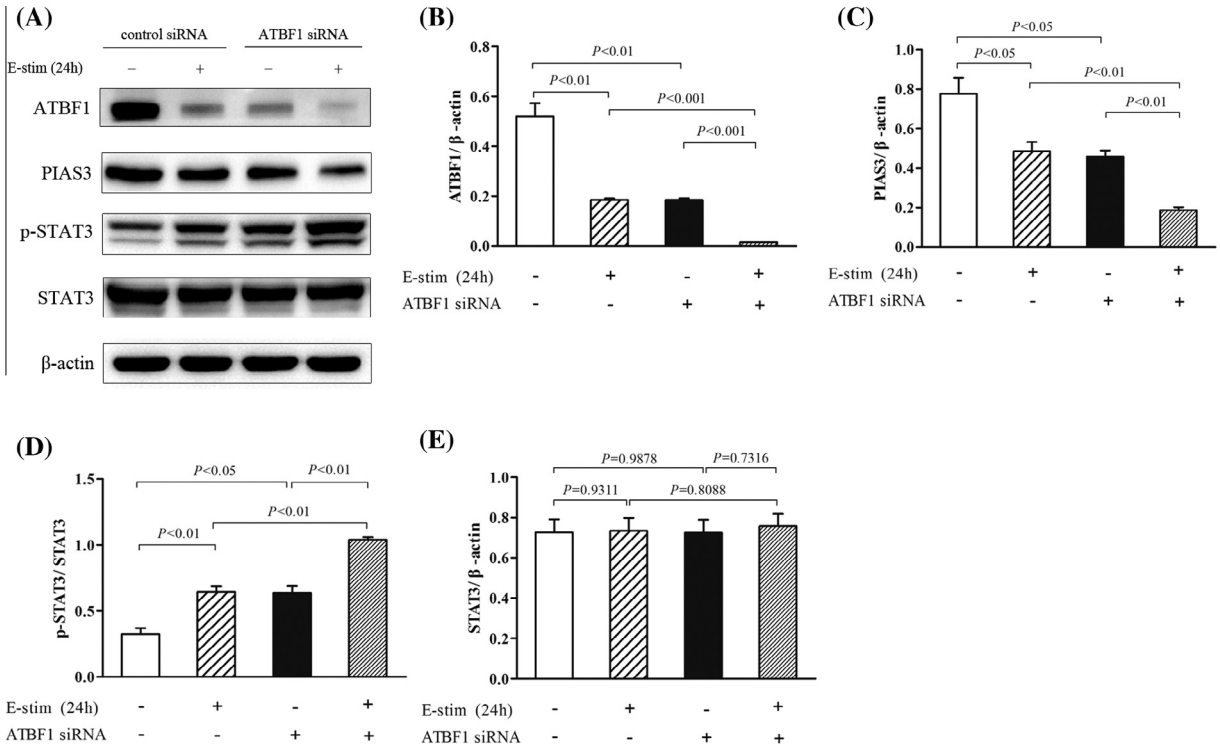

Fig. 1. ATBF1 knockdown enhances the activation of STAT3 signaling upon treatment with electrical stimulation (E-stim). (A) HL-1 cells were transfected with ATBF1 siRNA or control siRNA for 72 h. After transfection, the cells were subjected to field stimulation for 24 h; the expression of ATBF1, PIAS3, p-STAT3 and STAT3 protein was evaluated by Western blot analysis as described in Section 2. The expression of β-actin was used as an internal control. Cells transfected with ATBF1 siRNA or control siRNA were treated with (+) or without (−) E-stim for 24 h. The relative expression levels of ATBF1 (B), PIAS3 (C), p-STAT3 (D) and STAT3 (E) were quantified by densitometry and normalized to the control level. Each value represents the mean ± SEM of four independent experiments.

Classically, ATBF1 enhances the suppression of the STAT3 pathway via PIAS3 [15]. The reduction of ATBF1 then attenuates the suppression of STAT3 signaling through an interaction with PIAS3. Tachypacing led to a significant decrease in PIAS3 (Fig. 1A and C) and increase in p-STAT3 (Fig. 1A.and D) expression, whereas tachypacing had no effect on the total STAT3 protein level (Fig. 1A and E). Knockdown of ATBF1 in paced HL-1 cells made the trend of the above changes in PIAS3, p-STAT3 and STAT3 more apparent. These data indicate that tachypacing decreases the expression of ATBF1 and activates STAT3 signaling via PIAS3 in atrial myocytes. Knockdown of ATBF1 promotes the activation of a pacing-induced STAT3 pathway.

3.2. Overexpression of ATBF1 in pacing-induced HL-1 cells reverses the process of STAT3 signaling activation

Next, we examined whether overexpression of ATBF1 would reverse the activation of STAT3 signaling in pacing-induced HL-1 cells. The cells were transfected with pKXUa1-HA-ATBF1 and then subjected to electrical stimulation for 24 h. Seventy-two hours after transfection, we performed Western blot analysis to evaluate the expression of ATBF1, PIAS3, p-STAT3 and STAT3 (Fig. 2A and E), with β-actin as an internal control for quantification and normalization. Tachypacing led to similar changes in ATBF1, PIAS3, p-STAT3 and STAT3 in HL-1 cells as above (Fig. 1). Subsequently, the transfection of pKXUa1-HA-ATBF1 significantly increased the levels of ATBF1 (Fig. 2A and B) and PIAS3 (Fig. 2A and C) and reduced the level of p-STAT3 (Fig. 2A and D), while it had no effect on the level of total STAT3 protein (Fig. 2A and E). This finding indicates that overexpression of ATBF1 can inhibit the activation of STAT3 signaling and then reverse the process of STAT3 signaling activation that is induced by rapid field stimulation in HL-1 cells.

3.3. Co-transfection of ATBF1 siRNA and PIAS3 siRNA affects the activation of STAT3 signaling in HL-1 cells

To determine whether PIAS3 mediates the ATBF1-induced suppression of the STAT3 pathway in HL-1 cells, co-transfection of ATBF1 siRNA and PIAS3 siRNA was used. The transfection of ATBF1 siRNA or PIAS3 siRNA reduced ATBF1 or PIAS3 protein by approximately 70% in HL-1 cells compared with control siRNA transfection (Fig. 3A–C). This finding demonstrates that endogenous ATBF1 and PIAS3 can be efficiently knocked down by the transfection of ATBF1 siRNA and PIAS3 siRNA. Knockdown of ATBF1 led to a decrease in PIAS3 (Fig. 3A and C) and an increase in p-STAT3 (Fig. 3A and D), whereas it had no effect on the total STAT3 protein level (Fig. 3A and E). Knockdown of PIAS3 (instead of tachypacing) made the changes in PIAS3, p-STAT3 and STAT3 more obvious in HL-1 cells with the transfection of ATBF1 siRNA. Taken together, these results confirm that knockdown of ATBF1 siRNA and PIAS3 siRNA can activate STAT3 signaling in HL-1 cardiomyocytes. Furthermore, the interaction between ATBF1 and PIAS3 may play a role in mediating the activation of the STAT3 pathway.

3.4. Tachypacing reduces the formation of a binary complex of ATBF1 and PIAS3, which enhances the DNA-binding ability of activated STAT3 in HL-1 cells

ATBF1 and PIAS3 synergistically enhance the suppression of STAT3 signaling, and ATBF1 interacts with PIAS3 in vitro [15]. However, the exact manner in which ATBF1 promotes the activation of STAT3 signaling via PIAS3 is not known. To investigate the possibility of direct binding of ATBF1, PIAS3, p-STAT3 and STAT3 in vivo, we performed co-IP experiments. The cell lysates were immunoprecipitated with anti-ATBF1 antibody, and immunocomplexes were

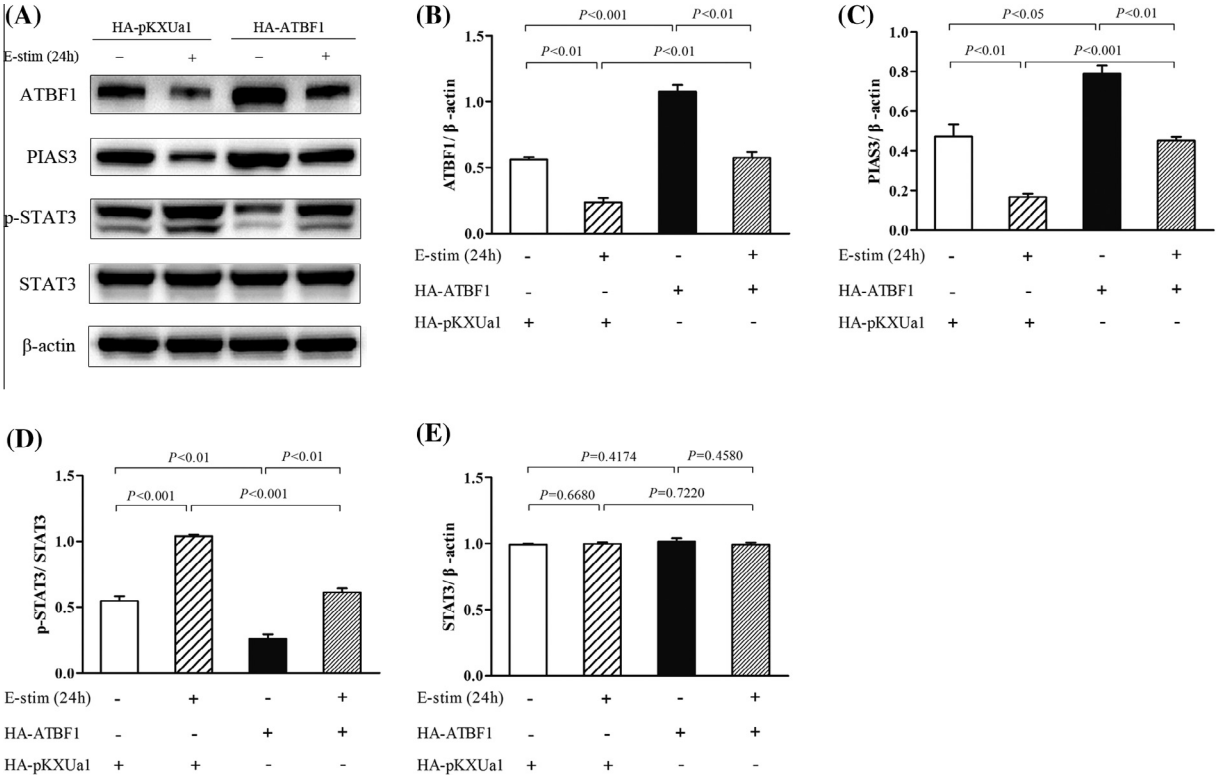

Fig. 2. Overexpression of ATBF1 in pacing-induced HL-1 cells reverses the process of STAT3 signaling activation. (A) After 24 h of electrical stimulation and 72 h of transfection with pKXUa1-HA-ATBF1, the expression of ATBF1, PIAS3, p-STAT3, STAT3 and β-actin was measured with Western blot analysis. The relative protein levels of ATBF1 (B), PIAS3 (C), p-STAT3 (D) and STAT3 (E) were quantified by densitometry and normalized to β-actin. Each value represents the mean ± SEM of four independent experiments.

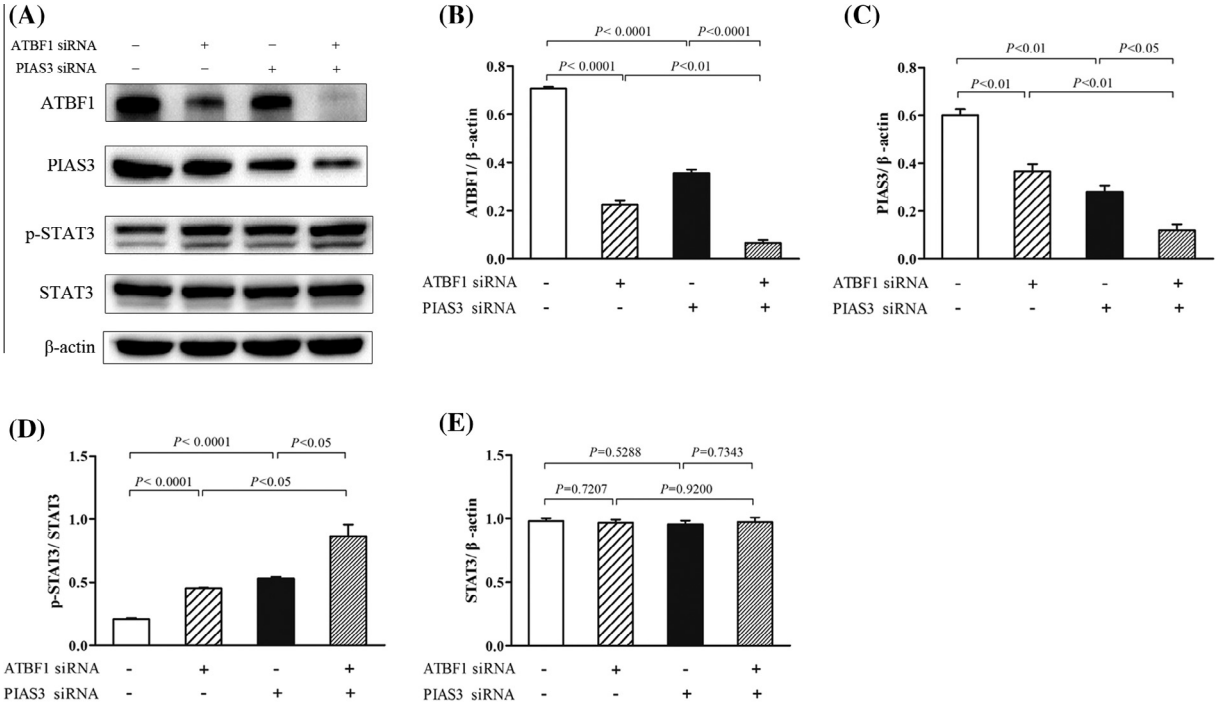

Fig. 3. Co-transfection of ATBF1 siRNA and PIAS3 siRNA activates the STAT3 signaling in HL-1 cardiomyocytes with a synergistic effect. (A) After 72 h of transfection with ATBF1 siRNA, PIAS3 siRNA or control siRNA, the expression of ATBF1, PIAS3, p-STAT3, STAT3 and β-actin was evaluated by Western blot. The relative protein levels of ATBF1 (B), PIAS3 (C), p-STAT3 (D) and STAT3 (E) were quantified by densitometry and normalized to β-actin. Each value represents the mean ± SEM of four independent experiments.

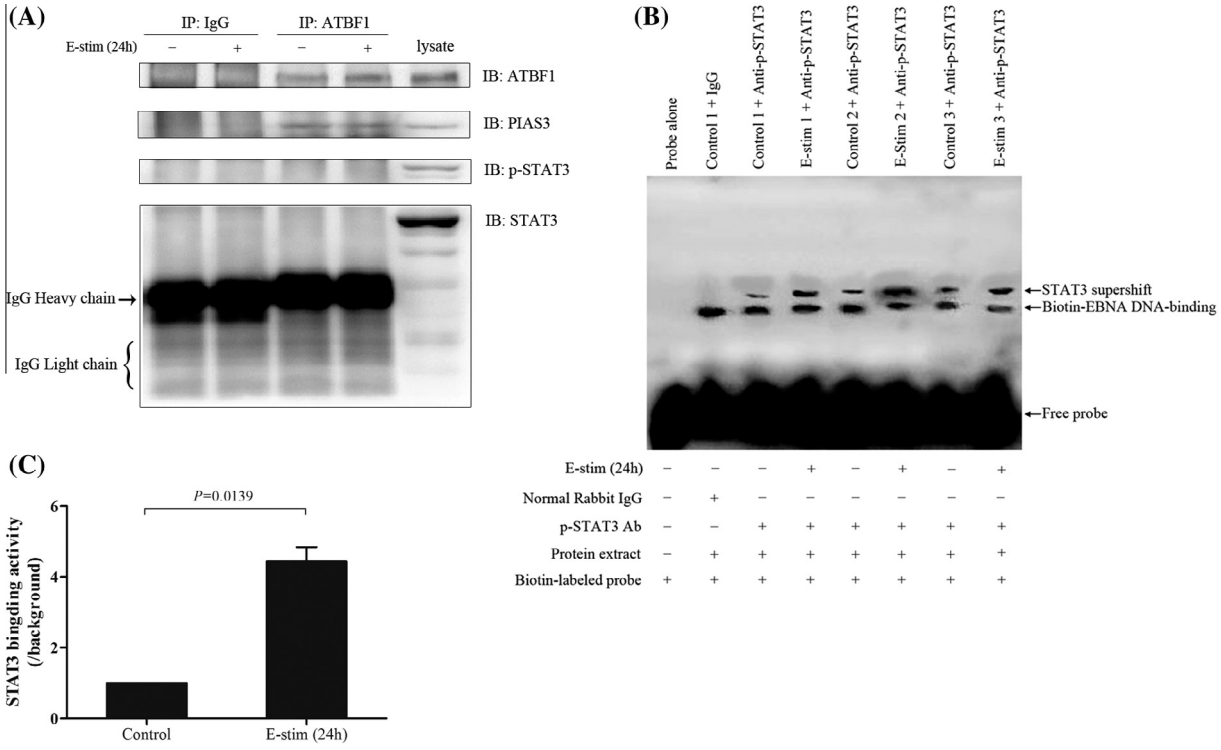

Fig. 4. The formation of a binary complex of ATBF1 and PIAS3 inhibits the DNA-binding ability of activated STAT3 in pacing-induced HL-1 cells. (A) Interaction of ATBF1 and PIAS3. Co-IP was used to evaluate the binding of ATBF1, PIAS3, p-STAT3 and STAT3 with or without stimulation. Normal Rabbit IgG was used as an internal control. ATBF1 and PIAS3 were detected in anti-ATBF1 immunoprecipitates from lysates of HL-1 cells with or without tachypacing, but p-STAT3 and STAT3 could not be detected in the above condition. (B) STAT3 DNA-binding activity in HL-1 cells was detected by EMSA in the control and E-stim (24 h) groups. (C) STAT3 DNA-binding activity significantly increased after electrical stimulation. There was a significant difference between the control and E-stim groups. Each value represents the mean ± SEM of four independent experiments.

resolved by SDS–PAGE. Normal Rabbit IgG was used as a control. Western blots were developed with anti-ATBF1, anti-PIAS3, anti-p-STAT3 and anti-STAT3 antibodies. ATBF1 and PIAS3 were detected in anti-ATBF1 immunoprecipitates from the lysates of HL-1 cells with or without tachypacing (Fig. 4A), while p-STAT3 and STAT3 were not detected in anti-ATBF1 immunoprecipitates from lysates without tachypacing. We found that a binary complex of ATBF1 and PIAS3 was formed in HL-1 atrial myocytes. To further examine the DNA-binding ability of activated STAT3 in pacing-induced HL-1 cells, EMSA was performed. After electrical stimulation, STAT3 DNA-binding activity was enhanced compared with the control group (Fig. 4B and C). These results reveal that down-regulation of the formation of a binary complex of ATBF1 and PIAS3 enhances STAT3 DNA-binding ability and activates STAT3 signaling in pacing-induced HL-1 cells.

4. Discussion

In this study, we first confirmed that in HL-1 atrial myocytes, tachypacing reduces the expression of ATBF1, which leads to the activation of STAT3 signaling via a diminution of ATBF1–PIAS3 complexes. Tachypacing down-regulated cardiac ATBF1 protein expression, and knockdown of ATBF1 promoted the activation of pacing-induced STAT3 signaling. However, overexpression of ATBF1 reversed the process of STAT3 signaling activation induced by rapid electrical stimulation in HL-1 cells. Thus, we found that ATBF1 promotes the activation of STAT3 signaling induced by tachypacing of HL-1 atrial cells. We also confirmed that co-transfection of ATBF1 siRNA and PIAS3 siRNA activated STAT3 signaling more effectively in HL-1 cardiomyocytes. Furthermore, our study is the first to experimentally demonstrate that tachypacing reduced the formation of a binary complex of ATBF1 and PIAS3, enhancing the ability of STAT3 to bind to DNA in HL-1 cells.

The notion that the inflammatory process has an important role in AF has garnered attention in recent years. Inflammation causes "atrial myocarditis" with subsequent electrical and structural changes that lead to the initiation and maintenance of AF [20,21]. Inflammation is considered an independent risk factor for the initiation and maintenance of AF [22]. Systemic inflammation is one of the pathophysiological mechanisms of AF. STATs are the major downstream mediators of many different inflammatory signaling pathways and mediate the inflammatory process in a pacing-induced AF porcine model [9]. Furthermore, activated Ang II/Rac1/STAT3 signaling contributes to electrical and structural remodeling in pacing-induced AF [9]. Therefore, we speculate that ZFHX3 variants reduce ATBF1 protein expression and increase the risk of AF by up-regulating STAT3 signaling.

ATBF1 is a negative regulatory factor for STAT3-mediated signaling. ATBF1 can enhance the suppression of STAT3 activation and its DNA-binding activity, by forming a complex with PIAS3 [15]. In other words, a decrease of ATBF1 would intensify the activation ability of STAT3 due to a decrease of active PIAS3. In our study, we found that tachypacing reduced ATBF1 and then promoted the activation of STAT3 signaling due to the decrease in PIAS3–STAT3 binding. This finding is consistent with the above finding and provides potential new insights into the molecular mechanisms underlying ATBF1 down-regulation in AF. PIAS3 inhibits the DNA binding of STAT3 by combining with activated (tyrosine-phosphorylated) STAT3 dimers [23].

Although the interplay between ATBF1, PIAS3 and STAT3 had been demonstrated in hepatocytes before [15], the exact

mechanism by which ATBF1 and PIAS3 synergistically suppress the STAT3-activated transcription was not established by the previous study. In this study, we explored a possible explanation for this observation. First, we confirmed the formation of either a binary complex of ATBF1 and PIAS3 or a tertiary complex of ATBF1, PIAS3 and STAT3. The binary complex bound to activated STAT3 may inhibit the DNA-binding activity of STAT3, resulting in the suppression of STAT3-activated transcription. The previous study stated another hypothesis which the tertiary complex may interfere with the recruitment of other co-activators without affecting the activated STAT3 DNA-binding ability [15]. In the present work, we discovered that a binary complex of ATBF1 and PIAS3 formed in HL-1 cardiomyocytes in the presence or absence of tachypacing. Second, we investigated the DNA-binding ability of activated STAT3 in tachypaced HL-1 myocytes by EMSA. In agreement with our hypothesis, STAT3 DNA-binding activity was enhanced in the presence of pacing in HL-1 cells compared with the control group. Taken together, our data reveal an important aspect of the mechanism by which STAT3 signaling is affected by ATBF1 and PIAS3 synergistically in AF.

In summary, our studies suggest that down-regulation of ATBF1 could contribute for the inflammation process of AF by enhancing the activation of STAT3 signaling and the DNA-binding activity of STAT3 due to the reduced the formation of a binary complex of ATBF1 and PIAS3.

5. Limitations

First, HL-1 atrial cells were stimulated for 24 h, which is a validated cellular model for atrial tachycardia remodeling [16–19,24]. However, the cell culture conditions do not completely replicate the in vivo environment. Second, the mechanism by which ATBF1 promotes or prevents AF is complex and still unclear. Although a decrease in ATBF1 protein contributed to the activation of STAT3 signaling via PIAS3 in the rapid pacing-induced AF cell model, a role for other factors such as IL 6 and IL 8 remains to be identified and shown in this study. Third, we made new observations in the AF cell model only while these are not equivalent to the notion that decreased ATBF1 expression or function promotes AF. So knockout and overexpression of ATBF1 mouse models should be applied in future study.

Conflict of interest

No disclosures are declared by the authors.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbrc.2014.05.041.

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