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CD7 expression and galectin-1-induced apoptosis of immature thymocytes are directly regulated by NF-κB upon T-cell activation

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ABSTRACT

CD7, one of the galectin-1 receptors, has crucial roles in galectin-1-mediated apoptosis of activated T-cells and T-lymphoma progression in peripheral tissues. In this study, we showed that CD7 promoter activity was increased by NF-κB and that this activity was synergistic when Sp1 was co-expressed in the immature T-cell line L7. Site-directed mutagenesis analysis of the CD7 promoter indicated that NF-κB specifically bound to the NF-κE2 site in cooperation with Sp1. Overexpression of E12 or Twist2 proteins negatively regulated NF-κB-mediated activity of the CD7 proximal promoter. In addition, CD7 expression was down-regulated by treatment with the p38 MAPK inhibitor SB20358, or the MSK1 inhibitor H-89. These signaling pathway inhibitors prevented galectin-1-mediated apoptosis of immature T-cells. From these results, we concluded that the regulation of CD7 gene expression through NF-κB activation induced by TCR/CD28 might have significant implications for T-cell homeostasis.

Gene expression during thymocyte development and activation is tightly controlled by the coordinated action of many transcription factors [1,2]. Among them, nuclear factor-kappa B (NF-κB) has been suggested as the key regulator of lymphocyte development and activation; it is involved in regulation of the immune response, cellular proliferation and cell death [3–5]. The roles of NF-κB, however, are controversial in different systems. Immature thymocytes become more sensitive to cell death by the ectopic expression of NF-κB, while the same stimulus has a role in the survival of mature $CD4^+$ T-cells by co-engagement of the T-cell receptor (TCR) and CD28, co-stimulatory receptors [4]. TCR/CD28 co-stimulation induces NF-κB transcriptional activity through a signaling pathway, which utilizes the p38 mitogen-activated protein kinase (MAPK) [6]. The p38 MAPK phosphorylates and activates mitogen- and stress-activated protein kinase 1 (MSK1), which in turn activates NF-κB by phosphorylation of RelA/p65, the major transcription activating NF-κB subunit [7,8]. Therefore, there are various mechanisms to modulate the activity of NF-κB and thereby affect the T-cell decision to survive or die [9].

Galectin-1, a member of the mammalian β-galactoside binding protein family, directly induces cell death of negatively selected immature thymocytes and activated T-cell lymphomas [10]. A sustained up-regulation of galectin-1 was observed when T-cells were stimulated with anti-CD3/CD28 antibodies whose downstream signaling routes involved the MAPK kinase 1 (MEK1)/extra-cellular signal-regulated kinase (ERK) and p38 MAPK pathways [11]. In this study, we found it worth investigating how the same signals mediated by p38 MAPK were involved in apoptosis through either NF-κB or galectin-1-mediated apoptosis during T-cell activation.

Galectin-1 binds to several glycoprotein receptors including CD7, which initiates a signaling cascade resulting in galectin-1-induced apoptosis of T-cells [12–14]. Previous studies have suggested a role for CD7 in lymphoid development and function. CD7-deficient mice demonstrated a total number of thymocytes that was significantly increased by 60% compared with wild-type [13]. Various stimuli such as increases in intracellular calcium and cyclic AMP and stimulation with anti-CD3 antibodies lead to increased CD7 expression in T-cells [15,16]. Meanwhile, surface expression of CD7 is decreased by activation of protein Kinase C or treatment with phorbol ester [17]. CD7 levels are dramatically down-regulated on Sezary cells ($CD4^+CD7^-$ memory T-cells), which induce cutaneous T-cell lymphoma (CTCL) in the skin, lymph nodes, and peripheral blood. Based on the relatively abundant expression of galectin-1 in human tissues, their lack of surface

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CD7 expression has been proposed to render these cells resistant to galectin-1-induced cell death, thereby favoring their accumulation within tissues during progression of the disease [14].

In this study, we showed that activity of the CD7 proximal promoter was regulated by NF-κB and Sp1 in response to T-cell activation signals. E-protein and Twist2, which share a common NF-kB binding site (NF-κE), prevented activation of the CD7 promoter. Signals through the p38 MAPK-MSK1 pathway provoked by TCR/CD28 co-stimulation increased CD7 expression, followed by galectin-1-induced apoptosis in immature T-cells.

Materials and methods

Cells and antibodies. The murine double-positive thymoma cell line, L7, was grown in IMDM (Hyclone) containing 20% FBS. The IκBα-SR expression vector was obtained from Dr. H. Kwon (Hallym University, Chuncheon Korea). Biotinylated anti-CD3 (145-2C11) and anti-CD28 (500A2) antibodies were purchased from BD Pharmigen. Anti-p65 antibody (sc-109) was purchased from Santa Cruz Biotechnology. Antiserum against murine CD7 was raised from rabbits in our laboratory.

Plasmids and PCR-based mutagenesis. The 1.1 kb fragment of the CD7 promoter region was amplified by PCR, and various sized fragments (−1138 to +53, −638 to +53, −270 to +53, and −210 to +53) of the CD7 promoter were cloned into the pGL3 basic vector (Promega). Mutagenesis of the two NF-κE sequences (M2; CAG GTG at -166 to CTCGAG, and M1; CACCTG at −152 to CTGCAG) in the CD7 proximal promoter was performed using PCR. For mutagenesis of the Sp1 binding site, CCCTGCCCA at −134 to −126 on the CD7 promoter was deleted using the following PCR primers: Sp1-mt5; 5′-CCAGATCTCCAAGCTCCACCT-3′ and Sp1-mt3; 5′-CCAGATCTAACACAA CAAGCCA-3′ The PCR primers for the double mutants of both NF-κE (M1) and the Sp1 binding site were 5′-CCCTGCAGGCTTGTTGTGTTCCAAG CTCCACCTT-3′ and 5′-GGAAGCTTGACGCCCA AATCATCTGAGCCAAATCAGCC-3′.

Transient transfection and reporter assays. L7 cells were plated onto six-well plates at 5.0×10^6 cells per well and transfected using Lipofectamine 2000 (Invitrogen) according to the manufacturer's instruction. The indicated luciferase reporter construct was co-transfected into L7 cells with varying amounts of expression plasmids. Control plasmid pCAGGS was used to adjust the total amount of DNA for each transfection. At 24 h after transfection, cells were harvested, and reporter gene activity was determined with the luciferase assay system (Promega). Luciferase activity was normalized against total protein concentration as determined by the Bio-Rad protein assay.

Thymocyte stimulation, Reverse transcription (RT)-PCR, and immunoblotting. For activation of thymocytes, L7 cells were incubated with 10 μg/ml biotinylated anti-CD3 and anti-CD28 monoclonal antibody for 10 min on ice. Cells were incubated at 37 °C for 1 h with 100 μg/ml streptavidin (Sigma). After cells were harvested, total RNA was prepared and used for reverse transcription by SuperScript III (Invitrogen). PCR Primers for CD7 were 5′-TGGCAGACACTGG AGACTAC-3′ and 5′-GATTCCTTAATCCCTGAGGC-3′. Primers for β-actin as a control were 5′-CTCTA GACTTCGAGCAGGAG-3′ and 5′CCAGACAACACTGTGTTGGC-3‘. The relative gene expression of CD7 was analyzed by normalizing against *β-actin* gene expression in all experiments. For immunoblot analysis, whole-cell extracts from the cells treated with SB203580, H-89 or stimulated with TCR/CD28 were subjected to immunoblotting. Proteins were subjected to 10% SDS–PAGE, transferred to a nitrocellulose membrane, and immunoblotted with anti-CD7 antiserum. Specific bands were visualized using the ECL system (Pierce).

Flow cytometry and measurement of galectin-1-induced apoptosis. L7 cells were stained with FITC-conjugated annexin V (BD Pharmigen). Stained cells were analyzed with CellQuest™ software using FACStar Plus (BD Biosciences). A total of 5×10^5 cells/100 μl were treated with the indicated concentration of galectin-1 (Santacruz) in 1.0 mM DTT or 1.1 mM DTT buffer control and rocked for 5 h at 37 °C. The cells were then treated with SB203580 (Calbiochem) or H-89 (Calbiochem) for 24 h. Cells were stained with FITC-conjugated annexin V for 15 min on ice and analyzed by flow cytometry. Percent specific apoptosis was calculated as previously described [18].

Chromatin-immunoprecipitation (ChIP) assays. L7 cells were transfected with or without 5 μg RelA expression vector. After incubation at 37 °C for 48 h, cells were treated with 1% formaldehyde for 15 min at 37 °C. Then, cells were collected and resuspended in lysis buffer (1% SDS, 10 mM EDTA, and 50 mM Tris–HCl, pH 8.1) with complete EDTA-free protease inhibitor mixture tablets (Roche). After DNA fragmentation (the average size was ~300 bp) by sonication, the lysates were cleared by centrifugation and incubated with anti-p65 antibody at 4 °C overnight with rotation. After washing, immunocomplexes were eluted two times with 250 μl of elution buffer (1% SDS, 0.1 M $NaHCO_3$) each time at room temperature for 15 min with rotation. For reverse crosslinking, 20 μl of 5 M NaCl was added and heated at 65 °C for 4 h and treated with 10 μl of 0.5 M EDTA and 20 μl of 1 M

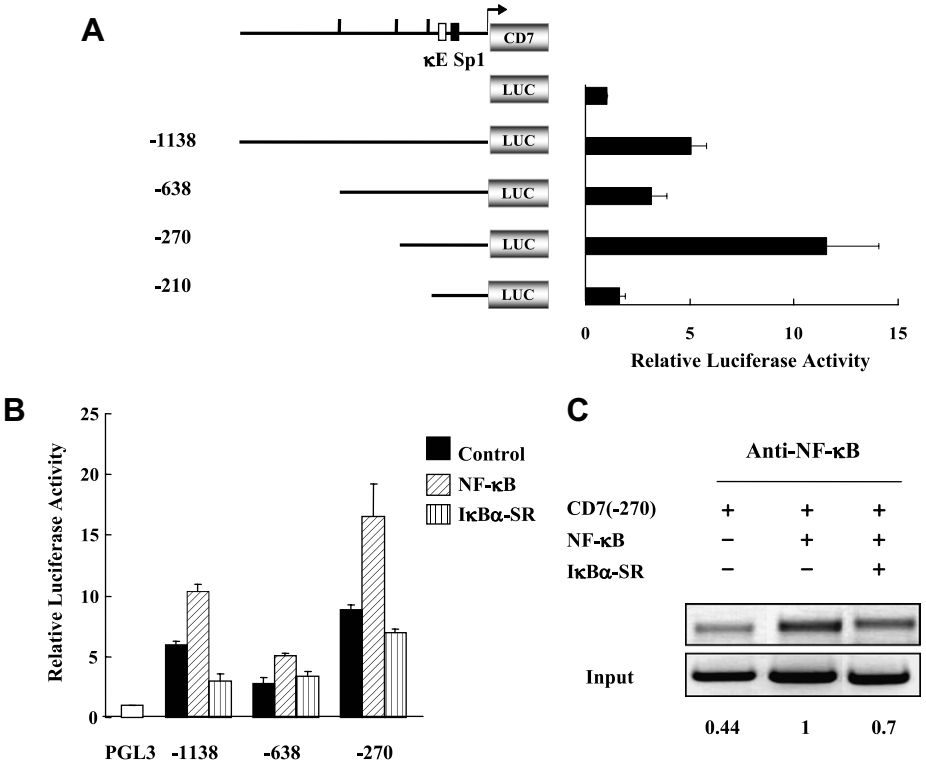

Fig. 1. NF-κB induces basal CD7 promoter activity. (A) Promoter activity of the reporter constructs driven by serially truncated forms of the CD7 promoter. κE or Sp1 denotes the putative binding site for NF-κB or Sp1, respectively. Bars = SE. (B) NF-κB up-regulates CD7 promoter activity, whereas IκBα-SR reduces its activity. Truncated forms of the CD7 promoter were co-transfected with each expression vector for NF-κB (RelA) or IκBα-SR as indicated. Bars = SE. (C) In vitro binding of NF-κB to the CD7 promoter was analyzed by ChIP assays as described in Materials and methods. L7 cells were transfected with pCD7(−270) plasmid containing the basal CD7 promoter region in the presence of NF-κB and/or IkBα-SR. The amount of input promoter DNA is presented as a loading control. The relative band intensity in each lane compared to that of the NF-κB PCR band is indicated.

Tris–HCl (pH 6.5) with 2 μl proteinase K (10 mg/ml). DNA was extracted with phenol/chloroform and precipitated with 70% ethanol. Pellets were resuspended in 30 μl of TE buffer containing RNase A (20 μg/ml). The PCR primers for detection of the CD7 fragment were 5′-CCGAGCTCATGATAAAGATGT-3′ and 5′-GGAAGCTT GACGCCCA AATCCAGGTG-3′.

Results and discussion

Identification of the CD7 proximal promoter with basal activity

To delimit the specific promoter element(s) responsible for CD7 promoter activity, we generated various reporter constructs driven by serially truncated forms of the CD7 promoter and assessed their activities in an immature T-cell line, L7 cells. The basal promoter activity of CD7 was considerably intact in the fragment from −270 to +53, and further deletion to −210 resulted in an almost complete loss of promoter activity (Fig. 1A). CD7 promoter activity was significantly increased by deletion of the region −638 to −270, suggesting that negative regulatory elements may be present in this region (data not shown). To understand the molecular basis underlying the transcriptional control of CD7 gene expression, we analyzed the transcription factors that may control the activity of the CD7 proximal promoter using Transcription Element Search System (TESS) database software [19]. A motif search of the −270 to +53 proximal promoter revealed that there were two possible NF-κB transcription factor binding sites (NF-κE, −166 and −152) and three possible Sp1 binding sites including one at −134 to −126.

NF-κB and Sp1 are cooperatively involved in activation of the CD7 proximal promoter

To test whether the NF-κB could functionally modulate CD7 promoter activity, the reporter gene construct containing the CD7 proximal promoter region was co-transfected into L7 cells with increasing amounts of expression vectors harboring RelA, the large subunit of NF-κB, or IκBα-SR, a super-repressor form of NF-kB inhibitor, IκBα [20]. As shown in Fig. 1B, CD7 promoter activity was up-regulated by exogenous overexpression of NF-κB, while it was down-regulated by addition of IκBα-SR. Consistent with the results of the promoter assay, the binding activity of NF-κB to the CD7 proximal promoter was significantly decreased by ~30% in the presence of IκBα-SR (Fig. 1C).

Interestingly, another transcription factor, Sp1 was also synergistically involved in NF-κB-induced activation of the CD7 promoter (Fig. 2B). To further elucidate the putative contribution of each transcription factor to CD7 promoter activation, their DNA binding sites were disrupted (Fig. 2A). Among the various constructs with mutations in the NF-κE or Sp1 binding sites, mutation of the NF-κE site at position -152 dramatically reduced promoter activity after induction with NF-κB (Fig. 2B). The other putative NF-κE site at position −166 had no effect on CD7 promoter activity (data not shown). There were 3 putative Sp1 binding sites on the CD7 proximal promoter, but only the Sp1 deletion mutant at −134 to −126, close to the NF-κE at −152, partially down-regulated CD7 promoter activity. Double mutations in the NF-κE (−152) and Sp1 (−134 to −126) sites, however, completely disrupted the NF-κB-induced CD7 promoter activity (Fig. 2B). The binding activity of NF-κB to the CD7 promoter was significantly reduced when each of NF-κE or Sp1 binding sites or both were disrupted (Fig. 2C). Interestingly, mutations in the Sp1 binding site significantly inhibited the binding of NF-κB even though the NF-κE binding site was intact. The binding of NF-κB to its interacting site may be unstable in the absence of Sp1. These results suggest that NF-κB cooperatively interacts with Sp1 to activate CD7 transcription as previously shown in other systems [21,22]. The amino-terminal region of RelA directly binds to the zinc-finger motif of Sp1, which acts as an activating transcription factor [21,23]. Sp1 may play a role as a basal transcription factor for the TATA-less promoters of CD7 by directly interacting with components of the general transcription complex such as TFIID [24–26].

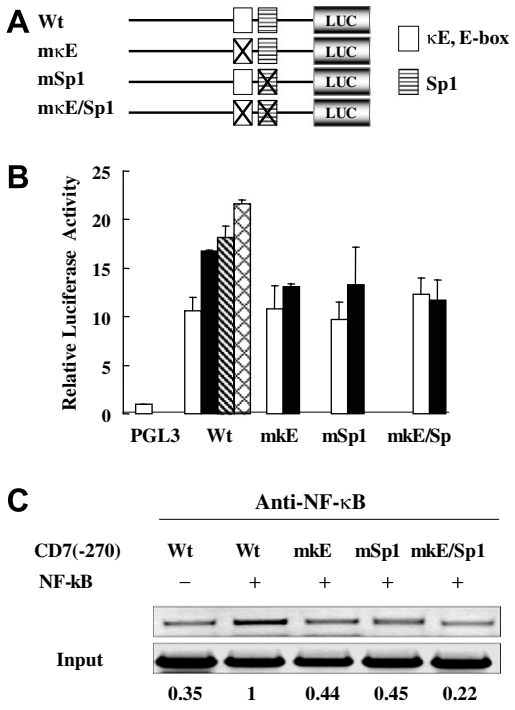

Fig. 2. NF-κB induces basal CD7 promoter activity by directly binding to the κE and Sp1 sites. (A) Site-directed mutagenesis was performed to alter the sequences of the κE and/or Sp1 sites as described in Materials and methods. Schematic representations of the wild-type and mutated CD7 proximal promoter constructs are shown as Wt, mκE, mSp1 and mκE/mSp1. The boxes with a cross represent a mutated sequence. (B) NF-κB responsiveness of κE and/or Sp1 sites on the CD7 proximal promoter was examined using various reporter constructs. L7 cells were co-transfected with the indicated luciferase reporter plasmids in the presence (closed bar) or absence (open bar) of NF-κB-expression vector. Wild type basal CD7 promoter activity was also measured in the presence of only Sp1-expression vector (▨) or NF-κB-expression vectors with Sp1-expression vectors (▩). Bars = SE. (C) In vitro binding of NF-κB to the various mutant forms of the CD7 promoter. NF-κB binding activity was analyzed by ChIP assays as shown in Fig. 1C.

E12 and Twist2 repress NF-κB-mediated activation of the CD7 promoter

The sequence of NF-κE in the CD7 proximal promoter is identical to that of the E-box element, CANNTG, which has been shown to be the optimal binding site for E-proteins [27–29]. Another transcription factor, Twist2, which was first identified as an E12 binding protein, is also involved in transcriptional regulation through binding to specific E-box elements [30]. Therefore, we examined the effects of these two transcription factors on NF-κB-induced CD7 promoter activity. Overexpression of either E12 or Twist2 significantly reduced NF-κB-mediated activation of the CD7 promoter in a dose-dependent manner (Fig. 3A and B). These repressive activities were recovered when Id3, the dominant negative regulator of E proteins, was introduced (data not shown). Moreover, binding of NF-κB to the CD7 promoter was significantly decreased (by 70–80%) in the presence of E12 or Twist2 (Fig. 3C). These proteins might act as competitors of NF-κB through binding to the E-box on the CD7 promoter or as suppressors of NF-κB-mediated activation through interaction with NF-κB itself.

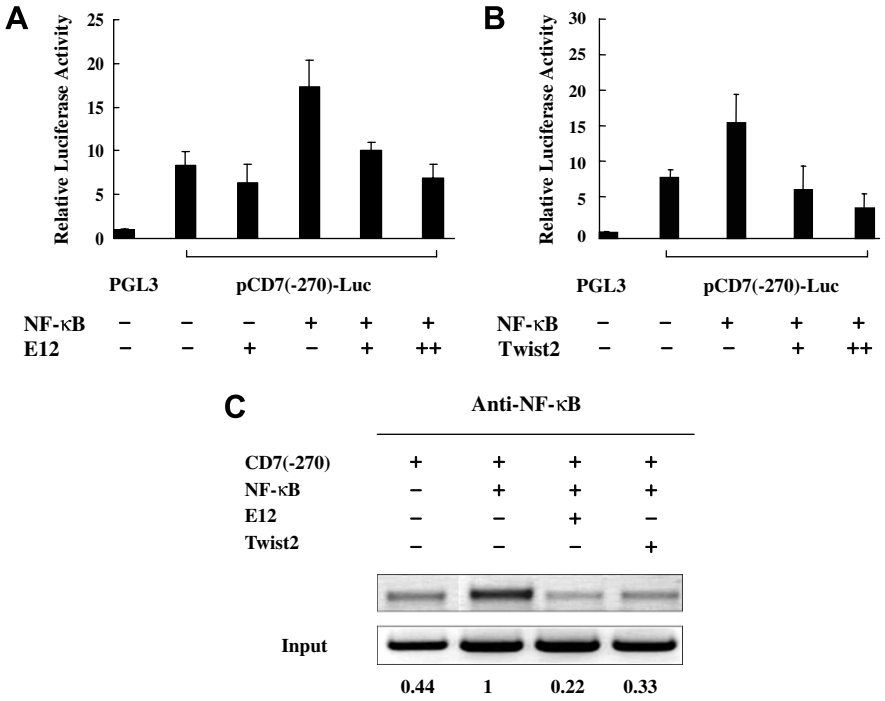

Fig. 3. E12 and Twist2 down-regulate NF-κB-mediated CD7 promoter activity. (A) pCD7(−270)-Luc construct and 2 μg of NF-κB expression vector (+) were co-transfected into L7 cells with various amounts (−; 0, +; 2, ++; 4 μg) of E12 expression vector as indicated. Bars = SE. (B) L7 cells were co-transfected with pCD7(−270)-Luc reporter construct and 2 μg NF-κB-expression vector along with increasing amounts (−; 0, +; 2, ++; 4 μg) of Twist2 expression vector as indicated. Bars = SE. (C) E12 and Twist2 prevent the binding of NF-κB to the κE/E-box elements on the CD7 proximal promoter. NF-κB binding activity to the CD7 proximal promoter was analyzed by ChIP assays as described in Fig. 1C.

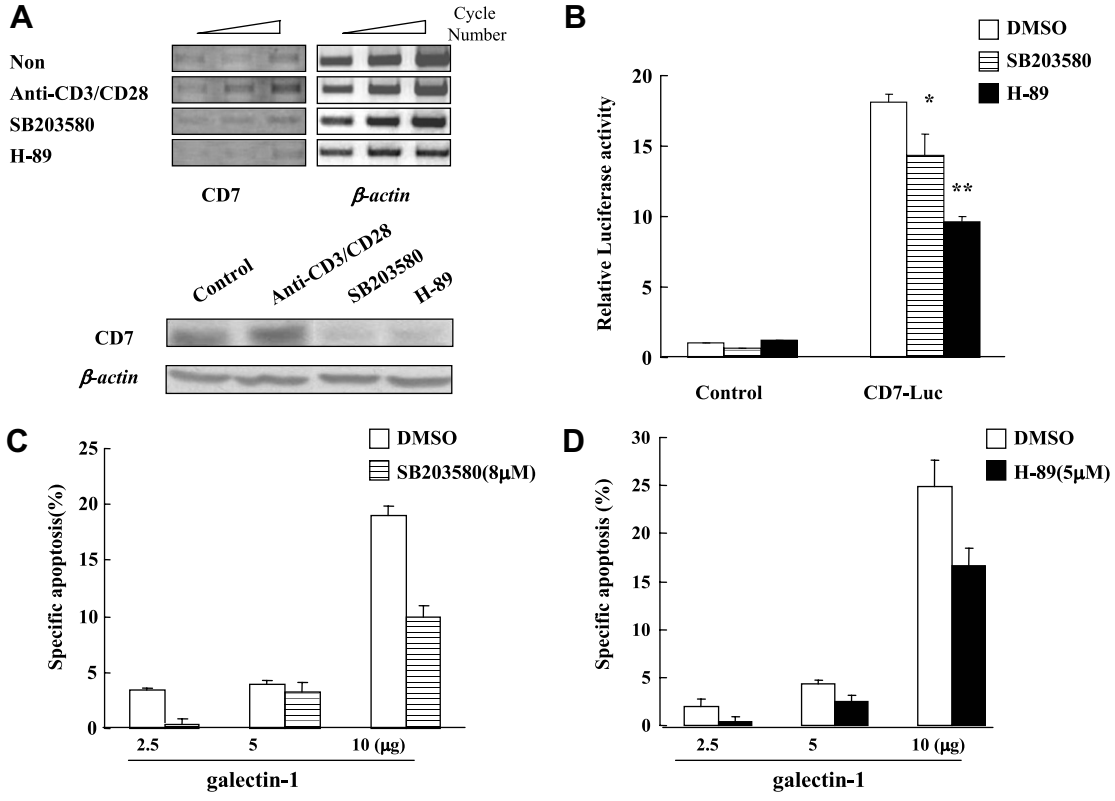

Fig. 4. Blocking the p38 MAPK and MSK1 signaling pathway prevents CD7 gene expression and involves galectin-1-mediated apoptosis of T-cells. (A) Inhibitors of the p38 MAPK (SB203580) and MSK1 (H-89) signaling pathways prevent TCR/CD28 mediated CD7 expression. L7 cells stimulated with anti-CD3/CD28 were incubated in the presence of inhibitors for 24 h. DMSO, the solvent for each inhibitor, was used as a negative control. Total RNA was prepared from untreated or treated cells, and RT-PCR was performed with specific primers. β-Actin was used as an internal control. Lysates were prepared from anti-CD3/CD28 stimulated or inhibitor treated thymocytes and immunoblotted with antibodies specific to CD7. The level of β-actin served as a control. (B) L7 cells were transfected with pCD7 (−270)-Luc reporter plasmid and then treated with DMSO or indicated inhibitors. Bars = SE. $^{*}P < 0.05$; $^{**}P < 0.01$. (C and D) L7 cells were cultured in the presence of inhibitors for 24 h and were treated with increasing amounts of galectin-1 for 5 h at 37 °C. The portion of apoptotic cells stained by annexin V was analyzed using flow cytometry. Specific apoptosis of L7 cells was analyzed as described previously [17].

Regulation of CD7 expression through NF-κB activation is mediated by the p38 MAPK-MSK1 pathway, which induces galectin-1-mediated apoptosis of immature thymocytes

The susceptibility of T-cells to galectin-1, which is abundantly expressed by thymic epithelial cells, is highly dependent on the activation state of the cells [31]. CD7 expression has been found to be altered on activated T-cells by various stimuli [15,16]. Consistent with previous results, CD7 expression was increased after anti-CD3/CD28 stimulation (Fig. 4A). Meanwhile, inhibitors of the p38 MAPK (SB203580) and MSK1 (H-89) pathways directly reduced CD7 promoter activity and its expression (Fig. 4A and B). Moreover, down-regulation of CD7 expression mediated by inhibition of the p38 MAPK-MSK1 pathway provoked the resistance of T-cells to galectin-1-induced apoptosis (Fig. 4C and D). These results imply that T-cell activation through the p38 MAPK-MSK1 pathway up-regulates CD7 expression and, thus, increases the sensitivity of T-cells to galectin-1-induced apoptosis.

It has been reported that NF-κB is involved in α-CD3-mediated apoptosis in DP thymocytes by down-regulating the expression of bcl-xL [5,32]. However, our results strongly demonstrated that intracellular pathways which control T-cell activation directly induced CD7 expression, triggering galectin-1-mediated apoptosis in immature thymocytes. Regulation of surface CD7 of T-cells might be directly related the fate of these cells. Although these studies suggest a role for CD7 in T-cell development and function, the exact regulatory mechanism of CD7 expression and its relationship with galectin-1 in mature peripheral T-cell remain to be further investigated. Both loss of CD7 expression and altered cellular glycosylation may contribute to the apoptosis resistance of malignant T-cells.

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