

IL-17 Stimulates Migration of Carotid Artery Vascular Smooth Muscle Cells in an MMP-9 Dependent Manner via p38 MAPK and ERK1/2-Dependent NF- κ B and AP-1 Activation

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Abstract Inappropriate vascular remodeling is thought to be the main cause of restenosis following angioplasty. Migration of vascular smooth muscle cells (VSMC) into lumina, which is promoted by degradation of the extracellular matrix by matrix metalloproteinases (MMPs) plays a causal role in pathological vascular remodeling. The aim of the present research is to explore the effects of a novel cytokine, IL-17, on migration of VSMC and MMP-9 secretion. Carotid artery VSMC was isolated from Sprague–Dawley rats. Expression of MMP-9 and cell migration induced by IL-17 and its related signal pathway were detected. The results showed that IL-17-induced migration

of VSMC in an MMP-9-dependent manner. IL-17-induced MMP-9 expression was via p38 MAPK and ERK1/2 dependent NF- κ B and AP-1 activation. The present results demonstrated that IL-17 may play a role in vascular remodeling and targeting IL-17 or its specific downstream mediators is a potentially novel therapeutic pathway for attenuating the post-angioplastic restenosis.

Keywords Vascular remodeling · IL-17 · MMP-9 · Restenosis

Introduction

Vascular remodeling, which is defined as a response to a variety of stimuli including hemodynamic changes, inflammation, and injury, leads to change in the size and/or composition of an adult blood vessel. However, inappropriate remodeling is currently thought to be the main cause of most prevalent vascular pathologies of arteries, such as atherosclerosis and restenosis following angioplasty (Gibbons and Dzau 1994). Smooth muscle cell (SMC) migration plays a causal role in pathological remodeling of the vessel walls (Ross 1999a, b; Schwartz 1997). Migration of SMC and neointimal hyperplasia are promoted by degradation of the extracellular matrix (ECM) by matrix metalloproteinases (MMPs), which are major components of the enzyme cascade responsible for degradation of the ECM and basement membrane proteins.

MMP-9, which belongs to the collagenases according to the substrate specificity, is expressed in many cell types including SMC, and induced by proinflammatory cytokines, such as IL-1 β , IL-18 and IL-17 (Cortez et al. 2007; Chandrasekar et al. 2006; Liang et al. 2007). IL-17 is a member of a novel group of proinflammatory cytokines

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which share little homology with other interleukins. Many cell types in the body express its receptors (IL-17R) and are therefore targets of IL-17 (Yao et al. 1995). Recently, it was found that IL-17 was involved in myocardial remodeling and atherosclerosis (Cortez et al. 2007; Patel et al. 2007). However, few studies have been done to observe the effects of IL-17 in vascular remodeling after balloon injury of carotid artery. Since migration of SMC plays a key role in the vascular remodeling, we target effects of IL-17 on SMC migration in the present research.

Materials and Methods

Recombinant human IL-17 (rhIL-17), anti-IL-1 β , IL-6, and TNF- α neutralizing antibodies, IL-1 β , IL-6 and TNF- α ELISA kit, and normal goat IgG were purchased from R & D Systems. Functional grade purified anti-human IL-17 antibodies and normal mouse IgG antibodies were obtained from eBioscience (San Diego, CA). Anti-MMP-9 monoclonal antibody was purchased from NeoMarkers (Fremont, CA). Cycloheximide (CHX), a protein synthesis inhibitor (10 μ g/ml in DMSO) and Actinomycin D (ActD), an RNA synthesis inhibitor (2.5 μ g/ml in DMSO) were from Sigma; GM-6001, a nonspecific MMP inhibitor with potent inhibitory activity against collagenase, gelatinases, and stromelysin (10 μ M in DMSO), was from Biomol. MEK1 inhibitor (PD98059) was from Cell Signaling and p38 MAPK inhibitor (SB203580) was from Promega.

Isolation, Culture and Characterization of CAVSMC

The investigation conforms with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85–23, revised 1996). Isolated CAVSMC from the common carotid arteries of Sprague–Dawley rats were prepared using a method described previously (Mnjoyan et al. 2008). Isolated CAVSMC was seeded on a chamber slide, allowed to differentiate in differentiation media (0.4% FCS and 50 μ g/ml heparin in DMEM) for 10 days, and stained with anti- α -actin antibody. Nuclei were counterstained with 4, 6-diamidino-2-phenylindole (DAPI). Only those batches of CAVSMC that showed a 90% or higher α -actin positivity were used for further analyses.

Detection of IL-17RA Expression in CAVSMC

Expression of IL-17RA in CAVSMC was determined by reverse transcriptional PCR (RT-PCR). Total RNA was isolated with Trizol (Invitrogen) and cDNA was synthesized. The primers used were as follows: Sense: 5'-CACGT TGAGTGGACCTTG-3'; Antisense: 5'-CCAGCAGGATC

TGGTA-3'. (Genebank no. NM 001107883, product length: 421 bp).

Cell Migration Analysis

CAVSMC migration was detected with the commercial kit as per the manufacturer's directions as reported previously (Chandrasekar et al. 2006). Cultured CAVSMC treated with trypsin were suspended in modified DMEM with 1% bovine serum albumin, and concentration of cells was adjusted to 4.0×10^5 /ml. Cells were layered on the coated insert filters and stimulated with IL-17 (20 ng/ml). Same concentration of IL-17 was added to the lower chamber. After incubation at 37°C for 24 h, we washed the membrane with PBS and removed the non-invading cells on the upper surface with cotton swabs. The Discovery Labware BD BioCoat™ invasion chambers (catalog no. 354481, BD Biosciences) and 8.0 μ m pore polyethylene terephthalate membranes with a thin layer of Matrigel basement membrane matrix were applied. The 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay was used to detect cells migrating to the lower surface of the membrane at $A_{540 \text{ nm}}$. A broad-spectrum MMP inhibitor GM-6001 (10 μ M) (Cortez et al. 2007) was added to the culture 15 min prior to stimulation with IL-17 to determine the role of MMPs in IL-17-mediated cell migration.

RNA Interference

siRNA targeting rat MMP-2 (NM 031054), MMP-9 (NM 031055), NF- κ B(XM 342346) and c-Jun (NM 021835) were synthesized commercially (Sigma). Efficiency of these siRNA was tested with Northern blotting and quantitative real-time RT-PCR in HEK293 cells, only those with inhibitory efficiency of mRNA expression >80% were used in the further experiments (data not shown). About 48 h prior to the addition of IL-17, CAVSMCs were transfected with siRNA using Lipofectamine 2000 (Invitrogen) following the manufacture's instructions. And a siRNA that did not target any genes was used as a negative control.

Northern Blotting

Total RNA was isolated by lysing cells in TRIzol reagent (GIBCO) and quantified using spectrophotometry at 260 nm. RNA (10 μ g) was separated by formaldehyde-containing 1% agarose gel electrophoresis, and gels were stained with SYBR green (Sigma) to visualize 28S/18S ribosomal RNA bands. Gels were transferred overnight to a nylon membrane (GeneScreen Plus; NEN Life Science Products) and probed with 32P-labeled MMP-9 cDNA. The membrane was exposed to film for 1 h to 7 days at -80°C . The film was developed and scanned, and densitometry

was performed using AlphaEase software. Loading was normalized to the 28S band.

Real-time Quantitative RT-PCR

DNA-free total RNA was extracted using RNAqueous-4 PCR kit (Ambion). RNA quality was assessed by capillary electrophoresis using the Agilent 2100 Bioanalyzer (Agilent Technologies, Palo Alto, CA). Real time quantitative PCR was performed using Quanti-Tect SYBR-Green Probe RT-PCR Kit (Qiagen) and Gene 3000 sequence detection system (Gene Corp.). Each sample was assayed in triplicate. For relative quantification, the C_t method: ratio = $2^{-[(C_t \text{ (MMPs)} - C_t \text{ (GAPDH)})]}$ was used, with GAPDH as a control. For copy number determination, a calibration curve was obtained using serial dilutions of linearized GAPDH cDNA as template and the primers used in the experiment were as follows: GAPDH primers 5'-GAAGGTGAAGGTCGGAGTC-3' and 5'-GAAGATGGTGATGGGATTTTC-3'; MMP-9: 5'-GATGGTCTACTGGCACACG-3' and 5'-GTCCCTCGAAGGTGAAGG-3'. The mRNA expression levels of target genes were expressed relative to the appropriate control, which was set to 1.0.

Western Blot Analysis

Nuclear cell extracts with the ReadyPrep Protein Extraction Kit (Cytoplasmic/Nuclear) were used for assessing nuclear import of NF- κ B (p65) and c-Jun. I κ B was detected in cytoplasmic fraction by Western blot. Antibodies (Santa Cruz Inc, CA, USA) used were as follows: anti-phospho-p65 (sc-101749), anti-I κ B (sc-74452), anti-phospho-c-Jun (sc-16312, specific to ser63/73) and anti-c-Jun (sc-45, specific to N-terminal).

MMP-1, 2, 9 and TIMP-1, 2 levels in supernatant and cell extractions were confirmed by Western blotting. Proteins were separated by 10% PAGE and electroblotted onto a Hybond-P polyvinylidene difluoride membrane (Amersham Biosciences). The membrane was incubated with rabbit anti-rat MMP 1,2,9 and TIMP 1,2 antibody (Boster Biological Technology Ltd. Wuhan, China. 1:1000 dilution) and subsequently with horseradish peroxidase-conjugated goat/donkey anti-rabbit/goat immunoglobulin G. The immunoreactive bands were detected by chemiluminescence (ECL Plus, GE Healthcare). The β -tubulin antibodies were used as internal control to confirm equal protein loading. The results were quantified using the Quantity One Software (Bio-Rad).

Stimulation of CAVSMC

Cells were treated with various concentrations (0–100 ng/ml) of IL-17 for 12 h to clarify the optimizational dose

for inducing MMP-9 expression. In another experiment, cells were stimulated with IL-17 (20 ng/ml) for 24 h and MMP-9 was determined at various time. To examine if the MMP-9 mRNA expression was dependent on IL-17, we used the IL-17(20 ng/ml) or IL-17RA (10 μ g/ml) neutralizing antibodies incubated with CAVSMC for 1 h before addition of IL-17 (Cortez et al. 2007). IL-17 has pleiotropic activities, including induction of other cytokines, such as IL-1 β , IL-6 and TNF- α (Shen et al. 2006). Since these cytokines are known to stimulate MMP-9 expression (Eberhardt et al. 2000; Yao et al. 2007; Moon et al. 2004), we determined whether IL-17-mediated MMP-9 expression is dependent on IL-1 β , IL-6, or TNF- α . CAVSMC was incubated with IL-1 β , IL-6, or TNF- α neutralizing antibodies (10 μ g/ml for 1 h; Boster Corp. Wuhan, China) 1 h before the addition of IL-17 (Cortez et al. 2007).

Protein synthesis inhibitor (CHX) or transcriptional inhibitor (ActD) was used to determine whether IL-17-mediated MMP-9 expression was regulated at the transcriptional and/or translational level. CAVSMC was treated with CHX or ActD for 1 h and then IL-17 (20 ng/ml for 12 h) was added, and RNA was isolated and analyzed for MMP-9 expression by quantitative RT-PCR.

We explored whether IL-17 induces TF activation via p38 MAPK and ERK1/2. Quiescent CAVSMC were treated with SB-203580 or PD-98059 before treating with IL-17. TF activation was detected after 2 h (C-jun) or 6 h (NF- κ B) by Western blotting of nuclear protein extracts. mRNA expression of MMP-9 was detected with quantitative RT-PCR at 12 h.

Statistical Analysis

All values are expressed as mean \pm SEM. For statistical analysis, a paired *t*-test was used for comparison between two groups. One-way ANOVA and Tukey–Kramer multiple range test were used for comparisons among multiple groups. $P < 0.05$ was considered significant.

Results

Effects of IL-17 in Stimulating MMP-9 Expression

First, we detected whether CAVSMC could express IL17RA using RT-PCR. As shown in Fig. 1a, CAVSMC expresses IL-17RA under basal conditions. CAVSMC expresses MMP-9 mRNA at low levels under basal conditions, and treatment with IL-17 for 12 h significantly increased MMP-9 expression, with peak levels obtained at 20 ng/ml (Fig. 1b). Time course studies revealed that IL-17 induced MMP-9 expression in a time-dependent manner.

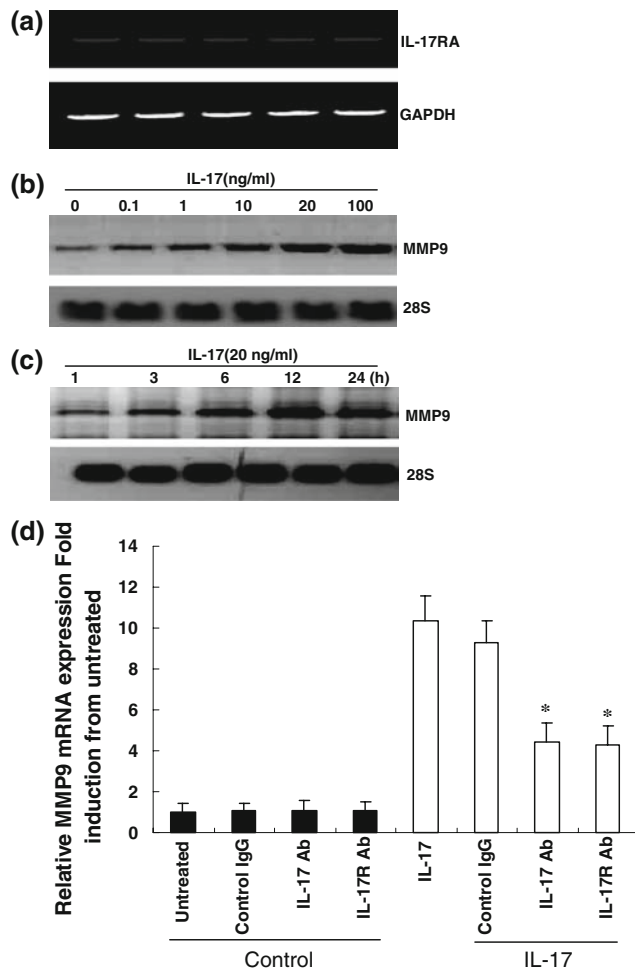


Fig. 1 IL-17 stimulates MMP-9 expression in CAVSMC. **a** Expression of IL-17RA was detected by RT-PCR in CAVSMC. **b** Dose-dependent manner of MMP-9 expression induced by IL-17. **c** Time-dependent manner of MMP-9 expression induced by IL-17. **d** Anti-IL-17 and IL-17RA neutralizing antibody attenuated mRNA expression of MMP-9. (*, $P < 0.05$ versus IL-17 group, AVONA)

The peak levels of mRNA were observed at 12 h, with no further increases detected at 24 h (Fig. 1c). MMP-9 mRNA expression was blocked by IL-17 and IL-17RA neutralizing antibody was detected by real-time RT-PCR (Fig. 1d). These results demonstrated that IL-17 can induce MMP-9 mRNA expression in a time- and dose-dependent manner in CAVSMC.

MMP-9 protein expression was significantly increased when stimulated with IL-17. When incubated with IL-17 or IL-17RA neutralizing antibody, the expression of MMP-9 was decreased (Fig. 2a). Elevated levels of IL-1 β , IL-6 and TNF- α were detected in the supernatant after CAVSMC was treated with IL-17 at 20 ng/ml for 12 h. (data not shown). Pretreatment with neutralizing antibodies against IL-1 β , IL-6, or TNF- α failed to block IL-17-mediated MMP-9 expression. (Fig. 2b).

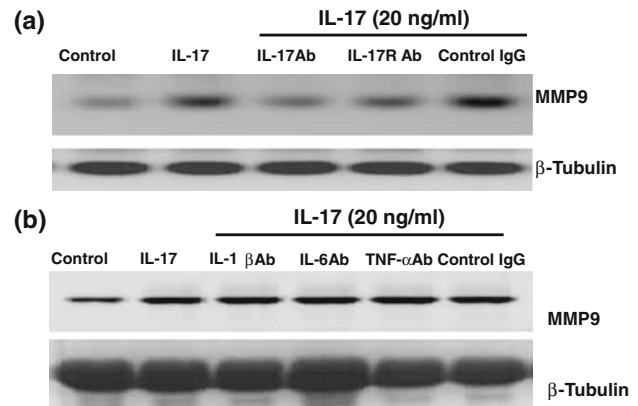


Fig. 2 MMP-9 expression was independent of IL-1 β , IL-6 and TNF- α . **a** MMP-9 expression blocked by anti-IL-17 and IL-17RA neutralizing antibody. **b** No obvious influence on MMP-9 expression was observed by neutralizing antibody which targets IL-1 β , IL-6 and TNF- α

Role of AP-1 and NF- κ B in IL-17-Induced MMP-9 mRNA Expression

IL-17-mediated MMP-9 expression was significantly inhibited by the RNA synthesis inhibitor ActD, but not by the protein synthesis inhibitor CHX (Fig. 3a), which showed that IL-17-induced MMP-9 expression was regulated at transcriptional level. Treatment of CAVSMC with IL-17 for 6 h caused an increase in nuclear p65 protein levels, whereas no significant changes could be observed at a very early time point (30 min). Degradation of I κ B in cytoplasmic fraction was observed at the same time. Similar to p65, nuclear import of c-Jun protein was efficiently increased by IL-17 at both time points tested (Fig. 3b). The possible regulation of MMP-9 mRNA transcription by AP-1 and NF- κ B were investigated using selective pharmacological inhibitors or siRNA. NF- κ B inhibitor (helenalin) significantly attenuated IL-17-induced MMP-9 mRNA accumulation assessed by real-time RT-PCR. Transfection with siRNA targeting c-Jun and NF- κ B also decreased the IL-17-induced MMP-9 mRNA expression (Fig. 3c).

Role of p38 MAPK and ERK1/2 in IL-17-Induced Transcription Factor (TF) Activation and MMP-9 Expression

IL-17-induced activation of p38 MAPK phosphorylation and activity, which were blocked by the inhibitor SB-203580 (1 μ M) and IL-17 neutralizing antibodies. Similarly, phosphorylation and activity of ERK1/2 were induced by IL-17 and blunted by PD-98059 (10 μ M) and IL-17 neutralizing antibodies (Fig. 4a).

As shown in Fig. 4b, nuclear translocation of NF- κ B p65 was significantly attenuated by SB-203580 and

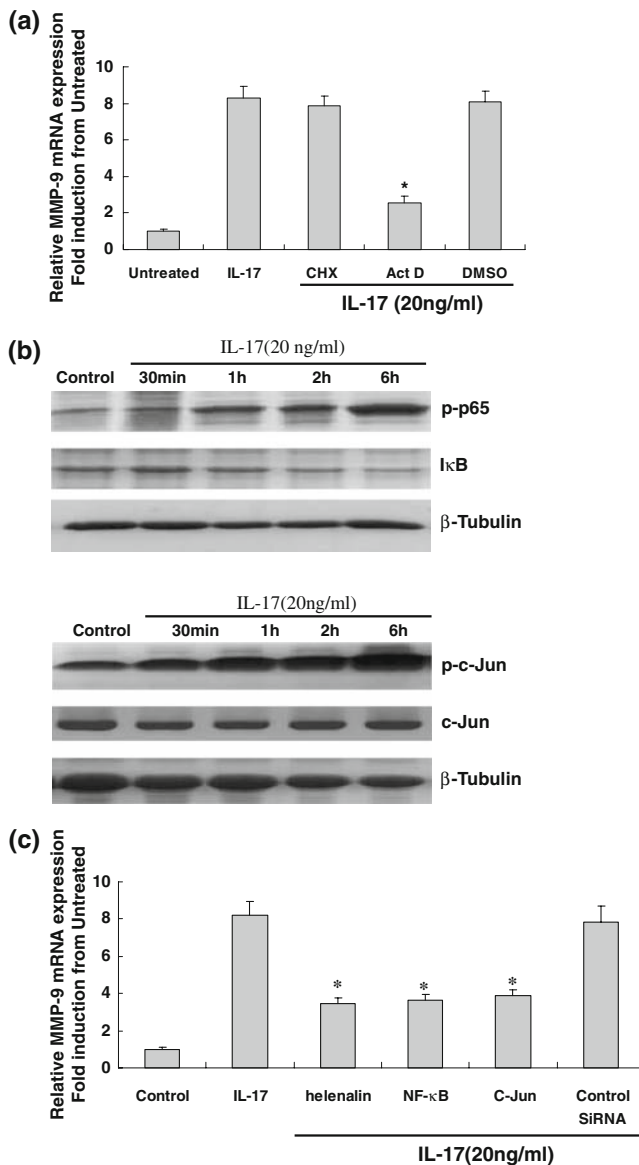


Fig. 3 IL-17-induced MMP-9 expression was dependent on NF-κB and AP-1. **a** Act D, while not CHX, inhibited IL-17 induced MMP-9 mRNA expression. **b** Nuclear transport of NF-κB and C-Jun was obtained with IL-17 stimulation. **c** Inhibition of NF-κB and AP-1 reduced expression of MMP-9 mRNA. (*, $P < 0.05$ versus IL-17 group, AVONA)

PD-98059. Similarly, IL-17-mediated AP-1 activation was attenuated by SB-203580 and PD-98059. Furthermore, SB-203580 and PD-98059 attenuated IL-17-mediated MMP-9 mRNA expression (Fig. 4c).

Effects of IL-17 on MMPs/TIMPs Balance

MMP-1, 2, 9 and TIMP-1, 2 were determined by ELISA in the supernatant and Western blotting from cell extractions after incubation with IL-17 (20 ng/ml) for 24 h. IL-17 induces MMPs expression in a time-dependent manner,

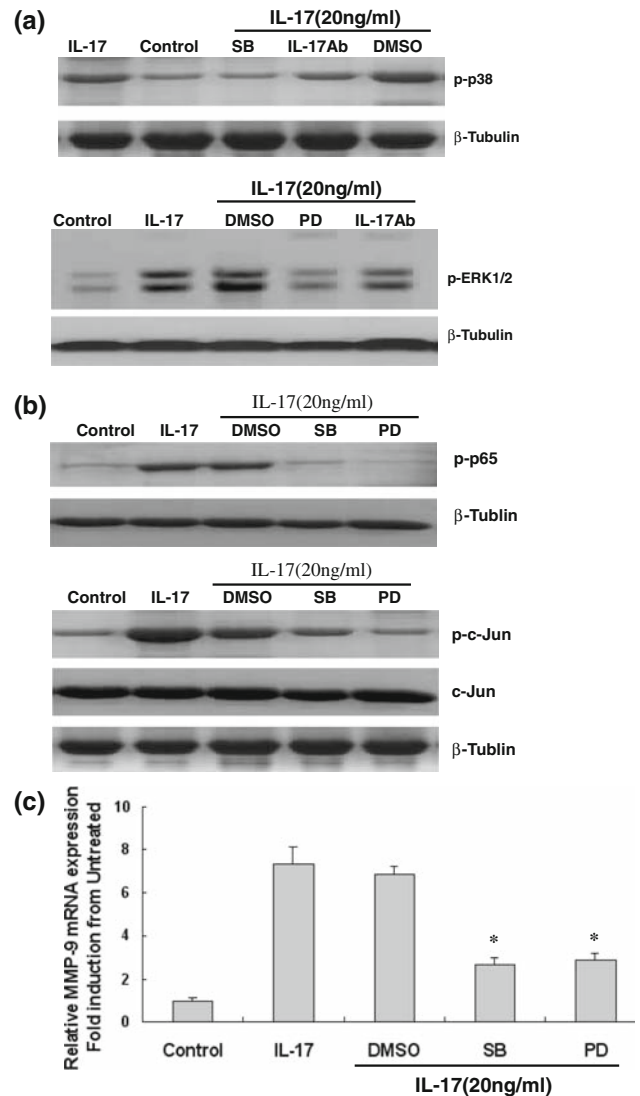


Fig. 4 Role of p38 MAPK and ERK1/2 in TF activation and MMP-9 expression. **a** IL-17-induced activation of p38 MAPK and ERK1/2 was blunted by SB-203580 and PD-98059, respectively. **b** Nuclear transport of TF induced by IL-17 was blocked by SB-203580 and PD-98059, respectively. **c** mRNA expression of MMP-9 was attenuated by MAPK inhibitors (*, $P < 0.05$ versus IL-17 group, AVONA)

with peak levels obtained at 12 h, but has no obvious effects on TIMPs expression (data not shown).

Effects of IL-17 in Stimulating CAVSMC Migration

Because IL-17 is a potent inducer of IL-1β, IL-6 and TNF-α production, we first investigated whether IL-17-induced CAVSMC migration is mediated by these cytokines. Pre-treatment with the respective neutralizing antibodies for 1 h prior to IL-17 treatment failed to modulate cell migration. In contrast, incubation with anti-IL-17 or anti-IL-17RA neutralizing antibody for 1 h blocked IL-17-induced cell migration. These results indicate that IL-17 is

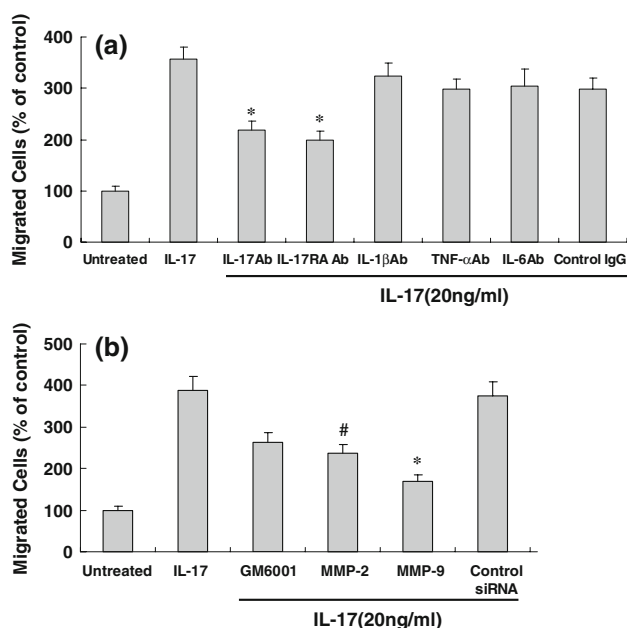


Fig. 5 Role of IL-17 in migration of CAVSMC. **a** IL-17 induced migration of CAVSMC was independent of IL-1 β , IL-6 and TNF- α . Anti-IL-17 and IL-17RA neutralizing antibody reduced the cell migration stimulated by IL-17. **b** MMP inhibitor (GM-6001) and siRNA targeting MMP2/9 reduced the IL-17-induced cell migration. The effects of inhibition of MMP-9 was more pronounced than that of MMP-2. (*, $P < 0.05$ versus IL-17 group. #, $P < 0.05$ versus MMP-9 group, AVONA)

a potent inducer of CAVSMC migration and mediates its effect independent of the proinflammatory cytokines IL-1 β , IL-6 and TNF- α . (Fig. 5a).

Whether IL-17 induces CAVSMC migration in an MMP-9-dependent manner was studied by using MMPs inhibitor or siRNA targeting MMP-2/MMP-9. Pretreatment with the broad-spectrum MMPs inhibitor GM-6001 attenuated IL-17-dependent CAVSMC migration. The effect of GM-6001 appeared to be more pronounced than was MMP-9 knockdown, which indicated that MMP-9 was not the sole mediator for CAVSMC migration. The siRNA mediated knockdown of both MMP-2 and MMP-9 attenuated IL-17-mediated CAVSMC migration (Fig. 5b). Inhibition of MMP2/9 expression was confirmed by Western blotting and RT-PCR (data not shown). However, knockdown of MMP-9 was more effective in inhibiting cell migration than that of MMP-2. Treatment with control siRNA had no obvious effect on CAVSMC migration.

Discussion

In the present study, induction of MMP-9 expression in CAVSMC by IL-17 was observed. The effects of IL-17 in stimulating MMP-9 expression are independent of IL-1 β ,

IL-6, and TNF- α . IL-17 regulates MMP-9 expression at the transcriptional level and is dependent on p38 MAPK and ERK1/2 mediated AP-1 and NF- κ B activation. IL-17 induces CAVSMC migration in an MMP-9-dependent manner. Since migration of SMC to lumina is a key process in neointimal formation and restenosis, MMPs degrade ECM and facilitate migration, our results suggest that IL-17 may be potentially important in neointimal formation and restenosis after balloon-injury induced vascular remodeling.

IL-17s constitute a unique family of cytokines that has no structural homology to other ILs (Bettelli et al. 2007) and is expressed mainly by a subset of CD4⁺ T cells, i.e., Th17 cells. The IL-17 group is composed of six major isoforms, IL-17A, -B, -C, -D, -E, and -F (Moseley et al. 2003). IL-17 signals via IL-17 receptors (IL-17R), which included IL-17RA, -B, -C, -D, and -E (Moseley et al. 2003). Many cell types express IL-17Rs and are targets of IL-17. In present research, expression of IL-17RA in CAVSMC was observed, which indicated that CAVSMC is target of IL-17.

Clinical and experimental data showed that IL-17 was involved in cardiovascular diseases. In unstable angina and acute myocardial infarction patients, increased IL-17 levels were detected in plasma (Hashmi and Zeng 2006). IL-17 stimulates MMP-1 expression in primary human cardiac fibroblasts (HCP) and mediates HCP migration via MMP-1-dependent pathway, which suggest that IL-17 plays a critical role in myocardial remodeling (Cortez et al. 2007). Upregulation of MMP-2 and MMP-9 by IL-17 was also observed in that research, which was consistent with our results. IL-17 stimulates C-reactive protein (CRP) expression via p38 MAPK and ERK1/2-dependent NF- κ B and C/EBP β activation in coronary artery smooth muscle cells (CASM), which suggest that IL-17 may mediate chronic inflammation, atherosclerosis, and thrombosis (Patel et al. 2007). However, it is unknown whether IL-17 plays a role in CAVSMC migration in carotid artery after balloon injury.

SMC migration and proliferation are important features of both normal physiological vessel growth and vascular pathology (Ross 1999a, b). In normal vessels, SMCs are largely confined to the tunica media. The proliferation of SMCs in the tunica media and their migration into the luminal surface are important factors which determined the intimal thickening and hyperplasia in post-angioplastic restenosis. Migration of SMCs were regulated by MMPs/TIMPs balance in ECM. The disruption of this delicate balance in favor of MMPs activation results in ECM degradation and induction of SMC motility and migration (Cortez et al. 2007; Galis and Khatri 2002; Ikeda and Shimada 2003; Cho and Reidy 2002). Among the MMPs, MMP-9 plays a key role in vascular remodeling by

degradation and reorganization of ECM (Galis and Khatri 2002; Cho and Reidy 2002). Inhibition of MMP-9 increases the collagen content of arteries and potentially their mechanical stability, decreases intimal hyperplasia and the lumen loss. Both MMP-2 and MMP-9 are expressed in SMC and excess activation of MMP-2 and MMP-9 results in destruction of the ECM and leads to pathological remodeling and vascular restenosis (Ikeda and Shimada 2003; Cho and Reidy 2002; Galis et al. 2002).

In the present study, MMPs (MMP-1,2 and 9) were induced by IL-17 in time- and dose-dependent manner, while TIMPs (TIMP-1, 2) were not significantly affected by IL-17, suggesting that IL-17 alters the MMPs/TIMPs balance in favor of MMPs expression and induces ECM degradation. Although the knockdown of MMP-2 and MMP-9 significantly inhibits IL-17-mediated CAVSMC migration, the effects are more pronounced when MMP-9 expression is targeted, indicating that MMP-9 might play a more dominant role in IL-17-mediated CAVSMC migration.

Our results also show that IL-17 stimulates MMP-9 expression at the transcriptional level. IL-17 stimulated MMP-9 mRNA expression and secretion. p65 and AP-1 protein (c-Jun) were markedly elevated after stimulation with IL-17. Selective inhibitor of NF- κ B or knockdown of NF- κ B and c-Jun using siRNA attenuated MMP-9 expression. These results suggest that both AP-1 and NF- κ B are critical mediators of IL-17-mediated MMP-9 gene transcription.

It has been reported previously that ERK1/2 was involved in IL-17-mediated MMP-1 expression in HCF (Cortez et al. 2007). The signal transduction pathways involved in IL-17-mediated MMP-9 expression in CAVSMC were determined in the present research. As shown in the results, IL-17 induced p38 MAPK and ERK1/2 activation, SB-203580 and PD-98059 blunted IL-17-mediated transcription factor activation and MMP-9 expression. These results demonstrated that IL-17 induced MMP-9 expression was dependent on MAPK-mediated NF- κ B and AP-1 activation. C-Jun N-terminal kinase (JNK) is an important member of MAPK family. In human airway smooth muscle cells, IL-17A mediated rapid phosphorylation of MAPK including JNK (Rahman et al. 2006). JNK was also involved in IL-1 β induced MMP-9 expression in human tracheal smooth muscle cells (Liang et al. 2007). This MAPK signal may also participate in the MMP-9 expression stimulated by IL-17 in CAVSMC, while it was not tested in the current research. It requires further study to clarify the role of JNK in IL-17-induced MMP-9 expression and cell migration. This will make the mechanisms related to the effects of IL-17 in migration of CAVSMC more precise.

Conclusions

Taken together, IL-17 induces CAVSMC migration through the induction of MMP-9 expression, which is mediated by p38 MAPK and ERK1/2 dependent AP-1 and NF- κ B activation. Targeting expression of IL-17 or its specific downstream mediators is a potentially novel therapeutic pathway for attenuating the post-angioplastic restenosis.

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