Essential role of mitogen-activated protein kinases in IL-17A-induced MMP-3 expression in human synovial sarcoma cells

Takuma Sakurai1,2, Daigo Yoshiga2, Wataru Ariyoshi1, Toshinori Okinaga1, Hiroyasu Kiyomiya1,2, Junya Furuta1,2, Izumi Yoshioka3, Kazuhiro Tominaga2 and Tatsuji Nishihara1*

Abstract

Background: The tumor cells were needed to rearrange the extracellular matrix (ECM) and reorganize their cytoskeleton to facilitate the cell motility during the tumor invasion. The proinflammatory cytokine interleukin-17A (IL-17A) is reported to up-regulate tumor invasiveness via ECM degradation by matrix metalloproteinases (MMPs). However the precise effects of IL-17A-dependent invasion remain to be characterized. The aim of this study was to elucidate the mechanisms underlying IL-17A-induced MMP-3 expression in the human synovial sarcoma cells HS-SY-II.

Methods: HS-SY-II cells were incubated with IL-17A. In some experiments, the cells were pre-incubated with an anti-IL-17 receptor polyclonal antibody (IL-17R Ab) or inhibitors for signaling cascade prior to addition of IL-17A. The expression of MMP-3 was determined by real-time reverse-transcription polymerase chain reaction (RT-PCR) and western blotting. IL-17R expression in HS-SY-II cells was assessed by immunofluorescence microscopy, while the phosphorylation of signaling molecules was measured by western blotting.

Results: IL-17A increased MMP-3 mRNA and protein expression. HS-SY-II cells express the IL-17R on their surface and blockage of IL-17A-IL-17R binding by IL-17R Ab suppressed IL-17A-mediated induction of MMP-3. IL-17A induced the phosphorylation of three components of the mitogen-activated protein kinase (MAPK) pathway including extracellular signal-regulated kinase 1/2 (ERK1/2), p38 MAPK, and c-Jun NH2-terminal kinase (JNK). Pre-treatment of the cells with inhibitors of ERK1/2, p38 MAPK, and JNK attenuated the IL-17A-induced phosphorylation of activator protein-1 (AP-1) subunits and the expression of MMP-3 mRNA.

Conclusion: Our results indicate an essential role for MAPKs in the induction of MMP-3 in synovial sarcoma cells, through AP-1 activation.

Keywords: Interleukin-17, Synovial sarcoma, Matrix metalloproteinase 3, Mitogen-activated protein kinases, Transcription factor AP-1

Background

Synovial sarcoma is a clinically aggressive malignant soft tissue tumor and the 5- and 10-year survival rates have been reported as low as 36 and 20 %, respectively [1]. Furthermore, synovial sarcomas have a high rate of local recurrence and metastasis [2]. Therefore, establishment of efficient therapeutic strategies are required to improve the prognosis of synovial sarcoma. Inflammation is a key regulatory process during tumor development. Continuous exposure to inflammatory cytokines is known to cause tumorigenesis [3]. Thus, these cytokines are of interest as therapeutic targets to prevent tumor progression.

Pro-inflammatory cytokine interleukin-17A (IL-17A) is a major member of IL-17 family and is secreted mainly by Th17 cells [4]. The elevated expression of IL-17A has been implicated in the pathogenesis of a wide range of
inflammatory, infectious, and autoimmune diseases [5].
In addition, accumulating data showed that the role of
IL-17A in cancer initiation, growth, and metastasis was
crucial [6–8].
Matrix metalloproteinases (MMPs) degrade a wide
range of substrates, including extracellular matrix (ECM)
components [9], and numerous studies demonstrated that
elevated levels of MMPs are associated with tumor growth,
cancer progression, metastasis, and shortened survival in
patients [10, 11]. MMP-3 has been recognized as one of
the major proteases responsible for ECM turnover and
cell–cell interactions, as well as tumor metastasis [12, 13].
The IL-17 family signals via their correspondent recep-
tors activate downstream pathways, including mitogen-
activated protein kinases (MAPKs). The MAPK signal
transduction pathway, comprising extracellular signal-
regulated kinase 1/2 (ERK1/2), p38 MAPK, and c-Jun
NH2-terminal kinase (JNK), controls gene expression, via
the phosphorylation and regulation of transcription fac-
tors, co-regulatory proteins, and chromatin.
Previous studies showed that IL-17A induces MMP-1
and MMP-9 via ERK1/2 and p38 MAPK-dependent
activation of the transcriptional factors activator pro-
tein-1 (AP-1) and nuclear factor-kappa B (NF-xB) [14,
15]. Although both IL-17A and MMP-3 are known to be
involved in the initiation and progression of tumor cells,
their interaction has yet to be determined. In the present
study, we examined the molecular mechanism by which
IL-17A-induced MMP-3 expression in synovial sarcoma
cells and demonstrated that IL-17 could regulate the
expression of MMP-3 through MAPKs-AP-1 activation.

Methods
Reagents
Recombinant human IL-17A and anti-JNK monoclo-
nal antibody were purchased from R&D systems (Min-
neapolis, MN, USA). Anti-phospho-ERK monoclonal,
anti-phospho-p38 MAPK monoclonal, anti-phospho-
JNK polyclonal, anti-phospho-c-Jun monoclonal, anti-
phospho-c-Fos monoclonal, anti-ERK monoclonal,
anti-p38 MAPK monoclonal, anti-JNK polyclonal, anti-
c-Jun monoclonal, and anti-c-Fos monoclonal antibodies
were purchased from Cell Signaling Technology (Beverly,
MA, USA). Anti-phospho-IκB-α monoclonal, and anti-
IκB-α polyclonal antibodies were purchased from Santa
Cruz Biotechnology (Dallas, TX, USA). Anti-MMP-3
polyclonal antibody was purchased from Abcam (Tokyo,
Japan). Anti-β-actin monocular antibody was obtained
from Sigma (St. Louis, MO, USA).

Cell culture
HS-SY-II human synovial sarcoma cells were pur-
 chased from Riken BRC (Ibaraki, Japan). The cells were
maintained in Dulbecco’s Modified Eagle Medium
(DMEM) supplemented with 10 % fetal bovine serum
(FBS), 100 units/ml penicillin G potassium salt, and
140 μg/ml streptomycin sulfate at 37 °C in an atmosphere
of 5 % CO2.
Quantitative real-time reverse transcription polymerase
chain reaction (real time RT–PCR)
Total RNA from HS-SY-II cells were extracted using an
RNeasy Mini Kit (Qiagen, Valencia, CA, USA) accord-
ing to the manufacturer’s instructions. The RNA was
transcribed with ReverTra Ace® quantitative PCR RT
Master Mix (Toyobo, Life Science Department, Osaka,
Japan) and amplified using a Mastercycler gradient
(Eppendorf, Hamburg, Germany). PCR products were
detected using FAST SYBR Green Master Mix (Applied
Biosystems, Foster City, CA, USA) with the follow-
ing primer sequences: GAPDH, forward 5′-ATG GAA
ATC CCA TCA CCA TCT T and reverse 5′-CGC CCC
ACT TGA TTT TGG; MMP-3, forward 5′-TCG TTT
CTG CTC ATG AAA TTG and reverse 5′-CGC CCC
ACT TGA TTT TGG; MMP-3, forward 5′-TCG TTT
CTG CTC ATG AAA TTG and reverse 5′-AGC CCC
AGT GTT GGC TGA GTG A. Thermal cycling and
fluorescence detection were performed using a StepOne
Real-Time PCR System (Applied Biosystems). Rela-
tive changes in gene expression were calculated using
the comparative CT method. Total cDNA abundance
between samples was normalized using primers specific
to the GAPDH gene.

Western blotting analysis
Total protein was extracted from the cells using sodium
dodecyl sulfate (SDS) lysis buffer (75 mM Tris–HCl
containing 2 % SDS and 10 % glycerol, pH 6.8) and pro-
tein contents were measured using a DC protein assay
kit (Bio-Rad, Hercules, CA, USA). Equivalent amounts
(30 μg) of total protein were electrophoresed using
e-PAGE® (Atto, Tokyo, Japan), then transferred to poly-
vinylidene difluoride membranes (Merck Millipore,
Billerica, MA, USA). Non-specific binding sites were
blocked by immersing the membrane in Blocking one
(Nakarai Tesque, Kyoto, Japan) for 1 h at room temper-
ature after which the membranes were treated with the
diluted primary antibodies overnight at 4 °C, followed by
horseradish-peroxidase-conjugated secondary antibod-
ies (GE Healthcare, Little Chalfont, UK) for 1 h at room
temperature. After washing the membranes, chemilumi-
nescence was produced using the ECL western blotting
detection reagent or the ECL Prime western blotting
kit (Bio-Rad, Hercules, CA, USA). The blots were quantified by meas-
uring the relative band intensity normalized to changes
in the β-actin intensity using Image Lab™ 2.0 software (Bio-Rad Laboratories).

MMP-3 expression in HS-SY-II cells stimulated with IL-17A
HS-SY-II cells were incubated with IL-17A (10 ng/ml) for 0–24 h. The mRNA level of MMP-3 was measured by real-time RT-PCR. To determine the expression of MMP-3 protein, whole-cell lysates were subjected to SDS-PAGE and western blot analysis, with the blots probed for MMP-3. Equivalent protein aliquots of cell lysates were also analyzed for β-actin.

Immunofluorescence microscopy for IL-17R
HS-SY-II cells were cultured in 4-well Lab-Tek™ parmanox chamber slides (Nagle Nunc International, Rochester, NY, USA) at a density of 1 × 10^4 cells/well. The cells were fixed with 4 % paraformaldehyde for 30 min at 4 °C, and quenched with 0.2 M glycine in phosphate-buffered saline (PBS, pH7.2). Specific binding sites were blocked with 1 % bovine serum albumin in PBS for 30 min at room temperature. The cells were then treated overnight at 4 °C with rabbit polyclonal anti-IL-17R (1:100; Santa Cruz Biotechnology), washed three times with PBS, and treated with Alexa Flour® 488 conjugated goat anti-rabbit IgG (1:100; Molecular Probe, Invitrogen, Carlsbad, CA, USA) for 1 h at room temperature. After washing in PBS, the cells were incubated with Alexa Fluor® 568 Phalloidin (1:150; Molecular Probe, Invitrogen) for 15 min at room temperature, followed by the addition of the nuclear staining agent 4′, 6-diamino-2-phenylidole (DAPI). The cells were visualized using a BZ-9000 fluorescence microscope (Keyence, Osaka, Japan). Images were captured digitally in real time and processed using the BZ-II imaging software (Keyence).

Effect of IL-17R neutralizing antibody on IL-17A-induced MMP-3 expression in HS-SY-II cells
HS-SY-II cells were pre-treated with neutralizing antibody against IL-17R (IL-17R Ab; 0.5-5 μM; Cell Signaling Technology) for 1 h, then incubated with or without IL-17A (10 ng/ml) for 12 h. The mRNA level of MMP-3 was measured by real-time RT-PCR.

MAPKs phosphorylation in HS-SY-II cells stimulated with IL-17A
HS-SY-II cells were stimulated with IL-17A (10 ng/ml) for 0–300 min. Whole-cell lysates were subjected to SDS-PAGE and western blot analysis, with the blots probed for phosphorylated ERK1/2, p38 MAPK, and JNK. Following visualization, the blots were stripped and re-probed for ERK1/2, p38 MAPK, and JNK. Equivalent protein aliquots of cell lysates were also analyzed for β-actin.

Effect of MAPKs inhibitors on IL-17A-induced MMP-3 expression in HS-SY-II cells
HS-SY-II cells were pretreated or not with inhibitors of ERK1/2 (U0126, 10 μM; Calbiochem, Darmstadt, Germany), p38 MAPK (SB239063, 10 μM; Calbiochem), and JNK (SP600125, 10 μM; Calbiochem) for 1 h, followed by incubation with 10 ng/ml IL-17A for 12 h. The mRNA level of MMP-3 was measured by real-time RT-PCR.

c-Fos, c-Jun and IκB-α activation in HS-SY-II cells stimulated with IL-17A
HS-SY-II cells were stimulated with IL-17A (10 ng/ml) for 0–300 min. Whole-cell lysates were subjected to SDS-PAGE and western blot analysis, with the blots probed for phosphorylated c-Fos, c-Jun, and IκB-α. Following visualization, the blots were stripped and re-probed for c-Fos, c-Jun and IκB-α. Equivalent protein aliquots of cell lysates were also analyzed for β-actin.

Effect of MAPKs inhibitors on IL-17A-induced MMP-3 expression in HS-SY-II cells
HS-SY-II cells were cultured with inhibitor of AP-1 (SR11302, 0.1-1 μM; R&D systems) for 1 h, then incubated in the presence or absence of IL-17A (10 ng/ml) for 12 h. The mRNA level of MMP-3 was measured by real-time RT-PCR.

Effect of MAPKs inhibitors on IL-17A-induced c-Fos and c-Jun phosphorylation in HS-SY-II cells
HS-SY-II cells were pretreated or not with 10 μM U0126, 10 μM SB239063, and 10 μM SP600125 for 1 h, followed by incubation with 10 ng/ml IL-17A for 3 h. Whole-cell lysates were subjected to SDS-PAGE and western blot analysis, with the blots probed for phosphorylated c-Fos and c-Jun. Following visualization, the blots were stripped and re-probed for c-Fos and c-Jun. Equivalent protein aliquots of cell lysates were also analyzed for β-actin.

Statistical analysis
All statistical analyses were carried out using statistical software EZR (Easy R, Saitama Medical center, Saitama, Japan: http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmed.html), which is based on the R and R commander [16]. All data were expressed as the mean ± standard deviation (SD) obtained from three independent experiments and analyzed by a pairwise t test with a Holm-Bonferroni correction for multiple comparisons. P < 0.01 were considered to be statistically significant.
Results

Effect of IL-17A-IL-17R interaction on MMP-3 production by HS-SY-II cells

HS-SY-II cells were incubated in the presence or absence of IL-17A. Figure 1a shows the time-dependent enhancement of MMP-3 mRNA by IL-17A. Maximum enhancement, as determined by real time RT-PCR analysis (3.2-fold increase), occurred after 12 h of stimulation. Western blotting showed that the expression of MMP-3 protein was substantially enhanced in HS-SY-II cells treated for 18 h with IL-17A (Fig. 1b). Immunofluorescence analysis revealed the constitutive cell-surface expression of IL-17R by HS-SY-II cells (Fig. 1c). To further examine the role of IL-17R as an IL-17A receptor in enhancement of MMP-3, HS-SY-II cells were pre-treated with IL-17R neutralizing antibody before the addition of IL-17A. The potent induction of MMP-3 mRNA induced by IL-17A was blocked by IL-17R neutralizing antibody in a dose-dependent manner (Fig. 1d).

Effect of ERK1/2, p38 MAPK, and JNK on IL-17A-induced MMP-3 expression

Treatment with IL-17A enhanced the phosphorylation of three components of the MAPks pathway, ERK1/2 (P-ERK1/2), p38 MAPK (P-p38) and JNK (P-JNK), after 15–180 min (Fig. 2a). Thus, we next investigated whether the inhibition of any of these proteins affected the IL-17A-induced expression of MMP-3 in HS-SY-II cells. The cells were pre-treated with specific inhibitors of ERK1/2 (U0126), p38 MAPK (SB239063), and JNK (SP600125), and then stimulated with IL-17A. Real time RT-PCR revealed that the inhibition of ERK1/2 (Fig. 2b), p38 MAPK (Fig. 2c), and JNK (Fig. 2d) abolished the ability of IL-17A to induce MMP-3 mRNA expression.

Effect of AP-1 activation on IL-17A-induced MMP-3 expression

IL-17A stimulation resulted in the phosphorylation of c-Fos (P–c-Fos) and c-Jun (P–c-Jun), the major components of the AP-1 transcription factor complex, in a

![Fig. 1 Effect of IL-17A on MMP-3 production by HS-SY-II cells.](image)
Activation occurred within 180 min (Fig. 3a), whereas IL-17A had no effect on NF-κB activation, as evidenced by phosphorylation (P-IκB-α) or degradation of IκB-α (Fig. 3b). To determine the role of AP-1 activity in IL-17A-induced expression of MMP-3, HS-SY-II cells were pre-treated with AP-1 blocking synthetic peptide (SR11302) prior to their stimulation with IL-17A. Real time RT-PCR revealed that SR11302 pre-treatment effectively blocked IL-17A-induced MMP-3 mRNA expression in a dose-dependent manner (Fig. 3c).

**Fig. 2** Effects of ERK1/2, p38 MAPK, and JNK on IL-17A-induced MMP-3 expression. a Western blot for components of the MAPks pathway in HS-SY-II cells stimulated with IL-17A. b–d Representative the mRNA level of MMP-3 in HS-SY-II cells pretreated with U0126 (b), SB239063 (c), and SP600125 (d), followed by incubation with IL-17A. Data are expressed as the mean ± SD of triplicate cultures. *Indicates statistical significance of $p < 0.01$

Effect of ERK1/2, p38 MAPK, and JNK inhibitors on AP-1 activation mediated by IL-17A

Since the activation of MAPKs and AP-1 was necessary for IL-17A-induced MMP-3 expression in HS-SY-II cells, we asked whether the phosphorylation of ERK1/2, p38 MAPK, and JNK was associated with AP-1 activation. HS-SY-II cells were pre-treated with the inhibitors U0126 (ERK1/2), SB239063 (p38 MAPK), and SP600125 (JNK) and then stimulated with IL-17A. Western blotting revealed that U0126 and SP600125 attenuated the IL-17A-induced phosphorylation of c-Fos and c-Jun (Fig. 4a,
c) whereas SB239063 suppressed the IL-17A-stimulated phosphorylation of c-Fos but not c-Jun (Fig. 4b).

## Discussion

Since previous studies have shown that MMP-3 is capable of stimulating spontaneous tumor development in mammary gland and lung [17–19], knowledge of MMP-3 regulation is of importance for developing therapeutic strategies. On the other hand, the link between inflammation and carcinogenesis is well known that extracellular factors, including cytokines and growth factors, have been implicated in the regulation in different types of tumor cells [20, 21]. Previous study reported that IL-17A and IL-17R interaction enhanced the metastasis of osteosarcoma cells via the expression of VEGF, MMP-9 and CXCR4 [22]. In this study, we have explored the role of IL-17A in the MMP-3 expression of synovial sarcoma cell lines, HS-SY-II.

The results of this study indicated that MMP-3 transcription and protein synthesis are stimulated in HS-SY-II cells in response to IL-17A. The binding of IL-17A to its receptor is thought to mediate the biological effects of IL-17A [23]. IL-17R is an ubiquitous transmembrane glycoprotein which is expressed by several types of cells including tumor cells [24, 25]. In this study, we first confirmed the constitutive cell-surface expression of IL-17R by HS-SY-II cells. We also demonstrated that IL-17R neutralizing antibody remarkably inhibited the effect of IL-17A on MMP-3 expression. These findings suggest that the stimulatory effect of IL-17A on MMP-3 expression is due to its interaction with IL-17R.

After the binding of IL-17A to its receptor, Act1 associates with IL-17R, followed by the activation of downstream signaling molecules including MAPKs [26], important mediators of a variety of physiopathological cellular processes, including cell death, cell survival, proliferation, and migration [27]. In the present study, we found that the ERK1/2, p38 MAPK and JNK pathways were rapidly and transiently activated in cells treated with IL-17A. Moreover, chemical inhibitors of ERK1/2, p38 MAPK, and JNK down-regulated the IL-17A-induced stimulation of MMP-3 mRNA expression. Therefore, we speculated that induction of MMP-3 expression in IL-17A-treated HS-SY-II cells may occur because of activation of MAPKs.

MMP promoters harbor cis-elements that allow the regulation of MMP gene expression by a diverse set of trans-activators, including AP-1 [28]. Various stimuli lead to the activation of c-Fos and c-Jun products, which heterodimerize and bind to AP-1 sites within MMP-3.

![Fig. 3](image-url) Effect of AP-1 activation on IL-17A-induced MMP-3 expression. a, b Western blot for components of the AP-1 transcription factor complex (a) and IκB-α (b) in HS-SY-II cells stimulated with IL-17A. c Representative the mRNA level of MMP-3 in HS-SY-II cells pretreated with SR11302, followed by incubation with IL-17A. Data are expressed as the mean ± SD of triplicate cultures. *Indicates statistical significance of p < 0.01.
gene promoters [29]. Previous studies reported that the phosphorylation of both c-Fos and c-Jun was involved in AP-1 activation [30] and that the translocation of phosphorylated c-Jun from the cytoplasm to the nucleus activated AP-1 [15, 31]. Western blotting revealed that the phosphorylation of c-Fos and c-Jun protein was enhanced by IL-17A. The importance of AP-1 activation in IL-17A-stimulated MMP-3 expression was demonstrated clearly by the dramatic decrease in MMP-3 gene expression induced by SR11302.

It is also well known that AP-1 transactivation, by increasing the abundance of AP-1 components and/or altering the phosphorylation of its subunits c-Fos and c-Jun, is regulated by the MAPKs pathway [32, 33]. We investigated the relationship between MAPKs and AP-1 in HS-SY-II cells stimulated with IL-17A and found that ERK1/2, p38 MAPK, and JNK, all of which are activated by IL-17A, were required for IL-17A-induced c-Fos phosphorylation. In addition, ERK1/2 and JNK activation were shown to be involved in IL-17A-induced c-Jun phosphorylation. These results provide evidence of an important link between MAPKs activation and AP-1 in HS-SY-II cells stimulated with IL-17A, and strongly support our speculation that MAPKs activation...
regulates MMP-3 expression. To further determine the interaction between MAPKs and AP-1 in HS-SY-II cells, silencing of MAPKs expression by siRNA or shRNA will be needed.

It has been reported that the chromosomal translocation t (X; 18) that produces the chimeric gene SYT-SSX at high frequency in synovial sarcomas [34–38] and that the expression of SYT-SSX is considered to play a central role in tumorigenesis [39]. HS-SXII cells genetically possess the SS18-SSX1, whereas other human sarcoma cell lines, SYO-1 and Fuji cells have another type of chimeric gene SS18-SSX2. Further studies are needed to examine the effect of IL-17A/IL-17R interaction on viability, migration and invasion of other human sarcoma cell lines, as well as of primary synovial sarcoma tissue.

These findings might provide mechanistic explanation for the pathogenesis in synovial sarcoma, and suggested that targeting IL-17A/IL-17R pathway was a novel promising strategy to treat patients with synovial sarcoma.

Conclusion
Our preliminary findings provide a valuable insight how IL-17A may contribute to the pathogenesis of synovial sarcoma by stimulating MMP-3 expression. We showed that the interaction of IL-17A with its receptor, IL-17R, stimulates ERK1/2, p38 MAPK, and JNK activation, which in turn initiates the activation of AP-1, followed by an increase in MMP-3 expression.

Abbreviations
IL-17A: interleukin-17A; MMPs: matrix metalloproteinases; ECM: extracellular matrix; MAPK: mitogen-activated protein kinase; ERK1/2: extracellular signal-regulated kinase ½; JNK: c-Jun NH2-terminal kinase; AP-1: activator protein-1; NF-kB: nuclear factor-kappa B; IL-17R: IL-17 receptor; DMEM: Dulbecco’s Modified Eagle Medium; FBS: fetal bovine serum; RT-PCR: reverse transcription polymerase chain reaction; SDS: sodium dodecyl sulfate; PBS: phosphate-buffered saline; DAPI: 4’,6-diamidino-2-phenylindole; SD: standard deviation.

Authors’ contributions
TS, WA, TO, HK and JF performed experiments and evaluated results. TS, DY and WA contributed in drafting manuscript. YI, KT, TN contributed in planning the study concept and performed critical revision of the manuscript. All authors read and approved the final manuscript.

Author details
1 Division of Infections and Molecular Biology, Department of Health Promotion, Kyushu Dental University, 2-6-1 Manazuru, Kokurakita-ku, Kitakyushu, Fukuoka 803-8580, Japan. 2 Division of Oral and Maxillofacial Surgery, Department of Science of Physical Functions, Kyushu Dental University, 2-6-1 Manazuru, Kokurakita-ku, Kitakyushu, Fukuoka 803-8580, Japan. 3 Division of Oral Medicine, Department of Science of Physical Functions, Kyushu Dental University, 2-6-1 Manazuru, Kokurakita-ku, Kitakyushu, Fukuoka 803-8580, Japan.

Acknowledgements
This work was supported by a Grant-in-Aid for Science Research from Japan Society for the Promotion of Science (No. 10507784).

Competing interests
The authors declare that they have no competing interests.

Received: 13 September 2015 Accepted: 27 January 2016 Published online: 05 February 2016

References
1. Mullen JR, Zargas GK. Synovial sarcoma outcome following conservation surgery and radiotherapy. Radiother Oncol. 1994;33:23–30.
2. Sakabe T, Murata H, Konishi E, Takeishi H, Ueda H, Matsui T, Horie N, et al. Evaluation of clinical outcomes and prognostic factors for synovial sarcoma arising from the extremities. Med Sci Monit. 2008;14:305–10.
3. Vendramini-Costa DB, Carvalho JE. Molecular link mechanisms between inflammation and cancer. Curr Pharm Des. 2012;18:3831–52.
4. Kolls JK, Lindén A. Interleukin-17 family members and inflammation. Immunity. 2004;21:467–76.
5. Fosseiz F, Djossou O, Chomarat P, Flores-Romo L, Ait-Yahia S, Maat C, et al. T cell interleukin-17 induces stromal cells to produce proinflammatory and hematopoietic cytokines. J Exp Med. 1996;183:2593–603.
6. Martin-Orozco N, Dong C. The IL-17/L17-23 axis of inflammation in cancer: friend or foe? Curr Opin Investig Drugs. 2009;10:543–9.
7. Ngio SF, Smyth MJ, Teng MW. Does IL-17 suppress tumor growth? Blood. 2010;115:2554–5.
8. Ji Y, Zhang W. Th17 cells: positive or negative role in tumor? Cancer Immunol Immunother. 2010;59:979–87.
9. Ganea E, Trifan M, Laslo AC, Putina G, Cristescu C. Matrix metalloproteinases: useful and deleterious. Biochem Soc Trans. 2007;35:689–91.
10. Benassi MS, Gambieri G, Magagnoli G, Molendini L, Ragazzini P, Merli M. Metalloproteinase expression and prognosis in soft tissue sarcomas. Ann Oncol. 2001;12:75–80.
11. Nelson AR, Fingleton B, Rothenberg ML, Matrisian LM. Matrix metalloproteinases: bioactive activity and clinical implications. J Clin Oncol. 2000;18:1135–49.
12. Woessner JF Jr. Matrix metalloproteinases and their inhibitors in connective tissue remodeling. FASEB J. 1991;5:2145–54.
13. Ye S, Eriksson P, Hamsten A, Kurkinen M, Humphries SE, Henney AM. Progression of coronary atherosclerosis is associated with a common genetic variant of the human stromelysin-1 promoter which results in reduced gene expression. J Biol Chem. 1996;271:13055–60.
14. Cortez DM, Feldman MD, Mummidii S, Valente AJ, Steffensen B, Vincenti M, Barnes JL, Chandrasekar B. IL-17 stimulates MMP-3 expression in primary human cardiac fibroblasts via p38 MAPK- and ERK1/2-dependent C/EBP-beta, NF-kappaB, and AP-1 activation. Am J Physiol Heart Circ Physiol. 2007;293:3356–65.
15. Cheng G, Wei L, Xiurong W, Xiangzhen L, Shiguang Z, Songbin F. 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-kappaB and AP-1 activation. Cell Mol Neurobiol. 2009;29:1161–8.
16. Kanda Y. Investigation of the freely available easy-to-use software EZR for medical statistics. Bone Marrow Transplant. 2013;48:452–8.
17. Sternlicht MD, Lochter A, Sympong CJ, Huey B, Rouger JP, Gray JW, et al. The stromal proteinase MMP9/stromelysin-1 promotes mammary carcinogenesis. Cell. 1999;98:137–46.
18. Stallings-Mann ML, Waldmann J, Zhang Y, Miller E, Gauthier ML, Visscher DW, et al. Matrix metalloproteinase induction of Rac1b, a key effector of lung cancer progression. Sci Transl Med. 2012;4:142ra95.
19. Kessenbrock K, Dijkgraaf GJP, Lawson DA, Littlepage LE, Shahi P, Pieper U, et al. A role for matrix metalloproteinases in regulating mammary stem cell function via the Wnt signaling pathway. Cell Stem Cell. 2013;13:300–13.
20. Ray JM, Stepler-Stevenson WG. The role of matrix metalloproteinases and their inhibitors in tumour invasion, metastasis and angiogenesis. Eur Respir J. 1999;7:2062–72.
21. Apodaca G, Rutka JT, Bouhana K, Berens ME, Giblin JR, Rosenblum ML, et al. Expression of metalloproteinases and metalloproteinase inhibitors by fetal astrocytes and glioma cells. Cancer Res. 1990;50:2322–9.
22. Wang M, Wang L, Ren T, Liu L, Wen Z, IL-17A/IL-17RA interaction promoted metastasis of osteosarcoma cells. Cancer Biol Ther. 2013;14:155–63.
23. Hwang SY, Kim HY. Expression of IL-17 homologs and their receptors in the synovial cells of rheumatoid arthritis patients. Mol Cells. 2005;19:180–4.
24. Yao Z, Spriggs MK, Derry JM, Stockbine L, Park LS, VandenBos T, Zappone JD, Painter SL, Armitage RJ. Molecular characterization of the human interleukin (IL)-17 receptor. Cytokine. 1997;9:794–800.
25. Honorati MC, Cattini L, Facchinetti A. Possible prognostic role of IL-17R in osteosarcoma. J Cancer Res Clin Oncol. 2007;133:1017–21.
26. Iwakura Y, Ishigame H, Saijo S, Nakae S. Functional specialization of interleukin-17 family members. Immunity. 2011;34:149–62.
27. Petrich BG, Wang Y. Stress-activated MAP kinases in cardiac remodeling and heart failure: new insights from transgenic studies. Trends Cardiovasc Med. 2004;14:50–5.
28. Yan C, Boyd DD. Regulation of matrix metalloproteinase gene expression. J Cell Physiol. 2007;211:19–26.
29. Chambers M, Kirkpatrick G, Evans M, Gorski G, Foster S, Borghaei RC. IL-4 inhibition of IL-1 induced matrix metalloproteinase-3 (MMP-3) expression in human fibroblasts involves decreased AP-1 activation via negative crosstalk involving of Jun N-terminal kinase (JNK). Exp Cell Res. 2013;319:1398–408.
30. Yen FL, Tsai MH, Yang CM, Liang CJ, Lin CC, Chiang YC, et al. Curcumin nanoparticles ameliorate ICAM-1 expression in TNF-α-treated lung epithelial cells through p47 (phox) and MAPKs/AP-1 pathways. PLoS ONE. 2013;8:e63845.
31. Dong Y, Liu HD, Zhao R, Yang CZ, Chen XQ, Wang XH, et al. Ischemia activates JNK/c-Jun/AP-1 pathway to up-regulate 14-3-3gamma in astrocyte. J Neurochem. 2009;109:182–8.
32. Gangnuss S, Cowin AJ, Daehn IS, Hatzirodos N, Rothnagel JA, Varelias A, et al. Regulation of MAPK activity, AP-1 transcription factor expression and keratinocyte differentiation in wounded fetal skin. J Invest Dermatol. 2004;122:791–804.
33. Kayahara M, Wang X, Tournier C. Selective regulation of c-jun gene expression by mitogen-activated protein kinases via the 12-o-tetradecanoylphorbol-13-acetate-responsive element and myocyte enhancer factor 2 binding sites. Mol Cell Biol. 2005;25:3784–92.
34. Turc-Carel C, Dal Cin P, Limon J, Rao L, Li FP, Corson KM, et al. Involvement of chromosome X in primary cytogenetic change in human neoplasia: nonrandom translocation in synovial sarcoma. Proc Natl Acad Sci USA. 1987;84:1981–5.
35. Wang-Wuu S, Soukup SW, Lange BJ. Another synovial sarcoma with t(X;18). Cancer Genet Cytoforgenet. 1987;29:179–81.
36. Nojima T, Wang YS, Abe S, Matsumo T, Yamawaki S, Nagashima K. Morphological and cytogenetic studies of a human synovial sarcoma xenotransplanted into nude mice. Acta Pathol Jpn. 1990;40:486–93.
37. Knight JC, Reeves BR, Kearney L, Monaco AP, Lehrach H, Cooper CS. Localization of the synovial sarcoma t(X;18)(p11.2;q11.2) breakpoint by fluorescence in situ hybridization. Hum Mol Genet. 1992;1:633–7.
38. Cooper CS. The molecular and genetic characterization of human soft tissue tumors. Adv Cancer Res. 1993;60:75–120.
39. Hiraga H, Nojima T, Abe S, Sawaya H, Yamashiro K, Yamawaki S, et al. Diagnosis of synovial sarcoma with the reverse transcriptase-polymerase chain reaction: analyses of 84 soft tissue and bone tumors. Diagn Mol Pathol. 1998;7:102–10.