Short Communication

Iranian Journal of Immunology

https://iji.sums.ac.ir

VEGF-A, HGF and bFGF are Involved in IL-17A-Mediated Migration and Capillary-like Vessel Formation of Vascular Endothelial Cells

Muneo Numasaki[1,2], Koyu Ito[3]

[1]Laboratory of Clinical Science and Biomedicine, Faculty of Pharmaceutical Sciences, Josai University, Sakado, [2]Department of Geriatrics and Gerontology, Institute of Development, Aging and Cancer, Tohoku University, [3]Department of Immunology, Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan

ABSTRACT

Background: Interleukin (IL)-17A possesses biological activities to promote vascular endothelial cell migration and microvessel development.

Objective: To clarify which angiogenic factors are involved in IL-17A-modified angiogenesis-related functions of vascular endothelial cells including migration and microtube development or not.

Methods: The potential contribution of various angiogenic stimulators to in vitro angiogenic activities of IL-17A was assessed with both modified Boyden Chemotaxicell chamber assay and in vitro angiogenesis assay.

Results: The addition of a neutralizing antibody (Ab) for hepatocyte growth factor (HGF), basic fibroblast growth factor (bFGF) or vascular endothelial growth factor (VEGF)-A to the upper and lower compartments in a modified Boyden Chemotaxicell chamber significantly attenuated human dermal microvascular endothelial cell (HMVEC) migration elicited by IL-17A. Moreover, IL-17A-induced capillary-like microvessel development in human umbilical vein endothelial cell (HUVEC) and human dermal fibroblast (HDF) co-culture system was significantly impaired by a neutralizing Ab against HGF, bFGF, VEGF-A, cysteine-x-cysteine ligand 8 (CXCL8)/IL-8 or cysteine-x-cysteine (CXC) chemokine receptor (CXCR)-2.

Conclusion: Our findings demonstrate the involvement of HGF, bFGF, VEGF-A and/or CXCL8/IL-8, to various degrees, in migration and microvessel development of vascular endothelial cells mediated by IL-17A.

Keywords: Angiogenesis, IL-17A, Migration, Tube formation, Vascular Endothelial Cells

*Corresponding author:
Muneo Numasaki,
Department of Geriatrics and Gerontology, Institute of Development, Aging and Cancer, Tohoku University, 1-1 Seiryo-machi, Aoba-ku, 980-8575, Japan
Tel/Fax: +81 22 7177182
Email: muneo.numasaki.c2@tohoku.ac.jp

Cite this article as:
Numasaki M, Ito K. VEGF-A, HGF and bFGF are Involved in IL-17A-Mediated Migration and Capillary-like Vessel Formation of Vascular Endothelial Cells. *Iran J Immunol.* 2021; 18(2):103-110, doi: 10.22034/iji.2021.91214.2059.

Received: 2021-05-17
Revised: 2021-06-07
Accepted: 2021-06-12

INTRODUCTION

Interleukin (IL)-17A was identified in 1993, and originally designated cytotoxic T-lymphocyte associated antigen (CTLA)-8 (1). Thereafter, additional five structurally related molecules with similar or different biologic activities, IL-17B, IL-17C, IL-17D, IL-17E/IL-25, and IL-17F, have been discovered (2, 3). Now, these six homologous proteins form a novel IL-17 cytokine family. Among members of this cytokine family, IL-17A, IL-17E, and IL-17F are predominantly secreted by CD4 T helper (Th) subset Th2 or Th17 cells. The other IL-17 family of cytokines IL-17B-D is mainly expressed in non-immune cells. Except IL-17B, which is elaborated as a noncovalently linked homodimer, all IL-17 family members are produced as disulfidelinked homodimers (4).

IL-17A, the prototypical cytokine of this family, plays a crucial role in inflammation, which primarily affects fibroblasts, epithelial and endothelial cells not only to increase production of various kinds of biological mediators including IL-6, cysteine-x-cysteine ligand 1 (CXCL1)/growth-related oncogene (GRO)-α, CXCL8/IL-8, granulocyte-colony stimulating factor (G-CSF), vascular endothelial growth factor (VEGF)-A and hepatocyte growth factor (HGF) but also to enhance adhesion molecule expression including vascular cell adhesion molecule (VCAM)-1 (1, 5-8). On the contrary, the IL-17 receptor family consists of five subunits IL-17 receptor A-E (1, 2).

Our and other laboratories have elucidated the roles of the IL-17 family of cytokines in neovascularization and neovascularization-associated functions of vascular endothelial cells (9-17). Among the members, both IL-17B and IL-17F are angiostatic factors, which suppress vascular endothelial cell migration and/or microtube development (12-14). Conversely, IL-17E is a direct angiogenic mediator, which promotes vascular endothelial cell growth (15, 16). In addition, Lee et al., demonstrated that IL-17C enhances intestinal microvascular endothelial cell tube formation, and induces neovascularization (18). We also demonstrated that IL-17A and IL-17A/F are indirect angiogenic mediators, which promote vascular endothelial cell migration and capillary-like vessel development, but not growth, through the transmembrane IL-17RA in complex with IL-17RC (1).

IL-17A up-regulates expression of a variety of biological molecules with angiogenic properties including HGF, VEGF-A, cysteine-cysteine (CC)-, and CXC-chemokines by various types of cells (7-11). HGF is a growth stimulator, which can exert a proliferative effect on endothelial cells more powerfully than basic fibroblast growth factor (bFGF), and VEGF-A, and induce endothelial cell migration (19). bFGF can also stimulate vascular endothelial cell growth and migration, and promote neovascularization *in vivo* (20). VEGF-A plays a central role in vasculogenesis and angiogenesis, which augments vascular endothelial cell proliferation, migration, and survival (21). Both CC-chemokine CCL2/monocyte chemotactic protein (MCP)-1, and CXC-chemokines with glutamic acid-leucine-arginine (ELR) motif including CXCL1, CXCL5/epithelial neutrophil-activating peptide (ENA)-78, and CXCL8 are involved in angiogenesis and the pathogenesis of atherosclerosis and cancer (22). Especially, CXCL8 induces VEGF expression in vascular endothelial cells and acts as an autocrine growth factor for endothelial cells. Therefore, there is a possibility that the multiple well-established angiogenic molecules might, at least in part, play a role in vascular endothelial cell migration and capillary-like vessel development elicited by IL-17A.

In this study, we elucidated the potential contribution of various angiogenic mediators including HGF, bFGF, VEGF-A, CXC-chemokines with ELR motif, CXC-chemokine receptors CXCR-1, and CXCR-2, and CC-chemokine CCL2 to IL-17A-stimulated vascular endothelial cell migration and/or capillary-like vessel development, and found

that HGF, bFGF, VEGF-A and/or CXCL8 are, to a varying degree, involved in vascular endothelial cell migration and capillary-like vessel development exerted by IL-17A.

MATERIALS AND METHODS

Reagents. Human IL-17A protein, human VEGF-A protein, goat polyclonal antibody (pAb) to human HGF, goat pAb to human bFGF, mouse pAb to human VEGF-A, goat pAb to human CXCL1, goat pAb to human CXCL5, mouse monoclonal Ab (mAb) to human CXCL8, mouse mAb to human CCL2, mouse mAb to human CXCR-1 and mouse mAb to human CXCR-2 were obtained from R&D Systems (Minneapolis, MN, USA).

Cells and cell cultures. Human dermal microvessel endothelial cells (HMVECs) were obtained from KURABO (Osaka, Japan). HuMedia-EB2 containing 5% fetal calf serum (FCS) and several supplements including epidermal growth factor (EGF), hydrocortisone, bFGF, heparin, dbcAMP, gentamycin, and amphotericin-B (all from KURABO) was used as a cultured medium for HMVECs. Angiogenesis assay kit was obtained from KURABO (Osaka, Japan).

Migration assay. Migration assay was carried out as described previously (1). VEGF-A (10 ng/ml) or IL-17A (10 ng/ml) in HuMedia-EB2 containing 1% FCS was added to the wells of a 24-well culture plate (Corning Costar, Corning, NY, USA). Chemotaxicell chambers with the polycarbonate membrane with 5-μm pores were inserted into wells of culture plates. HMVECs were cultured to ~80% confluence. Before the migration assay, cells were starved for 8 hours in HuMedia-EB2 containing 2% FCS. After starvation, cells were harvested, resuspended in HuMedia-EB2 containing 1% FCS, and added to the polycarbonate membrane of Chemotaxicell chambers at 12 x 10^4 cells/cm^2. Thereafter, the culture plates were incubated in a CO_2 incubator for 4.5 hours. In some experiments, a neutralizing Ab for HGF, bFGF, VEGF-A, CXCL1, CXCL5, CXCL8, or CCL2 was added to the medium.

The migratory cells were fixed and stained with Diff-Quick (Harleco, Gibbstown, NJ, USA). Migrated cells were counted in 9 randomly selected microscopic fields (×200) in each chamber.

Capillary-like microvessel development assay. In vitro neovascularization was evaluated as the development of capillary-like microvessel structures of vascular endothelial cells co-cultured with fibroblasts. Briefly, human umbilical vein endothelial cells (HUVECs) were cultured with human dermal fibroblasts (HDFs) in 24-well culture plates in the presence or absence of 10 ng/ml VEGF-A, 50 ng/ml IL-17A, or 50 ng/ml IL-17A plus a neutralizing Ab against HGF, bFGF, VEGF-A, CXCL1, CXCL5, CXCL8, CCL2, CXCR-1, or CXCR-2 for 11 days. Cells were fixed and treated with 1% bovine serum albumin on day 11. Endothelial cells were immunostained with mouse mAb to human CD31. The development of a capillary-like vessel network was evaluated by computerized image analysis of the number of pixels occupied by endothelial microvessels in a total of 15 random areas per well.

Statistical analysis. We first confirmed the normality of the data with the Shapiro-Wilk test. Then, data were analyzed with an unpaired 2-tailed Student t-test using JASP software. P-value<0.05 was considered statistically significant. Data are shown as mean number±standard deviation (SD).

RESULTS

As is consistent with our previous observation that IL-17A significantly enhanced HMVEC migration (9), 50 ng/ml IL-17A markedly promoted HMVEC migration (Figures 1a and b). To clarify which angiogenic mediators are involved in IL-17A-elicited chemotactic response of HMVECs, we used neutralizing Abs against angiogenic stimulators such as VEGF-A. HMVEC migration elicited by

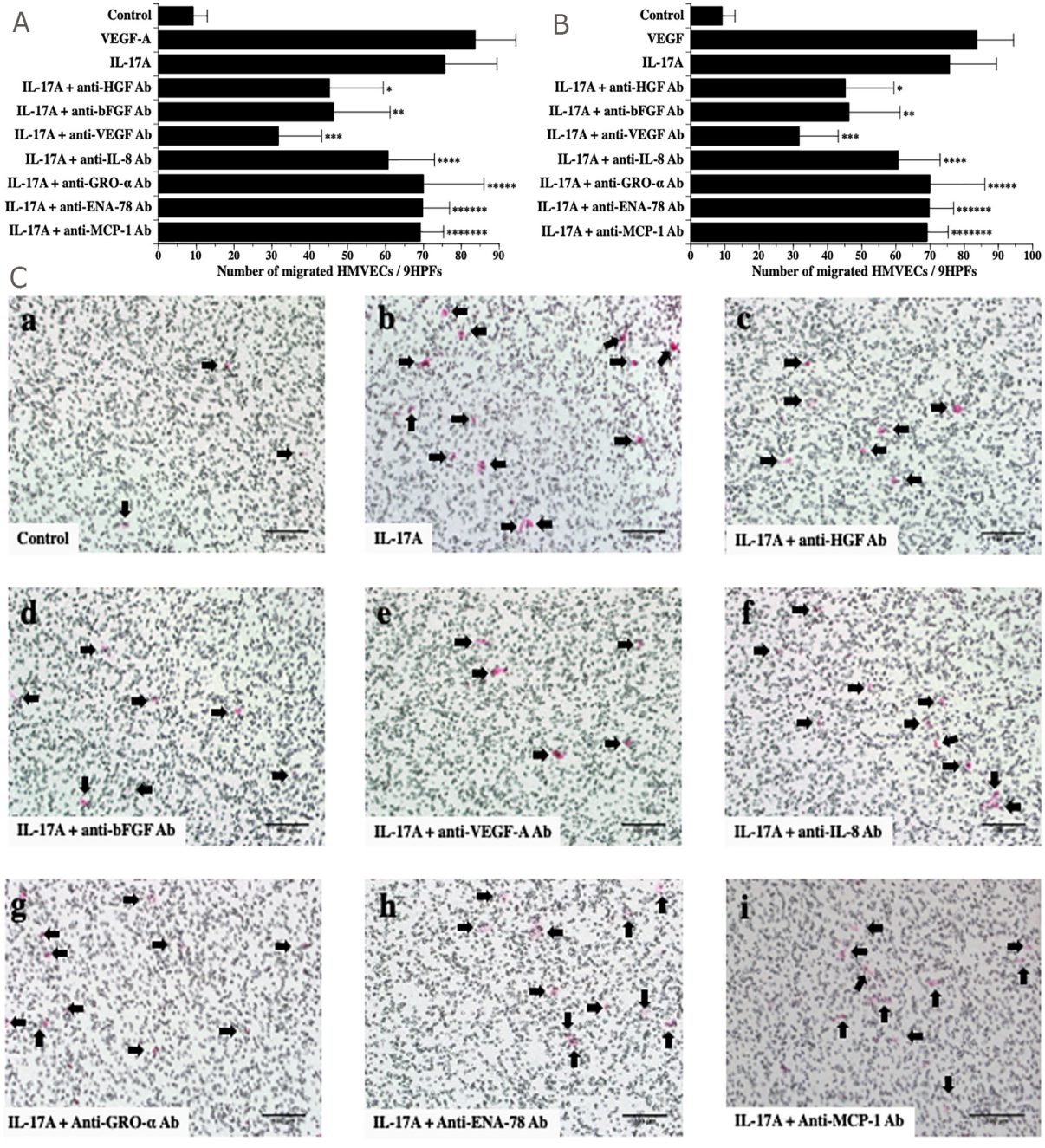

Figure 1. Suppression of IL-17A-elicited HMVEC migration by inhibition of HGF, bFGF or VEGF-A. (A, B) The effect of a neutralizing Ab for HGF, bFGF, VEGF-A, CXCL1, CXCL5, CXCL8 or CCL2 on the migration of HMVECs elicited by IL-17A was assessed using a modified Boyden Chemotaxicell chamber. Inhibition of HGF, bFGF, or VEGF-A significantly reduced HMVEC migration induced by IL-17A. Bars show the mean number of migrated cells±SD per 9 high power fields (HPFs) (×200) (n=3). The data of two independent experiments are shown. (A) IL-17A versus IL-17A+anti-HGF Ab *P<0.02; IL-17A versus IL-17A+anti-bFGF Ab, **P<0.0006; IL-17A versus IL-17A+anti-VEGF-A Ab, ***P<0.0003; IL-17A versus IL-17A+anti-CXCL8 Ab, ****P<0.06; IL-17A versus IL-17A+anti-CXCL1 Ab, *****P<0.6; IL-17A versus IL-17A+anti-CXCL5 Ab, ******P<0.4; IL-17A versus IL-17A+CCL2 Ab, *******P<0.3). (B) IL-17A versus IL-17A+anti-HGF Ab *P<0.03; IL-17A versus IL-17A+anti-bFGF Ab, **P<0.02; IL-17A versus IL-17A+anti-VEGF-A Ab, ***P<0.002; IL-17A versus IL-17A+anti-CXCL8 Ab, ****P<0.06; IL-17A versus IL-17A+anti-CXCL1 Ab, *****P<0.6; IL-17A versus IL-17A+anti-CXCL5 Ab, ******P<0.4; IL-17A versus IL-17A+anti-CCL2 Ab, *******P<0.4). (C) Representative photograph of migrated cells treated with (a) medium alone, (b) IL-17A, (c) IL-17A+anti-HGF Ab, (d) IL-17A+anti-bFGF Ab, (e) IL-17A+anti-VEGF-A Ab, (f) IL-17A+anti-CXCL8 Ab, (g) IL-17A+anti-CXCL5 Ab, (h) IL-17A+anti-CXCL1 Ab, (i) IL-17A+anti-CCL2 Ab (Scale bar=100 μm).

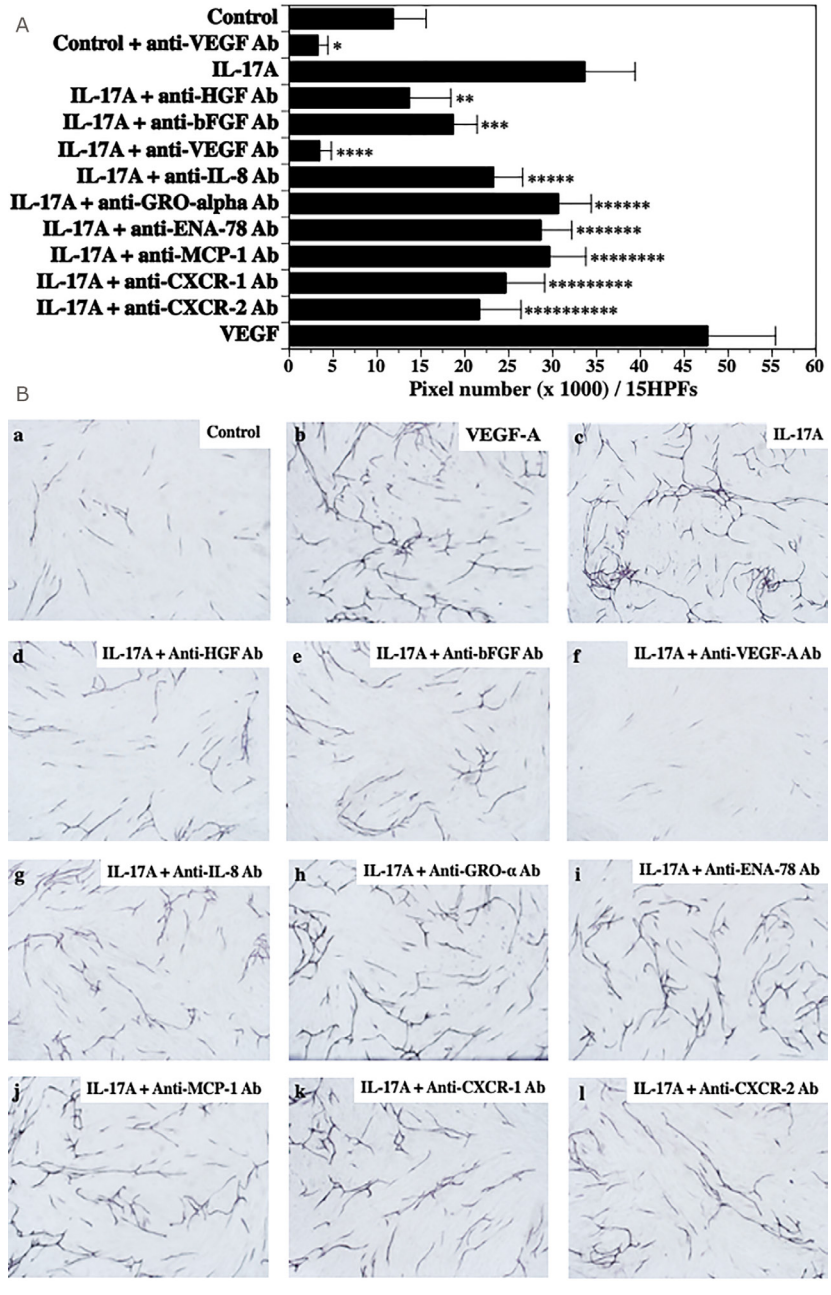

Figure 2. Inhibition of HGF, bFGF, VEGF-A, CXCL8, or CXCR-2 attenuated capillary vessel development elicited by IL-17A in a 2-dimensional co-culture system of HUVECs and HDFs. (A) An in vitro angiogenesis assay was carried out using a 2-dimensional HUVEC and HDF co-culture system. Cells were incubated with or without IL-17A, VEGF-A, or IL-17A+a neutralizing Ab toward HGF, bFGF, VEGF-A, CXCL8, CXCL1, CXCL5, CCL2, CXCR-1 or CXCR-2 for 11 days. (a) Inhibition of HGF, bFGF, VEGF-A, CXCL8, or CXCR-2 significantly impaired the capillary vessel development elicited by IL-17A. Bars show the mean number of pixels±SD per 15 HPFs (×40) (n=3). The data are representative of two independent experiments. (medium versus medium+anti-VEGF-A Ab, *P<0.01; IL-17A versus IL-17A+anti-HGF Ab, **P<0.0008; IL-17A versus IL-17A+anti-bFGF Ab, ***P<0.02; IL-17A versus anti-VEGF-A Ab, ****P<0.0003, IL-17A versus IL-17A+anti-CXCL8 Ab, *****P<0.04, IL-17A versus IL-17A+anti-CXCL1 Ab, ******P<0.8, IL-17A versus IL-17A+anti-CXCL5 Ab, *******P<0.6, IL-17A versus IL-17A+anti-CCL2 Ab, ********P<0.8; IL-17A versus IL-17A+anti-CXCR-1 Ab, *********P<0.07; IL-17A versus IL-17A+anti-CXCR-2 Ab, **********P<0.035). (B) Representative photograph of capillary-like vessels developed in 2-dimensional HUVEC and HDF co-culture system. Capillary vessels induced by (a) medium alone, (b) VEGF-A, (c) IL-17A, (d) IL-17A+anti-HGF Ab, (e) IL-17A+anti-bFGF Ab, (f) IL-17A+anti-VEGF-A Ab, (g) IL-17A+anti-CXCL8 Ab, (h) IL-17A+anti-CXCL1 Ab, (i) IL-17A+anti-CXCL5 Ab, (j) IL-17A+anti-CCL2 Ab, (k) IL-17A+anti-CXCR-1 Ab, or (l) IL-17A+anti-CXCR-2 Ab.

10 ng/ml IL-17A was significantly impaired when a neutralizing Ab against HGF, bFGF, or VEGF-A was added into both upper and lower chambers, respectively (Figures 1a and b). Among the Abs, the inhibitory activity of an Ab specific for VEGF-A was most prominent. Furthermore, neutralizing Abs against HGF and bFGF demonstrated similar inhibitory effects (Figures 1a and b). On the contrary, IL-17A-elicited migration of HMVECs was not significantly diminished by a neutralizing Ab against CXCL1, CXCL5, or CCL2 (Figures 1a and b). Inhibition of CXCL8 slightly reduced the migration mediated by IL-17A, but not statistically significant. These findings demonstrate that migratory activity of HMVECs enhanced by IL-17A is, at least in part, mediated by other angiogenic stimulators such as VEGF-A.

Moreover, we clarified the effect of IL-17A on vascular endothelial cell microvessel development utilizing the Angiogenesis assay kit. Control culture formed capillary-like microvessels to a certain degree as a background (Figure 2a). Ten ng/ml VEGF-A, as a positive control, markedly promoted the development of vessel-like structures (Figure 2a). Fifty ng/ml IL-17A also led to markedly increased formation of vessel-like structures similar to microvasculature bed (Figure 2a).

To delineate the involvement of other angiogenic factors, we evaluated whether neutralizing Abs specific for various angiogenic mediators could diminish IL-17A-mediated capillary-like microvessel development in HUVEC and HDF co-culture systems. Cells were co-cultured with or without IL-17A in the presence or absence of a neutralizing Ab against HGF, bFGF, VEGF-A, CXCL1, CXCL5, CXCL8, CCL2, CXCR-1, or CXCR-2. The control microvessel development was almost completely abolished by the inhibition of VEGF-A, as is consistent with a previous report (14). As shown in Figure 2a, IL-17A-dependent capillary-like microvessel development was significantly reduced when cells were treated with a neutralizing Ab to HGF, bFGF, VEGF-A, CXCL8, or CXCR-2. Especially, a neutralizing Ab specific for VEGF-A almost completely abolished IL-17A-dependent capillary development in this co-culture assay. Based on these experimental findings, we suggest that angiogenic activities of IL-17A might highly depend on VEGF-A.

DISCUSSION

In this study, we elucidated which angiogenic factors are involved in IL-17A-mediated angiogenesis-related functions of vascular endothelial cells such as migration and capillary-like vessel development or not, and found that VEGF-A contributes crucially to IL-17A-elicited vascular endothelial cell migration and microvessel development. In addition, the angiogenic activities of IL-17A also relied, at least in part, on HGF and bFGF. CXCL8 also plays a role in capillary-like microvessel development elicited by IL-17A in HUVEC and HDF co-culture system. These findings demonstrate that IL-17A-elicited vascular endothelial cell migration and capillary-like microvessel development are, at least in part, mediated by other well-established angiogenic mediators such as VEGF-A.

IL-17A-elicited migration of vascular endothelial cells was mainly dependent on a chemotactic effect of VEGF-A, since inhibition of VEGF-A with a neutralizing Ab against VEGF-A significantly impaired the transmembrane migration of HMVECs mediated by IL-17A. Pickens et al. previously demonstrated that inhibition of phosphoinositide 3-kinase (PI3K) with LY294002 significantly suppressed the migration of HMVECs induced by IL-17A (23). Relevant research results have been reported that VEGF-A promoted endothelial cell migration through PI3K signaling (24). PI3K signaling pathway also plays a critical role in VEGF-A production (24). PI3K promotes phosphorylation and activity of AKT, which leads to increased expression

of transcriptional factors such as hypoxia-induced factor-1α (HIF-1α) to augment VEGF production (24, 25). Taken together, there could be a possibility that suppression of IL-17A-mediated migration of HMVECs by PI3K inhibitor is related to the decrease in VEGF-A production elicited by IL-17A.

In this experiment, we utilized HUVEC and HDF co-culture systems as a model of *in vivo* neovascularization. This *in vitro* culture system is more similar to *in vivo* microenvironment than those in the frequently utilized extracellular matrix culture system, and the capillary-like structures formed by vascular endothelial cells are more stable (26). In this co-culture system, even without any added growth factors with angiogenic potential, capillary-like microvessel structures were developed to a certain extent as a control (Figures 2a and b). In our experiments, we found that inhibition of VEGF-A in HUVEC and fibroblast co-culture markedly attenuated basal tube development. Moreover, we found that IL-17A-induced capillary-like microvessel development was also markedly impaired by inhibition of VEGF-A using a neutralizing Ab in this co-culture system. In addition, to a lesser extent, inhibition of HGF or bFGF significantly diminished IL-17A-induced capillary-like microvessel development. Unlike migration assay, inhibition of CXCL8 or blocking of CXCR-2, the receptor for CXCL8, significantly reduced IL-17A-induced capillary-like microvessel development. Taken together, besides possible direct actions on vascular endothelial cells, IL-17A could promote capillary-like vessel development indirectly via other angiogenic molecules such as HGF, bFGF, VEGF-A, and CXCL8.

CONCLUSION

IL-17A-elicited HMVEC migration is, at least in part, mediated by HGF, bFGF, and VEGF-A. Moreover, endothelial capillary vessel development mediated by IL-17A in a 2-dimensional vascular endothelial cell and fibroblast co-culture system depends, to a large degree, on VEGF-A. To a lesser extent, HGF, bFGF, and CXCL8 are also involved. Further analysis would be necessary to understand the detailed molecular mechanisms for IL-17A to promote endothelial cell migration and capillary-like microvessel development.

ACKNOWLEDGMENTS

The authors are grateful to Dr. Jun Kobayashi and Dr. Keizo Kasono for their constructive discussions and kind help.

Conflicts of Interest: None declared.

REFERENCES

1. Yao Z, Fanslow WC, Seldin MF, Rousseau AM, Painter SL, Comeau MR, et al. Herpesvirus Saimiri encodes a new cytokine, IL-17, which binds to a novel cytokine receptor. Immunity.1995; 3:811–21.
2. Kolls JK, Lindén A. Interleukin-17 family members and inflammation. Immunity. 2004; 21(4): 467-76.
3. McGeachy MJ, Cua DJ, Gaffen SL. The IL-17 Family of Cytokines in Health and Disease. Immunity. 2019; 50(4): 892-906.
4. Li H, Chen J, Huang A, Stinson J, Heldens S, Foster J, et al. Cloning and characterization of IL-17B and IL-17C, two new members of the IL-17 cytokine family. Proc Natl Acad Sci U S A. 2000; 97(2): 773-8.
5. Yao Z, Painter SL, Fanslow WC, Ulrich D, Macduff BM, Spriggs MK, at al. Human IL-17: a novel cytokine derived from T cells. J Immunol. 1995; 155(12): 5483-6.
6. Catar RA, Chen L, Cuff SM, Kift-Morgan A, Eberl M, Kettritz R, et al. Control of neutrophil influx during peritonitis by transcriptional cross-regulation of chemokine CXCL1 by IL-17 and IFN-gamma. J Pathol. 2020; 251(2): 175-86.
7. Numasaki M, Lotze MT, Sasaki H. Interleukin-17 augments tumor necrosis factor-alpha-induced elaboration of proangiogenic factors from fibroblasts. Immunol Lett. 2004; 93(1):39-43.
8. Numasaki M, Takahashi H, Tomioka Y, Sasaki H. Regulatory roles of IL-17 and IL-17F in G-CSF production by lung microvascular endothelial

cells stimulated with IL-1beta and/or TNF-alpha. Immunol Lett. 2004; 95:97-104.
9. Numasaki M, Fukushi J, Ono M, Narula SK, Zavodny PJ, Kudo T, et al. Interleukin-17 promotes angiogenesis and tumor growth. Blood. 2003; 101:2620-7.
10. Numasaki M, Watanabe M, Suzuki T, Takahashi H, Nakamura A, McAllister F, et al. IL-17 enhances the net angiogenic activity and in vivo growth of human non-small cell lung cancer in SCID mice through promoting CXCR-2-dependent angiogenesis. J Immunol. 2011; 175:6177-89.
11. Takahashi H, Numasaki M, Lotze MT, Sasaki H. Interleukin-17 enhances bFGF-, HGF- and VEGF-induced growth of vascular endothelial cells. Immunol Lett. 2005; 98:189-93.
12. Starnes T, Robertson MJ, Sledge G, Kelich S, Nakshatri H, Broxmeyer HE, et al. IL-17F, a novel cytokine selectively expressed in activated T cells and monocytes, regulates angiogenesis and endothelial cell cytokine production. J Immunol. 2001; 167:4137-40.
13. Almahmoudi R, Salem A, Hadler-Olsen E, Svineng G, Salo T, Al-Samadi A. The effect of interleukin-17F on vasculogenic mimicry in oral tongue squamous cell carcinoma. Cancer Sci. 2021; 112(6): 2223-32.
14. Gelaleti GB, Borin TF, Maschio-Signorini LB, Moschetta MG, Jardim-Perassi BV, Calvinho GB, et al. Efficacy of melatonin, IL-25 and siIL-17B in tumorigenesis-associated properties of breast cancer cell lines. Life Sci. 2017; 183: 98-109.
15. Corrigan CJ, Wang W, Meng Q, Fang C, Wu H, Reay V, et al. T-helper cell type 2 (Th2) memory T cell-potentiating cytokine IL-25 has the potential to promote angiogenesis in asthma. Proc Natl Acad Sci. U S A. 2011; 108:1579-84.
16. Huang P, Li Y, Lv Z, Wang J, Zhang Q, Yao X, et al. Comprehensive attenuation of IL-25-induced airway hyperresponsiveness, inflammation, and remodeling by the PI3K inhibitor LY294002. Respirology. 2017; 22(1): 78-85.
17. Numasaki M, Tsukamoto H, Tomioka Y, Nishioka Y, Ohrui T. A Heterodimeric cytokine, consisting of IL-17A and IL-17F, promotes migration and capillary-like tube formation of human vascular endothelial cells. Tohoku J Exp Med. 2016; 240:47-56.
18. Lee Y, Kim SJ, Choo J, Heo G, Yoo JW, Jung Y, et al. miR-23a-3p is a Key Regulator of IL-17C-Induced Tumor Angiogenesis in Colorectal Cancer. Cells. 2020; 9(6): 1363.
19. Wang LS, Wang H, Zhang QL, Yang ZJ, Kong FX, Wu CT. Hepatocyte Growth Factor Gene Therapy for Ischemic Diseases. Hum Gene Ther. 2018; 29(4): 413-23.
20. Yu P, Wilhelm K, Dubrac A, Tung JK, Alves TC, Fang JS, et al. FGF-dependent metabolic control of vascular development. Nature. 2017; 545(7653): 224-8.
21. Apte RS, Chen DS, Ferrara N. VEGF in Signaling and Disease: Beyond Discovery and Development. Cell. 2019; 176(6): 1248-64.
22. Fousek K, Horn LA, Palena C. Interleukin-8: A chemokine at the intersection of cancer plasticity, angiogenesis, and immune suppression. Pharmacol Ther. 2021; 219: 107692.
23. Pickens SR, Volin MV, Mandelin AM 2nd, Kolls JK, Pope RM, Shahrara S. IL-17 contributes to angiogenesis in rheumatoid arthritis. J Immunol. 2010; 184: 3233-41.
24. Hayashi H, Nakagami H, Takami Y, Koriyama H, Mori M, Tamai K, et al. FHL-2 suppresses VEGF-induced phosphatidylinositol 3-kinase/Akt activation via interaction with sphingosine kinase-1. Arterioscler Thromb Vasc Biol. 2009; 29: 909-14.
25. Choi YK, Kim CK, Lee H, Jeoung D, Ha KS, et al. Carbon monoxide promotes VEGF expression by increasing HIF-1alpha protein level via two distinct mechanisms, translational activation, and stabilization of HIF-1alpha protein. J Biol Chem. 2010; 285(42): 32116-25.
26. Saito M, Hamasaki M, Shibuya M. Induction of tube formation by angiopoietin-1 in endothelial cell/fibroblast co-culture is dependent on endogenous VEGF. Cancer Sci. 2003; 94: 782-90.