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ORIGINAL ARTICLE

# CD147 participates in the activation function of circulating angiogenic T cells in patients with rheumatoid arthritis

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## Abstract

**Objective** Rheumatoid arthritis (RA) is a chronic inflammatory and angiogenic disease. This study aimed to explore the profiles of circulating angiogenic T cells (Tang cells) and the role of CD147 in Tang cell activation function in RA.

**Methods** Samples were obtained from patients with RA and health controls (HC). Then, Tang cells were quantified by flow cytometry (FCM) in the samples from 87 patients with RA and 29 HC. Tang cells were purified by magnetic cell sorting in cell culture–conditioned media, and the phosphorylation signals were determined by FCM. In addition, cytokine levels were assessed by enzyme-linked immunosorbent assay.

**Results** The percentage of circulating Tang cells increased and positively correlated with the number of endothelial progenitor cells in the RA group. Further, the percentage of Tang cells was closely related to disease activity, autoantibody positivity, and proangiogenic cytokine levels. Meanwhile, the expression of CD147 on Tang cells increased in patients with RA. CD147 participated in the Akt phosphorylation and VEGF level of the activated Tang cells.

**Conclusions** CD147 may play a critical role in regulating VEGF production of activated Tang cells by affecting Akt signaling, which in turn may serve an essential function in angiogenesis and RA pathogenesis.

**Keywords** CD147 · Circulating angiogenic T cells · Rheumatoid arthritis

## Introduction

Rheumatoid arthritis (RA) is a common autoimmune disease with main features including persistent synovitis, systemic inflammation, and progressive destruction of cartilage and bone, which is characterized by angiogenesis and infiltration of inflammatory cells. Although the precise etiology and pathogenesis of RA have not been completely identified, angiogenesis is implicated in the pathological process of RA [1, 2].

In RA, angiogenesis is an important feature of histologic changes in new blood vessels formed with synovial hyperplasia and inflammatory cell infiltration, supporting pannus growth and development of RA [2, 3]. The balance of angiogenesis regulation is broken in RA joints, and the dominated regulatory factors promote the formation of blood vessels. Excessive migration of circulating leukocytes into RA-inflamed joints necessitates the formation of new vessels to provide nutrients and oxygen to hypertrophic joints [2].

Recently, experiments in vitro and in vivo showed that circulating angiogenic T (Tang) cells, a specific T cell subset, defined as $CD3^+CD31^+CXCR4^+$, were required for colony formation and differentiation of early endothelial progenitor cells (EPC) and supposed to stimulate the endothelial cells by secreting angiogenic cytokines, including VEGF, IL-8, and G-CSF [4]. Tang cells enhanced the function of endothelial cells and their proliferation, suggesting that they may serve as a biomarker of cardiovascular risk [4]. Furthermore, it has been reported that the entry of T cells from the blood into the inflammatory process ensures the maintenance and progress of RA angiogenesis [5].

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CD147 is a protein membrane surface molecule expressed on the surface of immune cells [6]. Studies have reported that CD147 participates in thymocyte expansion, T cell development, and T cell activation [7]. Also, CD147 may have a crucial role in the process of angiogenesis. The levels of CD147 significantly positively correlated with VEGF and HIF-1 levels, as well as with vascular density, in RA synovium [8].

Therefore, this study aimed to analyze the profiles of circulating Tang cells and EPC in patients with RA and their potential relation to clinical features. Further, this study explored the role of CD147 on Tang cells in patients with RA.

## Materials and methods

### Participants

Eighty-seven patients with RA and 29 healthy controls (HC) were enrolled from the Department of Clinical Immunology, Xijing Hospital, Fourth Military Medical University. The baseline characteristics of participants are summarized in Table 1. All patients with RA fulfilled the 1987 revised American College of Rheumatology criteria and 2010 ACR/EULAR classification criteria [9, 10]. Routine clinical examinations, including 28-joint Disease Activity Score-Erythrocyte Sedimentation Rate (DAS28) calculation, were performed during the patients' visit. Then, patients' clinical records were exhaustively revised to obtain data on previous therapies, traditional cardiovascular risk factors (hypertension, diabetes, dyslipidemia, obesity, and smoking), and previous medical histories. Simultaneously, 29 HC were without any pathology or treatment. The study was approved by the ethical standards committee of Xijing Hospital, and all the participants gave written informed consent.

### Flow cytometry analysis

Peripheral blood mononuclear cells (PBMCs) and synovial fluid mononuclear cells (SFMCs) were isolated by Ficoll-Paque density gradient centrifugation (GE Healthcare, Pittsburgh, PA, USA). The samples were stained with the following monoclonal antibodies: peridin chlorophyll protein (Percp)-conjugated CD3, phycoerythrin (PE)-conjugated CD31, allophycocyanin (APC)-conjugated CXCR4, fluorescein isothiocyanate (FITC)-conjugated CD34, APC-conjugated CD133, PE-conjugated VEGFR2, FITC-conjugated CD147, PE-conjugated CD147, or with isotype-matched control IgG (all from BD Biosciences, San Diego, CA, USA). A minimum of 20,000 events per tube were acquired using a FACSCalibur flow cytometer (BD Biosciences) and analyzed using CellQuest software (BD Bioscience) and FlowJo 7.6.1 software (Tree Star).

**Table 1** Clinical and laboratory characteristics of RA patients and HC

| Characteristics | HC | RA |
|---|---|---|
| Number of patients | 29 | 87 |
| Female sex, *n* (%) | 23(79.32) | 70 (80.46) |
| Age at sampling, median (IQR),years | 40.6(18–68) | 48.3 (16–80) |
| Disease duration, median (IQR),years | NA | 6.7 (0.1–30) |
| Clinical features | | |
| DAS28, median (IQR) | NA | 4.6 (1.0–8.7) |
| ESR (mm/h), median (IQR) | NA | 43.5 (4.0–103) |
| CRP (mg/dL), median (IQR) | NA | 2.6 (0.1–24) |
| Positivity of RF, *n* (%) | NA | 65 (81.3) |
| Positivity of anti-ccp, *n* (%) | NA | 62 (77.5) |
| Interstitial lung disease, *n* (%) | NA | 9 (10.3) |
| Kidney disease, *n* (%) | NA | 6 (6.9) |
| Heart disease, *n* (%) | NA | 4 (4.6) |
| Nervous system disease, *n* (%) | NA | 3 (3.4) |
| Digestive system disease, *n* (%) | NA | 10 (11.5) |
| Skin lesions, *n* (%) | NA | 2 (2.3) |
| Cardiovascular risk factors, *n* (%) | | |
| Smoking, *n* (%) | 2(6.9) | 6 (6.9) |
| Hypertension, *n* (%) | 0(0) | 4 (4.6) |
| Diabetes mellitus, *n* (%) | 0(0) | 2 (2.3) |
| Hyperlipidemia, *n* (%) | 0(0) | 5 (5.7) |
| Treatment, *n* (%) | | |
| NSAIDs | NA | 70 (80.5) |
| DMARDs[a] | NA | 68 (78.2) |
| Glucocorticoids | NA | 15 (28.7) |
| Immunosuppresive durgs[b] | NA | 12 (13.8) |
| Tumor necrosis factor-alphainhibitors[c] | NA | 18 (20.7) |

*RA*, rheumatoid arthritis; *HC*, healthy controls; *IQR*, interquartile range; *n*, number; *DAS28*, RA disease activity score; *ESR*, erythrocyte sedimentation rate; *CRP*, C-reactive protein; *RF*, rheumatoid factor; *anti-ccp*, anti-cyclic citrulline polypeptide; *NSAIDs*, non-steroidal anti-inflammatory drugs; *NA*, not applicable; *DMARDs*, disease-modifying antirheumatic drugs

[a] methotrexate, leflunomide, hydroxychloroquine; [b] Azathioprine, mycophenolate mofetil; [c] Tumor necrosis factor-alphainhibitors: etanercept, infliximab, adalimumab

### Cytokine analysis

According to the manufacturer's instructions, the plasmatic levels of VEGF, IL-8, and G-CSF were measured by enzyme-linked immunosorbent assay (ELISA) kit (eBioscience, San Diego, CA, USA).

### Cell isolation

PBMCs were isolated from sodium-heparinized whole blood by Ficoll-Paque Plus density gradient centrifugation (GE Healthcare, PA, USA). Similar to a previous

work [11], SF samples were treated with 40 μg/mL hyaluronidase (Sigma–Aldrich, MO, USA) for 30 min at 37 °C, and the cells were then washed with phosphate-buffered saline (PBS) and subjected to density gradient centrifugation. Tang cells were purified by magnetic cell sorting (Miltenyi Biotec) through standard procedures. Briefly, $CD3^+$ T cells were isolated using a negative depletion kit. Then, $CD31^+$ cells were positively selected via CD31 microbeads (> 90% pure). Ultimately, the magnetic separation purity of $CD3^+$ $CD31^+$ Tang cells was > 90%.

### Cell activation and phosphorylation level assay

Tang cells were incubated with anti-CD147 mAb (20 μg/mL) and isotype-matched control antibody (20 μg/mL) for 1 h in 37 °C. They were stimulated with immobilized anti-CD3mAb (plates coated with 5 μg/mL) and soluble anti-CD28mAb (1 μg/mL) for 10 min at 37 °C. Then, the cells were fixed with 2% paraformaldehyde and permeabilized with 90% methanol. Surface and intracellular staining with antibodies included anti-CD3-percp and anti-pAkt (T308)-PE (all from BD Bioscience). The cells were washed and suspended in PBS and analyzed by flow cytometry.

### Statistical analysis

Differences between groups were determined using the nonparametric Mann–Whitney *U* test. Paired samples were compared using a Wilcoxon matched pairs signed rank sum test. Correlations were evaluated by nonparametric Spearman's rank correlation analysis. For all tests, a $p$ value < 0.05 was considered statistically significant. Data were analyzed using the SPSS 17.0 software (SPSS, IL, USA).

## Results

### Percentage of Tang cells increased in patients with RA

First, the percentage of Tang cells ($CD31^+CXCR4^+$ cells in $CD3^+$ T cells) from HC and patients with RA was detected by flow cytometry (Fig. 1a). The peripheral blood from patients with RA contained more Tang cells compared with HC (Fig. 1b). Also, the percentage of Tang cells was greater in synovial fluid (SF) than in peripheral blood (PB) (Fig. 1c). Additionally, the percentage of circulating Tang cells decreased in DAS28 < 2.6 group compared with DAS28 > 5.1 group (Fig. 1d). And the Tang cell percentage was positively

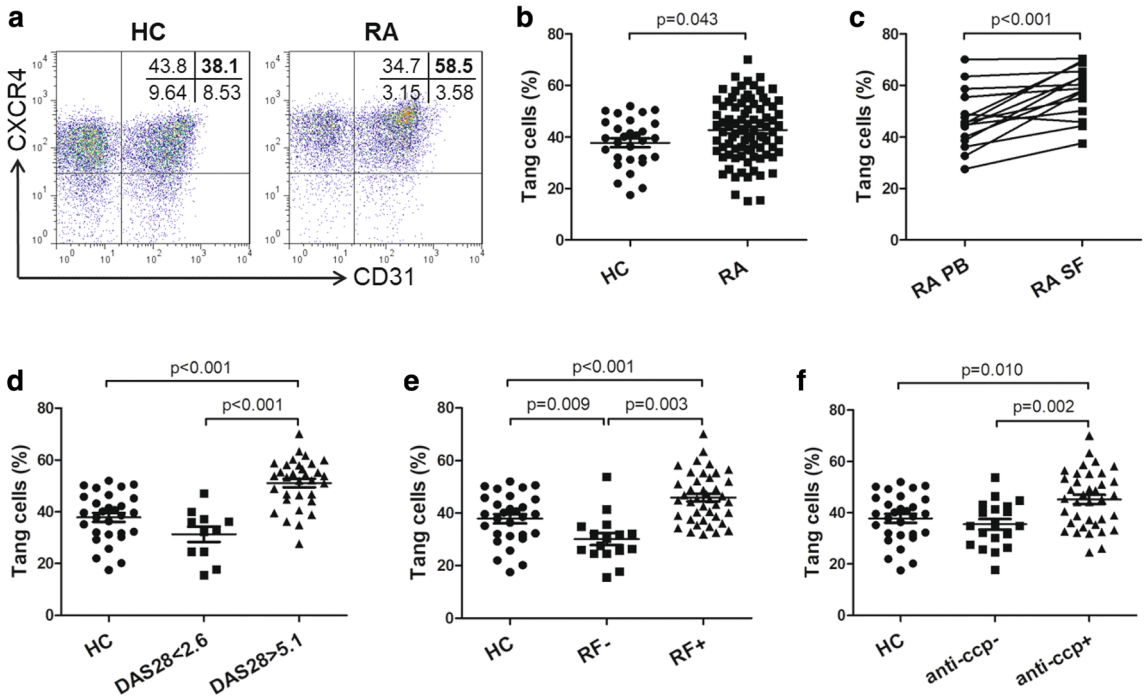


**Fig. 1** Percentage of Tang cells in RA patients and HC. **a** The representative examples of flow cytometric dot plots of circulating Tang cells ($CD31^+CXCR4^+$ cells in $CD3^+$ T cells) obtained from HC and RA groups. **b** Percentage of Tang cells in peripheral blood (PB) of RA patients ($n = 87$) and HC ($n = 29$). **c** Percentage of Tang cells in synovial fluid (SF) and paired PB of RA patients ($n = 15$). **d** Percentage of circulating Tang cells in HC and RA patients with low disease status (DAS28 < 2.6) and active disease status (DAS28 > 5.1). **e**, **f** Percentage of Tang cells in HC and RA patients with or without RF and anti-ccp autoantibodies

correlated with the DAS28 (Table 2). Patients with RA were grouped based on their RF autoantibody and anti-ccp autoantibody statuses (shown as $RF^-$, $RF^+$, anti-$ccp^-$, and anti-$ccp^+$). The percentage of circulating Tang cells was significantly increased in $RF^+$ and anti-$ccp^+$ groups compared with their negative counterparts and HC (Fig. 1e, f).

### VEGF level increased and correlated with the percentage of Tang cells in patients with RA

In this study, several proangiogenic cytokines associated with the differentiation and colony formation of EPC were detected, including G-CSF, IL-8, and VEGF. The concentration of plasmatic G-CSF, IL-8, and VEGF remarkably increased in patients with RA compared with HC (Fig. 2). Furthermore, the study assessed whether the presence of proangiogenic cytokines in RA correlated with the percentage of Tang cells. As shown in Table 2, the VEGF level positively correlated with the Tang cell percentage in patients with RA.

### EPC percentage increased and correlated with Tang cell percentage in patients with RA

The percentage of EPC ($CD133^+VEGFR2^+$ cells in $CD34^+$ cells) in HC and patients with RA was evaluated by flow cytometry. As shown in Fig. 3a and b, the percentage of circulating EPC was significantly higher in patients with RA than in HC. Further, the percentage of EPC in the RA SF significantly increased compared with HC PB and paired RA PB (Fig. 3c). Also, the percentage of EPC positively correlated with Tang cell percentage in HC PB, RA PB, and SF (Fig. 3d–f). In addition, EPC percentage was positively correlated with the DAS28 and VEGF level in patients with RA (Table 2).

### CD147 participated in the activation function of Tang cells in patients with RA

In the following tests, CD147 expression was detected on Tang cells. CD147 was more highly expressed on Tang cells in patients with RA compared with HC (Fig. 4a, b). Therefore, cell culture assays were performed to detect whether CD147 could affect the function of Tang cells. The data showed that the mean fluorescence intensity of CD147 was significantly upregulated when isolated Tang cells were activated with anti-CD3/CD28 mAb (Fig. 4c). Meanwhile, the levels of VEGF in the activated cell supernatant induced by CD3/CD28 activation were partly suppressed by anti-CD147 mAb compared with isotype control mAb (Fig. 4d). Further, CD3/CD28 co-stimulation resulted in a strong phosphorylation of pAkt in Tang cells (T308). However, the levels of pAkt (T308) were significantly reduced by anti-CD147 mAb compared with isotype control mAb (Fig. 4e).

**Table 2** Correlations between the Tang and EPC cell percentages and the DAS28 and concentration of angiogenesis cytokines in RA patients

| | Tang (%) | | EPC (%) | |
|---|---|---|---|---|
| | *r* | *p* | *r* | *p* |
| DAS28 | 0.661 | *<0.001* | 0.288 | *0.008* |
| G-CSF (pg/mL) | 0.131 | 0.225 | 0.106 | 0.328 |
| IL-8 (pg/mL) | 0.181 | 0.093 | 0.127 | 0.239 |
| VEGF (pg/mL) | 0.318 | *0.003* | 0.293 | *0.006* |

Italicize entries indicate significant correlation between the two groups

## Discussion

Circulating Tang cells may regulate EPC functions and promote the formation of new blood vessels and endothelial repair through stimulating these functions [4]. Therefore, in this study, the percentages of Tang cells and EPC were comprehensively assessed by flow cytometry in HC and patients with RA. The data showed that the circulating Tang cell percentage positively correlated with EPC percentage in HC and patients with RA. Also, the percentage of Tang cells from RA SF significantly correlated with EPC percentage. Consequently, these findings were in line with the idea that Tang cells were critical in the formation of EPC colonies, enhancing EPC differentiation and angiogenesis [4]. It also indicated that angiogenic response might act on EPC and Tang cell populations in patients with RA.

However, discrepant results have been reported with regard to the circulating Tang cell percentage in RA. Suarez et al. [12, 13] showed that the percentage of Tang cells was only about 8% and decreased in patients with RA compared with HC. In agreement with the data of a recent study and a previous study on patients with SLE [14], this study found that the Tang cell percentage was about 30–40% in HC and patients with RA. In fact, the populations in this study and the study by Kim et al. [4] comprised Asians, whereas the study by Suarez et al. [12, 13] recruited people from Europe. Therefore, it was speculated that the discrepancies in Tang cell percentage might be due to varied ethnicity. Hence, further investigations should be conducted on patients with RA from more races and research institutions to confirm the findings of the present study.

Similar to a recent study on patients with systemic sclerosis [15], the most important finding of this study was that the Tang cell percentage increased in patients with RA compared with HC. In addition, the percentage of Tang cells was higher in RA SF than in PB. The autoantibody status is associated with vasculopathy and cardiovascular risk in autoimmunity diseases, including RA [16, 17]. In the present study, the Tang cell percentage significantly increased in patients with RA having positive antibodies, compared with their negative

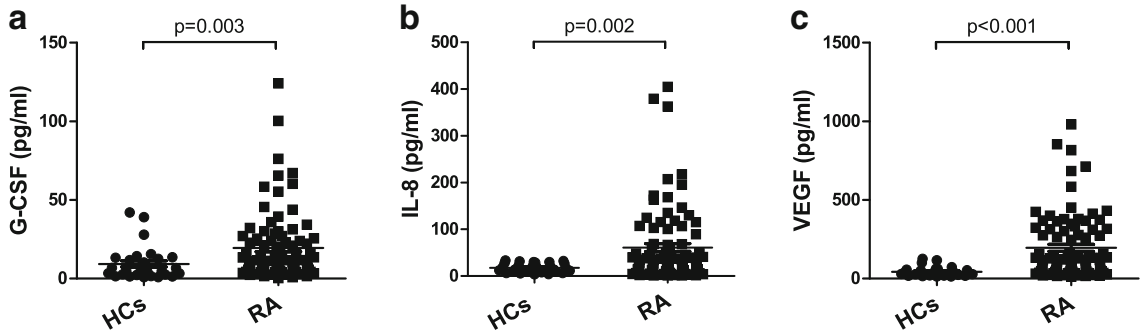


**Fig. 2** Plasmatic levels of proangiogenic cytokines in RA patients and HC. **a** G-CSF, **b** IL-8, and **c**)VEGF levels were detected in plasmatic of RA patients ($n = 87$) and HC ($n = 29$)

counterparts and HC. Meanwhile, the percentage of Tang and EPC in peripheral blood of RA patients was closely and positively correlated with disease activity. Therefore, these data indicated the involvement of Tang cells in the pathological process of angiogenesis in the inflammatory site of RA, suggesting that autoantibody (RF and anti-ccp) positivity might isolate a subset of patients with RA associated with endothelial damage and at a higher risk of vasculopathy.

CD147 increased in the activated T cells [18, 19]. Also, CD147 was involved in angiogenesis in melanoma [20], hepatocellular carcinoma [21], cervical squamous cell carcinoma [22], and RA [23]. This novel study identified the association between CD147 expression and Tang cell percentage. Indeed, the expression of CD147 on Tang cells increased in patients with RA. VEGF, also known as the most potent proangiogenic growth factor, acted as a growth stimulus and a survival factor for endothelial cells [24]. VEGF and its receptor were expressed in the synovial tissue of inflamed joints [25]. Accordingly, the data showed that the levels of plasmatic G-CSF, IL-8, and VEGF increased in patients with RA compared with HC. Furthermore, the VEGF level significantly correlated with the percentage of EPC and Tang cell subsets in RA.

CD147 can promote angiogenesis by regulating VEGF in RA [8], and Tang cells are supposed to facilitate early EPC differentiation and stimulate the local resident endothelial cells by producing VEGF [4]. Therefore, this study investigated whether CD147 directly participated in the production of VEGF in Tang cells. The CD147 expression on the purified Tang cells further increased after activation, and the anti-

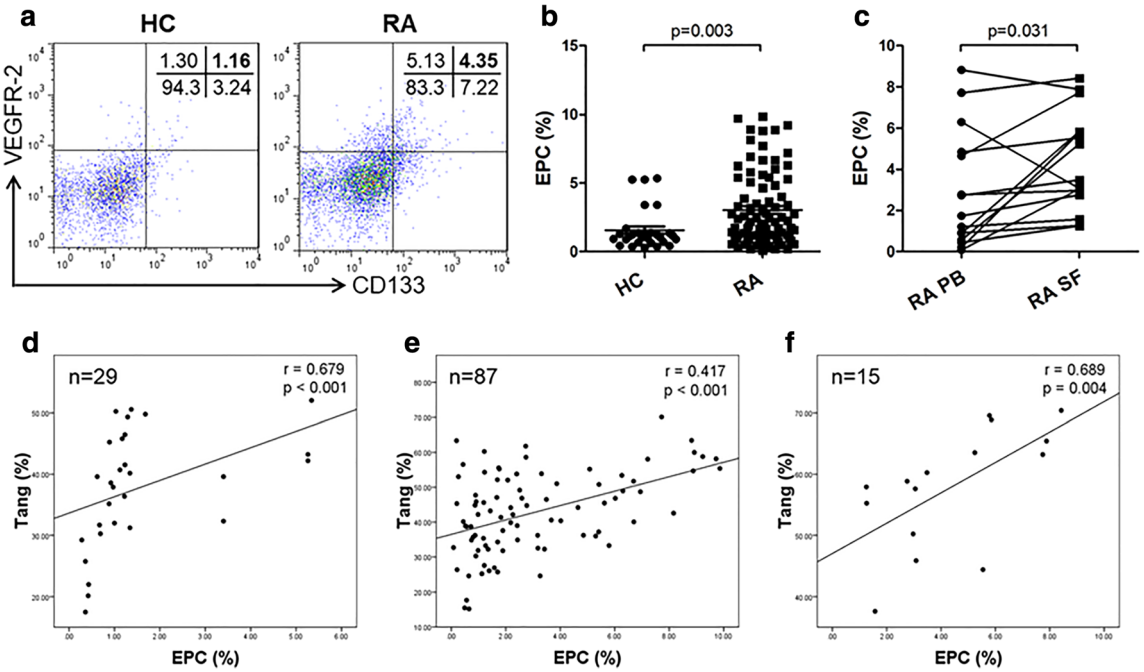


**Fig. 3** Percentage of EPC in RA patients and HC. **a** Flow cytometric dot plots of circulating EPC cells ($CD133^+$ $VEGFR\text{-}2^+$ cells in $CD34^+$ cells) obtained from one representative HC and RA patient. **b** Percentage of EPC in peripheral blood (PB) of RA patients ($n = 87$) and HC ($n = 29$). **c** Percentage of EPC in synovial fluid (SF) and paired PB of RA patients ($n = 15$). **d**–**f** Correlations between the EPC and Tang cell percentages in HC PB (**d**), RA PB (**e**), or RA SF (**f**)

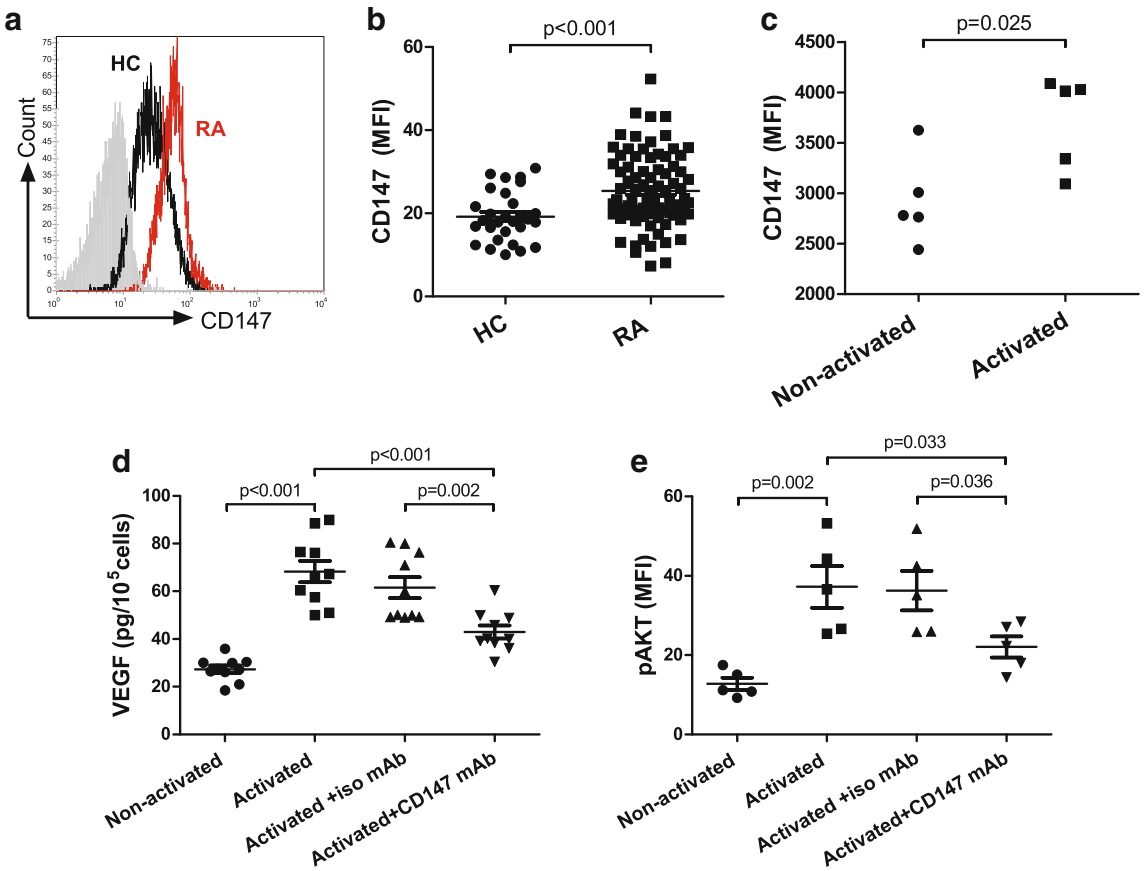


**Fig. 4** CD147 participates in the activation function of Tang cells in RA patients. **a** Flow cytometry analyses showed the expression of CD147 on Tang cells obtained from one representative HC (black line) and RA patient (red line). **b** Expression of CD147 on Tang cells in peripheral blood (PB) of RA patients and HC. **c** After activation with anti-CD3/CD28 mAb for 1 day, the expression of CD147 was assessed on isolated Tang cells. **d** Tang cell from RA patients were cultured with medium (non-activated) or anti-CD3/CD28 mAb (activated) in absence or presence of isotype control mAb (iso mAb) or anti-CD147 mAb for 3 days, then VEGF level in cell culture supernatants was assessed by ELISA ($n = 10$). **e** Phospho-flow analysis of pAkt (T308) in isolated Tang cells from RA patients with medium (non-activated) or anti-CD3/CD28 mAb (activated) in absence or presence of isotype control mAb (Iso mAb) or anti-CD147 mAb ($n = 5$).

CD147mAb (HAb18) significantly inhibited VEGF production from Tang cells. Then, we evaluated whether this result was due to anti-CD147mAb which affects the viability of Tang cells. Our preliminary results show that anti-CD147mAb has no significant effect on the percentages of Annexin $V^+7AAD^-$ and Annexin $V^+7AAD^+$ Tang cells. Although it still needed more work to explore the possible effects of anti-CD147mAb, the current data indicated that, instead of affecting apoptosis, CD147 could promote the secretion of VEGF in Tang cell.

Then, this study explored the possible mechanisms of CD147 promoting VEGF secretion in Tang cells. VEGF is the most important regulator in the angiogenesis process [26], and it exerts its effects after binding with its homologous membrane tyrosine kinase. However, VEGFR2 is critical in VEGF-induced angiogenesis [27]. VEGFR2, on activation, further activates PI3K/Akt pathways, which is responsible for endothelial cell proliferation [28]. More importantly, a previous study showed that CD147 upregulated VEGF expression and promoted angiogenesis via the PI3K/Akt signaling pathway in RA synovial tissue [8]. Consistently, this study found an important role of CD147 in the process of angiogenesis in RA via VEGF, and the possible mechanism was through the PI3K/Akt signaling pathway, regulating cell proliferation, survival, growth, and vitality [29]. These data suggested that CD147 might affect Tang cell function via Akt signaling, at least in RA.

This study had several limitations. First, most of the patients with RA in this study were included after treatment. Although the treatment characteristics between analysis groups were nearly equal, further investigations are needed to clarify the expression of Tang cells in treatment-naive patients. Secondly, as a subset of $CD3^+$ T cells, Tang cells also express CD4 or CD8. Similar to a previous study [14], it is believed that further studies are needed to evaluate the profiles of Tang cell subsets (including $CD4^+$ and $CD8^+$ Tang cells) in RA and the potential role of CD147 in these Tang cell subsets. Thus, further studies with a larger sample size and follow-up observation should be performed to confirm the present findings.

In conclusion, the data indicated that the Tang cell and EPC percentages increased, which was associated with the formation of blood vessels in patients with RA. In the present study, a high percentage of circulating Tang cells was closely related to disease-specific parameters. Specifically, high disease activity and autoantibody positivity were strong indicators of increased Tang cell percentage. Curbing Tang cell function might be a promising intervention in patients with RA, although further studies are needed to investigate the functionality of these cells under different conditions. Importantly, CD147 were highly expressed in Tang cells. The results also highlighted a proangiogenic role of CD147 in RA. CD147 may promote VEGF secretion in activated Tang cells by affecting Akt signaling, which in turn can be conducive to angiogenesis and RA pathogenesis. Based on these facts, further studies on circulating Tang cells and CD147 molecules might have a considerable clinical impact. This study provided a new point of view on the development of anti-CD147 antibody therapy for patients with RA via regulating circulating Tang cell activation function.

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## Compliance with ethical standards

Our research was approved by ethical standards committee of Xijing Hospital, Fourth Military Medical University, and all the participants gave written informed consent (REB registration number: XJYYLL-2014142).

**Disclosures** None.

## References

1. Mackey RH, Kuller LH, Moreland LW (2017) Cardiovascular disease risk in patients with rheumatic diseases. Clin Geriatr Med 33: 105–117
2. Elshabrawy HA, Chen Z, Volin MV, Ravella S, Virupannavar S, Shahrara S (2015) The pathogenic role of angiogenesis in rheumatoid arthritis. Angiogenesis 18:433–448
3. Roccaro AM, Russo F, Cirulli T, Di Pietro G, Vacca A, Dammacco F (2005) Antiangiogenesis for rheumatoid arthritis. Curr Drug Targets Inflamm Allergy 4:27–30
4. Hur J, Yang HM, Yoon CH, Lee CS, Park KW, Kim JH, Kim TY, Kim JY, Kang HJ, Chae IH, Oh BH, Park YB, Kim HS (2007) Identification of a novel role of T cells in postnatal vasculogenesis: characterization of endothelial progenitor cell colonies. Circulation 116:1671–1682
5. MacDonald IJ, Liu SC, Su CM, Wang YH, Tsai CH, Tang CH (2018) Implications of angiogenesis involvement in arthritis. Int J Mol Sci 19
6. Zhai Y, Wu B, Li J, Yao XY, Zhu P, Chen ZN (2016) CD147 promotes IKK/IkappaB/NF-kappaB pathway to resist TNF-induced apoptosis in rheumatoid arthritis synovial fibroblasts. J Mol Med (Berl) 94:71–82
7. Wang ZZ, Wang Y, Li JM, Mou FX, Wu H (2013) Significance of serum MMP-3, TIMP-1, and monocyte CD147 in rheumatoid arthritis patients of damp-heat bi-syndrome and of cold-damp bi-syndrome. Zhongguo Zhong Xi Yi Jie He Za Zhi 33:770–773
8. Wang CH, Yao H, Chen LN, Jia JF, Wang L, Dai JY, Zheng ZH, Chen ZN, Zhu P (2012) CD147 induces angiogenesis through a vascular endothelial growth factor and hypoxia-inducible transcription factor 1alpha-mediated pathway in rheumatoid arthritis. Arthritis Rheum 64:1818–1827
9. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS et al (1988) The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 31:315–324
10. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CR et al (2010) 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 69:1580–1588
11. Miao J, Zhang K, Qiu F, Li T, Lv M, Guo N et al (2015) Percentages of CD4+CD161+ and CD4-CD8-CD161+ T cells in the synovial fluid are correlated with disease activity in rheumatoid arthritis. Mediat Inflamm 2015:563713
12. Rodriguez-Carrio J, Alperi-Lopez M, Lopez P, Alonso-Castro S, Ballina-Garcia FJ, Suarez A (2015) Angiogenic T cells are decreased in rheumatoid arthritis patients. Ann Rheum Dis 74:921–927
13. Lopez P, Rodriguez-Carrio J, Martinez-Zapico A, Caminal-Montero L, Suarez A (2016) Senescent profile of angiogenic T cells from systemic lupus erythematosus patients. J Leukoc Biol 99: 405–412
14. Miao J, Qiu F, Li T, Zhao P, Zhang K, Lv M et al (2016) Circulating angiogenic T cells and their subpopulations in patients with systemic lupus erythematosus. Mediat Inflamm 2016:2842143
15. Manetti M, Pratesi S, Romano E, Bellando-Randone S, Rosa I, Guiducci S et al (2017) Angiogenic T cell expansion correlates with severity of peripheral vascular damage in systemic sclerosis. PLoS One 12:e183102
16. Lopez-Longo FJ, Oliver-Minarro D, de la Torre I, Gonzalez-Diaz DRE, Sanchez-Ramon S, Rodriguez-Mahou M et al (2009) Association between anti-cyclic citrullinated peptide antibodies and ischemic heart disease in patients with rheumatoid arthritis. Arthritis Rheum 61:419–424
17. Liang KP, Kremers HM, Crowson CS, Snyder MR, Therneau TM, Roger VL et al (2009) Autoantibodies and the risk of cardiovascular events. J Rheumatol 36:2462–2469
18. Koch C, Staffler G, Huttinger R, Hilgert I, Prager E, Cerny J et al (1999) T cell activation-associated epitopes of CD147 in regulation of the T cell response, and their definition by antibody affinity and antigen density. Int Immunol 11:777–786
19. Hu J, Dang N, Yao H, Li Y, Zhang H, Yang X, Xu J, Bian H, Xing J, Zhu P, Chen Z (2010) Involvement of HAb18G/CD147 in T cell activation and immunological synapse formation. J Cell Mol Med 14:2132–2143
20. Hatanaka M, Higashi Y, Fukushige T, Baba N, Kawai K, Hashiguchi T et al (2014) Cleaved CD147 shed from the surface of malignant melanoma cells activates MMP2 produced by fibroblasts. Anticancer Res 34:7091–7096
21. Pinheiro C, Garcia EA, Morais-Santos F, Scapulatempo-Neto C, Mafra A, Steenbergen RD et al (2014) Lactate transporters and vascular factors in HPV-induced squamous cell carcinoma of the uterine cervix. BMC Cancer 14:751
22. Wang CH, Chen LN, Zhu P, Fan CM, Wang YH, Jia JF (2007) CD147 stimulates the angiogenesis in rheumatoid synovium via the activation of vascular endothelial growth factor. Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi 23:426–428

23. Han SW, Kim GW, Seo JS, Kim SJ, Sa KH, Park JY et al (2004) VEGF gene polymorphisms and susceptibility to rheumatoid arthritis. Rheumatology (Oxford) 43:1173–1177
24. Ikeda M, Hosoda Y, Hirose S, Okada Y, Ikeda E (2000) Expression of vascular endothelial growth factor isoforms and their receptors Flt-1, KDR, and neuropilin-1 in synovial tissues of rheumatoid arthritis. J Pathol 191:426–433
25. Shinkaruk S, Bayle M, Lain G, Deleris G (2003) Vascular endothelial cell growth factor (VEGF), an emerging target for cancer chemotherapy. Curr Med Chem Anticancer Agents 3:95–117
26. Neufeld G, Cohen T, Gengrinovitch S, Poltorak Z (1999) Vascular endothelial growth factor (VEGF) and its receptors. FASEB J 13:9–22
27. Karar J, Maity A (2011) PI3K/AKT/mTOR pathway in angiogenesis. Front Mol Neurosci 4:51
28. Wang M, Huang ZX, Pan YF, Zhang FC, Zheng BR, Deng WM et al (2010) Expressions of CD147 in peripheral monocytes and T lymphocytes of patients with ankylosing spondylitis. Zhonghua Yi Xue Za Zhi 90:2902–2906
29. Tamura N (2012) Recent findings on phosphoinositide-3 kinase in rheumatic diseases. Nihon Rinsho Meneki Gakkai Kaishi 35:8–13