

Original Article

# Role of CD204-Positive Tumor-Associated Macrophages in Adult T-Cell Leukemia/Lymphoma

Yoichi Saito,<sup>1)\*</sup> Yoshihiro Komohara,<sup>1)\*</sup> Daisuke Niino,<sup>2)</sup> Hasita Horlad,<sup>1)</sup> Koji Ohnishi,<sup>1)</sup> Hiroto Takeya,<sup>1)</sup> Hiroya Kawaguchi,<sup>1)</sup> Hirokazu Shimizu,<sup>1)</sup> Koichi Ohshima,<sup>2)</sup> and Motohiro Takeya<sup>1)</sup>

Adult T-cell leukemia/lymphoma (ATLL) is endemic in southwestern Japan, the Caribbean basin, and parts of central Africa, and is considered to be caused by long-term infection with human T-cell leukemia virus type I. CD204 is a scavenger receptor that is overexpressed on alternatively activated macrophages and is known to be overexpressed in tumor-associated macrophages (TAMs). CD206 is also considered a marker of alternatively activated macrophages. However, no studies have investigated CD206 and TAMs. In the present study, we investigated the significance of CD204<sup>+</sup> and CD206<sup>+</sup> TAMs in ATLL tissue samples. We also investigated the correlations with the Ki-67 labeling index (Ki-67LI) and the number of CD31<sup>+</sup> vessels. We found that the number and ratio of CD204<sup>+</sup> TAMs were closely associated with the Ki-67LI, which reflects lymphoma cell proliferation. The number of CD31<sup>+</sup> vessels was not correlated with the number or ratio of CD204<sup>+</sup> and CD206<sup>+</sup> TAMs. The number and ratio of CD204<sup>+</sup> and CD206<sup>+</sup> TAMs, number of CD31<sup>+</sup> vessels, and the Ki-67LI were not associated with the clinical outcome of patients with ATLL. Although further studies are necessary to uncover the detailed mechanisms of CD204 and lymphoma proliferation, these data may provide novel insight into the pathogenesis of ATLL. [*J Clin Exp Hematop* 54(1): 59-65, 2014]

**Keywords:** ATLL, TAM, CD204, CD206, Ki-67

## INTRODUCTION

Adult T-cell leukemia/lymphoma (ATLL) develops in individuals infected with human T-cell leukemia virus type I (HTLV-1), and p40 tax and HTLV-1 basic leucine zipper factor are considered to be important for oncogenesis.<sup>1-5</sup> Acute and lymphomatous ATLL are aggressive diseases, and the median survival time is reported to be around 1 year.<sup>2-6</sup>

Macrophages that infiltrate tumor tissues are referred to as “tumor-associated macrophages” (TAMs) and are closely involved in tumorigenesis by inducing angiogenesis, immunosuppression, and invasion.<sup>7-9</sup> Many reports of studies focused on TAMs in human malignant tumors have been published in this decade, and they have demonstrated an association of TAMs with histological grading or clinical prognosis in many

kinds of malignant tumor including hematological malignancies.<sup>10,11</sup> In our previous paper, we showed that a higher ratio of CD163<sup>+</sup> TAMs is closely associated with a more clinical course in patients with ATLL.<sup>12</sup> However, other M2 markers such as CD204 or CD206 were not analyzed in ATLL tissues.

CD204 (macrophage scavenger receptor class A, types I and II) is one of the major scavenger receptors expressed on human and murine macrophages and dendritic cells.<sup>13</sup> Immunohistochemical studies in gliomas,<sup>14</sup> pancreatic cancer,<sup>15</sup> kidney cancer,<sup>16</sup> esophageal cancer,<sup>17</sup> and lung cancer<sup>18</sup> have shown that CD204 expression in tumor tissues is closely restricted to TAMs and that high expression of CD204 is associated with a high malignant potential of tumor cells. In our previous study,<sup>19</sup> we showed that CD204 inhibits macrophage activation by scavenging ligands of Toll-like receptor 4 and suppresses inflammatory cytokine production. In a murine experimental model, we previously showed that the development of subcutaneously implanted EL4 lymphoma was significantly abrogated in CD204-deficient mice.<sup>20</sup> Neyen and colleagues<sup>21</sup> demonstrated that CD204 is involved in cell-cell interactions between macrophages and cancer cells and that CD204 deficiency inhibits tumor development in murine ovarian cancer and pancreatic cancer models. These results suggest that CD204 plays an important role in protu-

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<sup>1)</sup>Department of Cell Pathology, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan

<sup>2)</sup>Department of Pathology, School of Medicine, Kurume University, Kurume, Japan

\*These authors contributed equally to this work.

Corresponding author: Yoshihiro Komohara, M.D., Ph.D., Department of Cell Pathology, Graduate School of Medical Sciences, Kumamoto University, Honjo 1-1-1, Kumamoto 860-8556, Japan

E-mail : ycomo@kumamoto-u.ac.jp

moral macrophage activation and tumor cell growth.

CD206 has broad ligands including microbial and endogenous glycoproteins and is involved in immune responses.<sup>22</sup> CD206 is up-regulated by interleukin-4 and -13 and is also considered a marker of alternatively activated macrophages.<sup>23</sup> In ovarian cancer, CD206 engagement by tumor-derived mucins induced polarization of TAMs to the M2 phenotype.<sup>24</sup> However, few studies have investigated the significance of CD206<sup>+</sup> TAMs in human malignant diseases.

In the present study, we evaluated the significance of CD204<sup>+</sup> and/or CD206<sup>+</sup> TAMs in the progression of ATLL. In addition, we compared the ratio of CD204<sup>+</sup> and/or CD206<sup>+</sup> TAMs and CD163<sup>+</sup> TAMs using the same tissue samples as in a previous study.<sup>12</sup>

## MATERIALS AND METHODS

### *Tissue samples*

Paraffin-embedded tumor samples from the lymph nodes of 58 patients with ATLL (lymphomatous and acute type) were examined. Patients diagnosed during 1993-2003 were treated by conventional chemotherapy and none was treated by bone marrow transplantation. Twenty-seven patients showed leukemic change. Written informed consent was obtained from all patients in accordance with protocols approved by Fukuoka University and Kurume University Review Board. We previously published characteristics of this same set of ATLL specimens,<sup>12</sup> and thus the numbers of CD68<sup>+</sup> and CD163<sup>+</sup> cells published in that previous report were used in this study.

### *Immunohistochemistry*

Paraffin-embedded tumor tissue samples were used for analysis of macrophage infiltration, lymphoma cell proliferation, and neovascularization. The following mouse monoclonal antibodies were used: CD68 (PG-M1; DAKO, Glostrup, Denmark), CD163 (10D6; Novocastra, Newcastle, UK), CD204 (SRA-E5; TransGenic, Kumamoto, Japan), CD206 (5C11; Acris Antibodies, San Diego, CA, USA), Ki-67 (MIB-1; DAKO, Glostrup, Denmark), and CD31 (JC70A; DAKO). Normal mouse immunoglobulin (DAKO) was used as a negative control and no signal was observed in these sections. Each immunostaining was performed at the same time. Infiltration of CD204<sup>+</sup> and CD206<sup>+</sup> macrophages, the percentage of Ki-67<sup>+</sup> lymphoma cells (Ki-67 labeling index, Ki-67LI), and CD31<sup>+</sup> vessels were evaluated by two investigators who were blinded to any information on the samples, and the data were averaged. The number of positive cells was counted in four randomly selected high-power fields and finally calculated as the number per mm<sup>2</sup>. In some analyses, the ratio of CD204<sup>+</sup> or CD206<sup>+</sup> cells among CD68<sup>+</sup> macro-

phages was used for statistical analysis.

### *Statistics*

Statistical analysis of *in vitro* and *in vivo* data was carried out using JMP10 (SAS Institute, Chicago, IL, USA). Spearman's correlation test was used for two-group comparisons. The simultaneous relationship between multiple factors for survival was assessed using the Cox proportional hazards model. A value of  $p < 0.05$  was considered statistically significant.

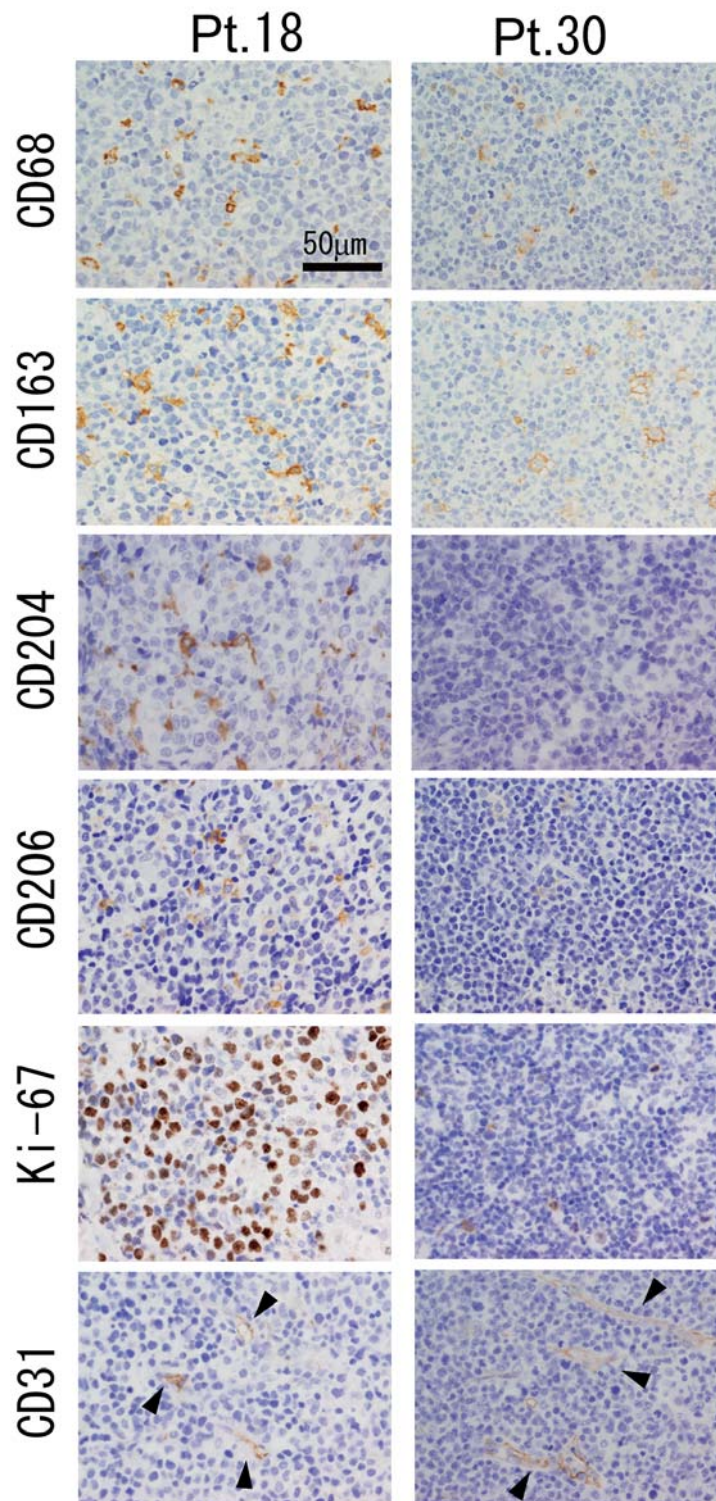
## RESULTS

### *The number and ratio of CD204-positive TAMs are closely correlated to the Ki-67LI*

Immunostaining for CD204, CD206, Ki-67, and CD31 was performed in 58 cases of lymphomatous ATLL (Fig. 1). Mutual correlations of their expression and the association with clinical outcome were statistically evaluated. CD204 was strongly expressed on TAMs, but CD206 was weakly detected on them (Fig. 1). The number of CD163<sup>+</sup> cells was closely linked to the number of CD204<sup>+</sup> or CD206<sup>+</sup> cells (Fig. 2A, 2B), but we found no correlation between the numbers of CD204<sup>+</sup> cells and CD206<sup>+</sup> cells (Fig. 2C). Lymphoma cell proliferation was evaluated by Ki-67LI. The number of CD163<sup>+</sup> cells was not statistically linked to the Ki-67LI (Fig. 2D). Interestingly, the number of CD204<sup>+</sup> TAMs and the ratio of CD204<sup>+</sup> cells among CD68<sup>+</sup> TAMs were both strongly correlated with the Ki-67LI (Fig. 2E, 2F). In addition, the correlation between macrophages and neovascularization was evaluated, and the results showed that the numbers of CD68<sup>+</sup>, CD163<sup>+</sup>, CD204<sup>+</sup>, and CD206<sup>+</sup> cells were each not correlated with the number of CD31<sup>+</sup> vessels (data not shown). The numbers and ratios of CD204<sup>+</sup> or CD206<sup>+</sup> TAMs, the Ki-67LI, and the number of CD31<sup>+</sup> vessels were all not correlated with the clinical prognosis (Table 1). In our samples, 27 patients showed leukemic change. Although we re-analyzed 27 patients with leukemic change, there was no significant difference of TAM infiltration, Ki-67LI, and the number of CD31<sup>+</sup> vessels between leukemic and non-leukemic cases (data not shown).

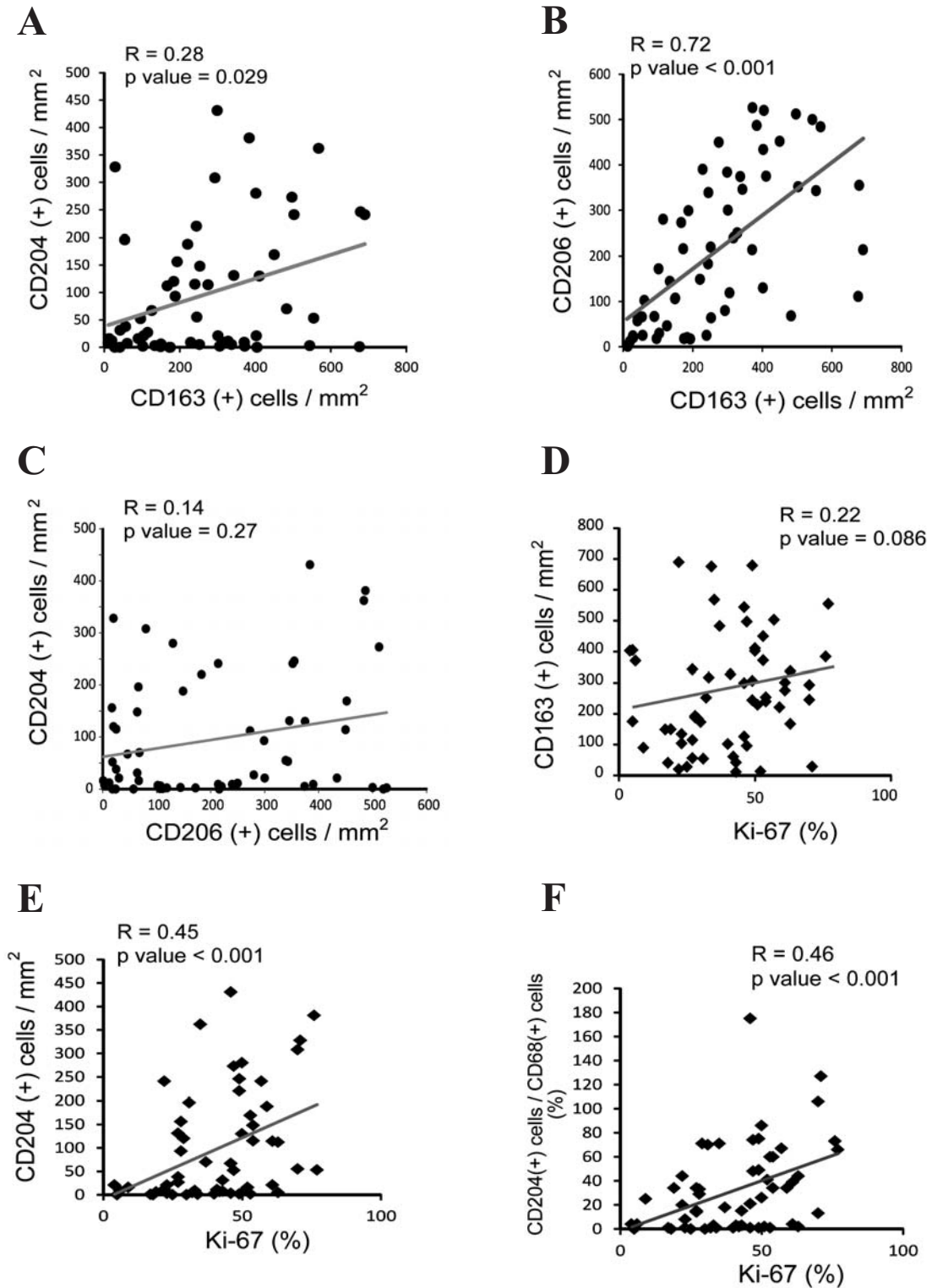
## DISCUSSION

Recent studies have focused on TAMs in malignant lymphomas such as Hodgkin lymphoma, angioimmunoblastic T-cell lymphoma, and diffuse large B-cell lymphoma.<sup>25</sup> The significant correlations between CD163<sup>+</sup> TAMs and clinical outcome have been thoroughly investigated, and the results demonstrated that patients with a higher number or ratio of CD163<sup>+</sup> TAMs generally showed worse clinical outcome in



**Fig. 1.** Immunostaining of adult T-cell leukemia/lymphoma tissues. Anti-CD68, anti-CD204, and anti-CD206 antibodies were used to detect pan-macrophages (CD68) and alternatively activated macrophages (CD204 and CD206). Ki-67 was used to detect proliferating cells, and CD31 was used to label blood vessels (*arrows*).





**Fig. 2.** Statistical analysis of macrophage infiltration, the Ki-67LI, and CD31<sup>+</sup> vessels. The correlations between the numbers of CD204<sup>+</sup> and CD163<sup>+</sup> cells (2A), the numbers of CD206<sup>+</sup> and CD163<sup>+</sup> cells (2B), the Ki-67LI and the number of CD163<sup>+</sup> cells (2C), the Ki-67 LI and the number of CD204<sup>+</sup> cells (2D), the Ki-67LI and the ratio of CD204<sup>+</sup> cells (2E), and the number of CD31<sup>+</sup> vessels and the ratio of CD204<sup>+</sup> cells (2F) are shown.

**Table 1.** Univariate analysis of tumor-associated macrophages and pathological factors in patients with adult T-cell leukemia/lymphoma

Antibody	Frequency	N =	Median survival (months)	Univariate analysis	
				<i>p</i> value Log-rank	<i>p</i> value Wilcoxon
CD204	High ( $\geq 100/\text{mm}^2$ )	22	21.8	0.79	0.92
	Low ( $< 100/\text{mm}^2$ )	36	21.1		
CD204 (%)	High ( $\geq 30\%$ )	25	19.1	0.88	0.96
	Low ( $< 30\%$ )	33	23.3		
CD206	High ( $\geq 250/\text{mm}^2$ )	23	19.4	0.63	0.44
	Low ( $< 250/\text{mm}^2$ )	35	22.7		
CD206 (%)	High ( $\geq 70\%$ )	24	19.7	0.71	0.6
	Low ( $< 70\%$ )	34	22.5		
CD31	High ( $\geq 60/\text{mm}^2$ )	27	18.7	0.55	0.61
	Low ( $< 60/\text{mm}^2$ )	31	23.8		
MIB-1	High ( $\geq 40\%$ )	32	20.1	0.72	0.62
	Low ( $< 40\%$ )	26	21.9		

Each threshold is set as the average.

these diseases.<sup>26-28</sup> Not only CD163 but also CD204 or CD206 is preferentially expressed on alternatively activated macrophages.<sup>29</sup> However, the significance of CD204 and CD206 expressed on TAMs has never been investigated in malignant lymphoma.

In this study, a significant association between CD204<sup>+</sup> TAMs and the Ki-67LI was found in ATLL samples, suggesting that CD204<sup>+</sup> TAMs may be involved in lymphoma cell proliferation. However, no correlation was found between CD204<sup>+</sup> TAMs and clinical outcome. The reasons for this discrepancy may be that a higher Ki-67LI was not always correlated with a worse clinical outcome and that complex mechanisms are involved in the effectiveness of clinical treatment. Although we found no correlation between CD206 and pathological factors in ATLL, further studies are necessary to uncover the role of CD206 in the tumor microenvironment.

In some malignant tumors including breast cancer tumors, a higher Ki-67LI is associated with a worse clinical outcome and is a prognostic marker.<sup>30</sup> In malignant lymphoma, a higher Ki-67LI is a prognostic factor in patients with diffuse large B-cell lymphoma and mantle cell lymphoma.<sup>31,32</sup> Our present work is the first to investigate the correlation between the Ki-67LI and overall survival in patients with ATLL. We showed no significant association between the Ki-67LI and overall survival. A high number of Ki-67<sup>+</sup> cells in peripheral blood was found to be correlated with a worse clinical outcome in patients with ATLL.<sup>33</sup> However, that study was not a histological study using tumor tissue samples.

TAMs, especially alternative phenotype TAMs, are considered to be involved in angiogenesis in tumor tissues by secreting several angiogenic factors such as vascular endothelial growth factors, thymidine phosphorylase, and matrix metalloproteinases.<sup>34</sup> Co-culture with tumor cells induces

macrophage activation, and activated macrophages stimulate endothelial cell activation and vessel formation in culture studies.<sup>35-37</sup> However, our observation that TAMs are not associated with neovascularization in ATLL may indicate that cell-cell interactions with ATLL cells are not associated with the angiogenic functions of macrophages.

Since increased apoptosis is associated with lymphoma proliferation<sup>38</sup> and CD204 is involved in the phagocytosis of apoptotic cells,<sup>39-40</sup> close association of CD204 expression and Ki-67LI might partly be due to the induction of CD204 in TAMs engulfing apoptotic cells. Further studies are necessary to elucidate the relationship between CD204 induction and apoptotic cell clearance in ATLL.

Although the ratio of CD163-positive TAMs was significantly correlated to poor prognosis in ATLL in our previous study,<sup>12</sup> the number or ratio of CD204-positive or CD206-positive TAMs was not. CD163 expression is preferentially up-regulated in the IL-10-induced M2c phenotype, whereas CD206 expression is increased in the IL-4-induced M2a phenotype.<sup>41</sup> In glioma and kidney cancer, the number of CD204-positive cells is higher than the number of CD163-positive cells.<sup>14,16</sup> In this study, the numbers of CD163-positive, CD204-positive, and CD206-positive cells differ. It is well known that these antigens are expressed on M2 macrophages; however, these antigens might be differently up-regulated in subtypes of M2 macrophages.

In conclusion, we demonstrated a close association between the number or ratio of CD204<sup>+</sup> TAMs and lymphoma cell proliferation in lymphomatous ATLL, although we found no significant correlation between these factors and clinical outcome. Further studies are required to reveal the detailed mechanisms of CD204-associated cell-cell interactions between TAMs and lymphoma cells. However, our present

findings may provide useful insight into the pathogenesis of ATLL.

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## DISCLOSURE STATEMENT

Conflict of interest: The authors declare no competing financial interests.

## REFERENCES

- Oshima K, Jaffe ES, Kikuchi M: Adult T-cell leukemia/lymphoma. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, *et al.* (eds): World Health Organization Classification of Tumours, WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed, Lyon, International Agency for Research on Cancer (IARC), pp.281-284, 2008
- Shirono K, Hattori T, Hata H, Nishimura H, Takatsuki K: Profiles of expression of activated cell antigens on peripheral blood and lymph node cells from different clinical stages of adult T-cell leukemia. *Blood* 73:1664-1671, 1989
- Takasaki Y, Iwanaga M, Imaizumi Y, Tawara M, Joh T, *et al.*: Long-term study of indolent adult T-cell leukemia-lymphoma. *Blood* 115:4337-4343, 2010
- Ohshima K: Pathological features of diseases associated with human T-cell leukemia virus type I. *Cancer Sci* 98:772-778, 2007
- Satou Y, Matsuoka M: HTLV-1 and the host immune system: how the virus disrupts immune regulation, leading to HTLV-1 associated diseases. *J Clin Exp Hematop* 50:1-8, 2010
- Uozumi K: Treatment of adult T-cell leukemia. *J Clin Exp Hematop* 50:9-25, 2010
- Mantovani A, Sozzani S, Locati M, Allavena P, Sica A: Macrophage polarization: tumor-associated macrophages as a paradigm for polarized M2 mononuclear phagocytes. *Trends Immunol* 23:549-555, 2002
- Bingle L, Brown NJ, Lewis CE: The role of tumour-associated macrophages in tumour progression: implications for new anti-cancer therapies. *J Pathol* 196:254-265, 2002
- Pollard JW: Tumour-educated macrophages promote tumour progression and metastasis. *Nat Rev Cancer* 4:71-78, 2004
- Rogers TL, Holen I: Tumour macrophages as potential targets of bisphosphonates. *J Transl Med* 9:177, 2011
- Komohara Y, Jinushi M, Takeya M: Clinical significance of macrophage heterogeneity in human malignant tumors. *Cancer Sci* 105:1-8, 2014
- Komohara Y, Niino D, Saito Y, Ohnishi K, Horlad H, *et al.*: Clinical significance of CD163<sup>+</sup> tumor-associated macrophages in patients with adult T-cell leukemia/lymphoma. *Cancer Sci* 104:945-951, 2013
- Platt N, Gordon S: Is the class A macrophage scavenger receptor (SR-A) multifunctional ? - The mouse's tale. *J Clin Invest* 108:649-654, 2001
- Komohara Y, Ohnishi K, Kuratsu J, Takeya M: Possible involvement of the M2 anti-inflammatory macrophage phenotype in growth of human gliomas. *J Pathol* 216:15-24, 2008
- Yoshikawa K, Mitsunaga S, Kinoshita T, Konishi M, Takahashi S, *et al.*: Impact of tumor-associated macrophages on invasive ductal carcinoma of the pancreas head. *Cancer Sci* 103:2012-2020, 2012
- Komohara Y, Hasita H, Ohnishi K, Fujiwara Y, Suzu S, *et al.*: Macrophage infiltration and its prognostic relevance in clear cell renal cell carcinoma. *Cancer Sci* 102:1424-1431, 2011
- Shigeoka M, Urakawa N, Nakamura T, Nishio M, Watajima T, *et al.*: Tumor associated macrophage expressing CD204 is associated with tumor aggressiveness of esophageal squamous cell carcinoma. *Cancer Sci* 104:1112-1119, 2013
- Hirayama S, Ishii G, Nagai K, Ono S, Kojima M, *et al.*: Prognostic impact of CD204-positive macrophages in lung squamous cell carcinoma: possible contribution of Cd204-positive macrophages to the tumor-promoting microenvironment. *J Thorac Oncol* 7:1790-1797, 2012.
- Ohnishi K, Komohara Y, Fujiwara Y, Takemura K, Lei X, *et al.*: Suppression of TLR4-mediated inflammatory response by macrophage class A scavenger receptor (CD204). *Biochem Biophys Res Commun* 411:516-522, 2011
- Komohara Y, Takemura K, Lei XF, Sakashita N, Harada M, *et al.*: Delayed growth of EL4 lymphoma in SR-A-deficient mice is due to upregulation of nitric oxide and interferon- $\gamma$  production by tumor-associated macrophages. *Cancer Sci* 100:2160-2166, 2009
- Neyen C, Plüddemann A, Mukhopadhyay S, Maniati E, Bossard M, *et al.*: Macrophage scavenger receptor promotes tumor progression in murine models of ovarian and pancreatic cancer. *J Immunol* 190:3798-3805, 2013
- Martinez-Pomares L: The mannose receptor. *J Leukoc Biol* 92:1177-1186, 2012
- Goerdts S, Orfanos CE: Other functions, other genes: alternative activation of antigen-presenting cells. *Immunity* 10:137-142, 1999
- Dangaj D, Abbott KL, Mookerjee A, Zhao A, Kirby PS, *et al.*: Mannose receptor (MR) engagement by mesothelin GPI anchor polarizes tumor-associated macrophages and is blocked by anti-MR human recombinant antibody. *PLoS One* 6:e28386, 2011
- Aldinucci D, Gloghini A, Pinto A, De Filippi R, Carbone A: The classical Hodgkin's lymphoma microenvironment and its role in promoting tumour growth and immune escape. *J Pathol* 221:248-263, 2010
- Zaki MA, Wada N, Ikeda J, Shibayama H, Hashimoto K, *et al.*: Prognostic implication of types of tumor-associated macrophages in Hodgkin lymphoma. *Virchows Arch* 459:361-366, 2011
- Niino D, Komohara Y, Murayama T, Aoki R, Kimura Y, *et al.*: Ratio of M2 macrophage expression is closely associated with

- poor prognosis for angioimmunoblastic T-cell lymphoma (AITL). *Pathol Int* 60:278-283, 2010
- 28 Wada N, Zaki MA, Hori Y, Hashimoto K, Tsukaguchi M, *et al.*: Tumour-associated macrophages in diffuse large B-cell lymphoma: a study of the Osaka Lymphoma Study Group. *Histopathology* 60:313-319, 2012
- 29 Gordon S: Alternative activation of macrophages. *Nat Rev Immunol* 3:23-35, 2003
- 30 Ohta T, Fukuda M: Cell cycle regulators as prognostic factors of breast cancers. *Nihon Rinsho* 58:448-453, 2000 (*in Japanese*)
- 31 Gaudio F, Giordano A, Perrone T, Pastore D, Curci P, *et al.*: High Ki67 index and bulky disease remain significant adverse prognostic factors in patients with diffuse large B cell lymphoma before and after the introduction of rituximab. *Acta Haematol* 126:44-51, 2011
- 32 Hartmann EM, Ott G, Rosenwald A: Molecular outcome prediction in mantle cell lymphoma. *Future Oncol* 5:63-73, 2009
- 33 Yamada Y, Murata K, Kamihira S, Atogami S, Tsukasaki K, *et al.*: Prognostic significance of the proportion of Ki-67-positive cells in adult T-cell leukemia. *Cancer* 67:2605-2609, 1991
- 34 Goda N: Guest editorial: hypoxia biology in health and disease. *Int J Hematol* 95:455-456, 2012
- 35 Gabrilovich DI, Ostrand-Rosenberg S, Bronte V: Coordinated regulation of myeloid cells by tumours. *Nat Rev Immunol* 12:253-268, 2012
- 36 Kujawski M, Kortylewski M, Lee H, Herrmann A, Kay H, *et al.*: Stat3 mediates myeloid cell-dependent tumor angiogenesis in mice. *J Clin Invest* 118:3367-3377, 2008
- 37 Wang X, Zhao X, Wang K, Wu L, Duan T: Interaction of monocytes/macrophages with ovarian cancer cells promotes angiogenesis *in vitro*. *Cancer Sci* 104:516-523, 2013
- 38 Wang J, Hasui K, Utsunomiya A, Jia X, Matsuyama T, *et al.*: Association of high proliferation in adult T-cell leukemia cells with apoptosis, and expression of p53 protein in acute type ATL. *J Clin Exp Hematop* 48:1-10, 2008
- 39 Platt N, Suzuki H, Kurihara Y, Kodama T, Gordon S: Role for the class A macrophage scavenger receptor in the phagocytosis of apoptotic thymocytes *in vitro*. *Proc Natl Acad Sci U S A* 93:12456-12460, 1996
- 40 Komohara Y, Terasaki Y, Kaikita K, Suzuki H, Kodama T, *et al.*: Clearance of apoptotic cells is not impaired in mouse embryos deficient in class A scavenger receptor types I and II (CD204). *Dev Dyn* 232:67-74, 2005
- 41 Mantovani A, Sica A, Sozzani S, Allavena P, Vecchi A, *et al.*: The chemokine system in diverse forms of macrophage activation and polarization. *Trends Immunol* 25:677-686, 2004