Letter to the Editor

Circulating intermediate monocytes produce TARC in sarcoidosis

Dear Editor,

Sarcoidosis is a systemic granulomatous disorder, but its mechanism is largely unknown. Chemotactic molecules may contribute to granuloma formation by immobilizing leukocytes at affected sites.1 We have recently found that thymus- and activation-regulated chemokine (TARC), also known as CCL17, was elevated in the sera of patients with sarcoidosis, and TARC was abundantly expressed in the epithelioid cells of cutaneous granulomas.2

Peripheral monocytes have been classified into 3 subsets according to the expression of CD14 and CD16. Based on this nomenclature, approximately 90% of human peripheral monocytes express high levels of CD14, but not CD16, and have been categorized as classical monocytes (CD14+CD16–). Two minor populations include intermediate monocytes (CD14+CD16+) and non-classical monocytes (CD14–CD16+).3 Among them, intermediate monocytes reportedly expand in a number of inflammatory conditions, including sarcoidosis.4–2 Because monocytes were reported to be a source of TARC in peripheral blood,8 we sought to evaluate the role of intermediate monocytes in sarcoidosis by evaluating their capacity for TARC production.

The study protocol was approved by the Internal Review Board of Kansai Medical University (approval number 2016610), and we newly recruited 13 sarcoidosis patients. Their clinical characteristics are summarized in Table 1. Among 3 subsets of peripheral monocytes, intermediate monocytes produced significantly higher levels of TARC than did classical and non-classical monocytes (Fig. 1A, B). We examined TARC levels in 13 patients using flow cytometry to determine the mean fluorescent intensity (MFI) in monocyte populations. We observed that intermediate monocytes produced significantly higher amounts of TARC (MFI: 2043; range, 1384–2515) than did classical monocytes (MFI, 1121; range, 848–1384; p < 0.0001) and non-classical monocytes (MFI, 1585; range, 960–2330; p = 0.002) (Fig. 1C). Furthermore, we analyzed that the monocyte counts and each subset in sarcoidosis (Fig. 1D, E) were significantly higher than that in control donors (mean, 2.01%; range, 1.4–2.7%; p = 0.006) (Fig. 1F, left), as previously reported.5 A positive correlation was also observed between the frequency of the intermediate subset and serum TARC concentrations (r = 0.644, p = 0.018, Fig. 1F, right).

In our previous report,2 we examined 82 sarcoidosis patients, we have reported that sarcoidosis patients with elevated serum TARC levels showed more severe clinical symptoms and significantly higher levels of other serum markers.6 In comparison with our previous report,2 the levels of these markers were lower in this present study (Table 1), because the 13 patients in this study were likely less severe cases than those in the previous one, and actually most patients evaluated by chest radiography were classified as mild disease.

A recent study in mice showed that intermediate monocytes could migrate into tissue and drive the inflammatory response as M1.1 Those M1 cells were associated with more TARC production than other subsets.10 The identification of TARC-producing intermediate monocytes in circulation suggests that these expanded pro-inflammatory cells could enter into affected tissue11 and could be crucial for building and maintaining granuloma formation by giving rise to monocyte/macrophage lineage cells, even though his hypothesis will need to be elucidated in further study. TARC activates CC chemokine receptor 4 (CCR4), which is selectively expressed on T helper type 2 (Th2) lymphocytes, and it recruits CCR4+ T lymphocytes into inflamed sites, priming a Th2-type immune response.12–14 Systemic inhibition of the cellular immunity is one of the characteristics for sarcoidosis. The expression of TARC within granulomas and its presence in the circulation may suggests that TARC plays some key roles in driving the immune response toward a Th2 environment in sarcoidosis.

From the data reported herein, we believe that increased circulating intermediate monocytes that have more potential of TARC-

Table 1

| Number, no | 13 |
| Age (years) | 71.0 ± 2.6 |
| Male: female, no | 6:7 |
| Duration of disease (years) | 6.10 ± 1.30 |
| Chest radiographic stage, no [%] | 0 | 6 [46%] |
| I | 6 [46%] |
| II | 1 [7%] |
| III, IV | 0 [0%] |
| Laboratory makers | |
| TARC (pg/ml) | 1064.1 ± 421.6 |
| sIL-2R (U/ml) | 480.6 ± 39.1 |
| ACE (U/l) | 16.30 ± 1.93 |
| Lysozyme (µg/ml) | 7.56 ± 0.96 |
| CRP (mg/dl) | 0.054 ± 0.013 |
| WBC count (cell/µl) | 4646.1 ± 242.7 |
| Lymphocyte count (cell/µl) | 1184.4 ± 89.1 |
| Eosinophils (%) | 2.50 ± 0.38 |
| Monocyte (%) | 6.30 ± 0.63 |

All values with normal distributions are shown as mean ± standard deviation.

https://doi.org/10.1016/j.alit.2019.09.005
1323-8930 (Copyright © 2019, Japanese Society of Allergology. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).)

Peer review under responsibility of Japanese Society of Allergology.
production, compared with other 2 populations, could be considered key players in the pathogenesis of sarcoidosis, even though a burden of serum TARC will be derived from epithelioid cells in the lesion as in the case of atopic dermatitis where local keratinocytes more abundantly produced TARC. This finding highlights the important role of this inflammatory monocyte subset and should lead to additional studies focusing on their exact function in the pathogenesis of this challenging disease.

Acknowledgements

This work was supported in part by the research grant D2 from Kansai Medical University, a Grant from Novartis in 2018, and the branding program as a world-leading research university on intractable immune and allergic diseases from MEXT, Japan.

Conflict of interest

The authors have no conflict of interest to declare.

Izumi Kishimoto a,b, Chuyen Thi Hong Nguyen a,c,1, Naotomo Kambe a,b,1, Nhung Thi My Ly a, Yoko Ueki a, Ikuko Ueda-Hayakawa a, Hiroyuki Okamoto a

* Department of Dermatology, Kansai Medical University, Osaka, Japan
a Allergy Center, Kansai Medical University, Osaka, Japan
b Department of Dermatology and Venerology, University of Medicine and Pharmacy at Ho Chi Minh City, Ho Chi Minh, Viet Nam

* Corresponding author. Department of Dermatology, Kansai Medical University, 2-5-1 Shin-machi, Hirakata, Osaka 573-1010, Japan.
E-mail address: nkambe@hirakata.kmu.ac.jp (N. Kambe).

References


1 These authors contributed equally.

Fig. 1. (A) Representative dot plots show the gating strategy for the identification of classical (yellow in right panel), intermediate (dark red) and non-classical (purple) subsets based on the expression of Pacific blue-CD14 (BD, San Jose, CA) and APC-CD16 (BD) of peripheral blood samples collected in EDTA and analyzed with a FACS Canto II (BD). Forward scatter (FSC) and side scatter (SSC) were used to select the cell number of circulating monocytes in sarcoidosis patients (n = 9) (left panels) and were analyzed for the correlation with levels of TARC (right panels).