

Editorial

T lymphocytes in pleural effusion

YANG Hai-bo and SHI Huan-zhong

The development of the inflammatory processes in the pleural space may result in increased pleural vascular permeability leading to the accumulation of fluid enriched in proteins and the recruitment of cells into the pleural space.¹ Although pleural effusion (PE) is common, very little information is available on the inflammatory and immune mechanisms that are involved in its development. In particular, it is unclear which cells and mediators are involved in the inflammatory processes and whether resident immunocompetent cells may orchestrate the development of an inflammatory response. Lymphocytic PEs refers to those in which lymphocytes account for more than 50% of the total leukocytes in PE. Lymphocytic effusions are commonly (>90% of cases) the result of malignancy and tuberculous pleurisy, but can also occur with rheumatic diseases, chronic postcoronary artery bypass effusion, chylothorax, acute lung allograft rejection and yellow nail syndrome.²

In normal humans a small amount of PE is present, but the exact volume of this fluid is unknown. In normal PE, there is a predominance of macrophages and lymphocytes; mesothelial cells, neutrophils and eosinophils are only marginally present.³ In an early study, it has been demonstrated that both the percentage and absolute numbers of T lymphocytes in tuberculous PE were significantly higher than in the corresponding peripheral blood. On the other hand, in patients with pulmonary tuberculosis, pulmonary malignancy or nonspecific pleurisy the percentages and absolute numbers of B lymphocytes were significantly lower in PE than in peripheral blood.⁴

It has been reported that PE is enriched with CD4⁺CDw29⁺ T cells, which are thought to represent "memory" T cells, and these PE CD4⁺CDw29⁺ cells, but not CD4⁺CDw29⁻ cells, proliferated vigorously and produced high levels of interferon (IFN)- γ when stimulated with a purified protein derivative of *Mycobacterium tuberculosis*.⁵ Therefore, in tuberculous PE, CD4⁺CDw29⁺ cells are concentrated at the site of disease activity, produce IFN- γ and are likely to play an important role in the local human cell-mediated immune response to *Mycobacterium tuberculosis*. Malignant PE is frequently observed in lung cancer and a diagnosis of malignant PE with lung cancer carries a poor prognosis. In malignant PE, CD4⁺ T cells are dominant and the proportion of CD8⁺ T cells is significantly lower than that of CD4⁺ T cells.⁶ In contrast, the proportion of CD4⁺ T cells in the pleural cavity of patients with lung cancer without malignant PE is significantly lower than that of

CD8⁺ T cells.⁷ Furthermore the proportion of PE CD4⁺ T cells may help to select patients who are likely to have a poorer prognosis after surgery and therefore may be suitable for consideration of adjuvant treatments.⁸

Immunoregulatory T cells have been believed to be involved in the control of the local immune response and in the growth of malignant tumors.⁹ Studies ongoing for more than a decade have provided firm evidence for the existence of a unique CD4⁺CD25⁺ T-cell population of "professional" regulatory/suppressor T cells that actively and dominantly prevent both the activation and the effector function of autoreactive T cells that have escaped other mechanisms of tolerance.^{10,11} Our previous study has shown that CD4⁺CD25⁺ T-cell numbers in malignant PE were much higher than those in PE from patients with lung cancer without malignant effusion and higher than numbers in peripheral blood. Our data also revealed that CD4⁺CD25⁺ T cells infiltrating PE were regulatory T cells as they express high levels of Foxp3 transcription factor. Moreover, pleural CD4⁺CD25⁺ T cells could potentially suppress the proliferation of CD4⁺CD25⁻ T cells and cytotoxic lymphocyte-associated antigen-4 was involved in the suppressive activity of pleural CD4⁺CD25⁺ T cells.¹² In addition, we have demonstrated that CD4⁺CD25⁺ T cell numbers in tuberculous PE were much higher than those in peripheral blood from patients with tuberculous PE and from healthy subjects, and that the CD4⁺CD25⁺ T cells infiltrating pleural space were regulatory T cells as they expressed high levels of Foxp3 transcription factor. Moreover, tuberculous PE-derived CD4⁺CD25⁺ T cells could potentially suppress the proliferation of responding T cells.¹³

It has been reported that the long-term effects of adoptively transferred CD4⁺CD25⁺ T cells induced *ex vivo* are due to their ability to generate new cytokine-producing CD4⁺CD25⁺ T cells *in vivo*.¹⁴ We speculated that an increased percentage of CD4⁺CD25⁺ T cells in PE might be due to either active recruitment or local differentiation. It has been demonstrated that human

Institute of Respiratory Diseases, First Affiliated Hospital, Guangxi Medical University, Nanning, Guangxi 530021, China (Yang HB and Shi HZ)

Correspondence to: Dr. SHI Huan-zhong, Institute of Respiratory Diseases, First Affiliated Hospital, Guangxi Medical University, Nanning, Guangxi 530021, China (Tel: 86-771-5359226. Fax: 86-771-5359226. Email: shihuanzhong@sina.com)

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CD4⁺CD25⁺ T cells preferentially move to and accumulate in tumors and ascites, but rarely enter draining lymph nodes in later cancer stages.¹⁵ In a previous study, we provided direct evidence that interleukin (IL)-16 is capable of inducing CD4⁺ T-cell infiltration into the pleural space.¹⁶ Therefore, as a subpopulation of CD4⁺ T cells, CD4⁺CD25⁺ T cells might also be recruited into PE by local production of IL-16, because the IL-16 level is significantly higher in PE than in serum.¹⁶

Since we observed that CD4⁺CD25⁺ T cells were overrepresented in malignant and tuberculous PEs, this raised the question whether these cells could be recruited from the circulation. In a recent study, we have found that the level of chemokine CCL22 in PE correlated best with the numbers of CD4⁺CD25⁺ T cells, and that an anti-CCL22 antibody inhibited the ability of the PE to stimulate peripheral CD4⁺CD25⁺ T cell chemotaxis *in vitro*. Moreover, intrapleural administration of human recombinant CCL22, but not vehicle, into patients with PE produced a marked progressive influx of CD4⁺CD25⁺ T cells into the pleural space when studied by flow cytometry (our unpublished data). Our results demonstrated that CCL22 is produced by pleural cells and would appear to play a crucial role in the directed migration of CD4⁺CD25⁺ regulatory T cells into the pleural space.

The role of T cells as active players in the mediation of pleural pathologies is beginning to be recognized. Understanding the exact roles of T cells in pleural space may provide a foundation for potential future attempts to augment lymphocyte responses. Further study of specific cellular responses may provide insight into disease pathogenesis and may offer unique opportunities in the diagnosis and management of lymphocytic PE. For example, since CD4⁺CD25⁺ T-cell numbers are increased in malignant PE, and these pleural CD4⁺CD25⁺ T cells can potently suppress the proliferation of CD4⁺CD25⁻ T cells, it is very possible to develop novel immune-boosting strategies based on eliminating this regulatory cell population in patients with cancer. Also, more work is required to delineate the role of CD4⁺CD25⁺ T cells in tuberculous PE. Further studies should be directed at identifying the mediators and mechanisms involved in the immunoregulatory properties of pleural CD4⁺CD25⁺ T cells in patients with tuberculous PE.

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