

Lung inflammation regulates autoimmunity in the central nervous system

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ABSTRACT

Autoimmune diseases of the central nervous system (CNS), such as multiple sclerosis (MS), are characterized by infiltration of pathogenic immune cells in the CNS. Cells infiltrated in the CNS express pro-inflammatory molecules and cause demyelination. The direct impact of lung immune responses was not previously considered in the pathogenesis of CNS inflammation. However, it recently became clear that the lung acts as a hub organ of pathogenic T cells that are migrating to the CNS. More recent studies further showed that inflamed lung has a critical impact on autoimmune CNS inflammation. Here, we discuss the contribution of the lung in the pathogenesis of CNS autoimmune diseases based on recent reports.

Abbreviations: BBB: blood brain barrier; CNS: central nervous system; CKO: conditional knockout; EAE: experimental autoimmune encephalomyelitis; LAP: LC3-associated phagocytosis; MS: multiple sclerosis.

Background

The central nervous system (CNS), including the brain and the spinal cord, is a vital organ to maintain our life. To maintain its integrity by evacuating from influences of peripheral immune responses, the CNS is segregated by the blood brain barrier (BBB). However, immune cells, especially autoreactive T cells, invade into the CNS by exceeding BBB and cause inflammation and tissue damages during autoimmune CNS inflammation. Such events are seen in multiple sclerosis (MS) and its animal model experimental autoimmune encephalomyelitis (EAE). Thus, infiltration of peripheral immune cells into the CNS is a critical event, disturbing immune homeostasis in the CNS. Because MS and EAE are T cell-dependent autoimmune diseases, infiltration of T cells is considered to be essential to develop the diseases. In particular, Th17 cells, an encephalitogenic helper T cell subset producing a cytokine IL-17, are known to play a critical role in the pathogenesis of MS and EAE^{1,2}. Therefore, multiple therapeutic approaches, which target the mobility or functions of T cells including Th17 cells, have been approved by Food and Drug Administration or studied on clinical trial³.

The lung is a respiratory organ, which converts blood carbon dioxide to oxygen. Circulating blood passes through the lung before circulating through the body. Since the lung is at the center of the circulation system, its strong influence on blood cells is expected. A

seminal article by Odoardi *et al.* reported that pathogenic T cells are licensed in the lung to migrate into the CNS during EAE⁴. The licensing in the lung was demonstrated as enhanced expression of genes encoding chemokine receptors and integrins to promote T cell migration⁴. After T cells' temporary stay in the lung, licensed T cells re-enter the blood stream, then migrate to the CNS. In contrast, T cells that have not licensed in the lungs fail to migrate to the CNS⁴. Although the detailed molecular mechanism of T cell licensing in the lung remains largely unknown, the lung clearly plays a critical role in the development of CNS autoimmunity. In next section, we discuss impacts of lung inflammation during EAE development by reviewing two recent articles.

Inflammation and infection in the lungs affect the development of EAE

The lungs are constantly exposed to environmental stimuli such as pathogens, air dust, and oxidative stress. To maintain the immune homeostasis, the lung has a unique immune system to avoid overreacting to the environmental stimuli^{5,6}. Recent reports from another group and us demonstrated that the course of EAE development is altered when the lung immune homeostasis is disturbed by inflammation or infections^{7,8}. Below, we discuss the two cases of scenario in EAE.

Case 1 - Spontaneous lung inflammation protecting mice from EAE

We found that the lung-specific inflammation caused delayed EAE onset⁷. The finding was seen in mice lacking ATG7 (Autophagy Related 7) in myeloid cells. Since ATG7 is an essential protein for autophagy and LC3-associated phagocytosis (LAP)^{9,10}, ATG7-deficient cells do not perform autophagy and LAP. Myeloid cell-specific ATG7 conditional

knockout mice (*Atg7* CKO mice) develop spontaneous pulmonary inflammation due to the heightened sensitivity to environmental microbes^{11,12}. However, importantly, inflammation in the mice is subclinical and restricted in the lungs¹¹. The lungs of the *Atg7* CKO mice is characterized by enhanced expression of pro-inflammatory cytokines and chemokines, in addition to the infiltration of innate immune cells¹¹.

Delayed EAE onset is found in the *Atg7* CKO mice¹¹. Interestingly, lungs of the *Atg7* CKO mice stall pathogenic T cells, Th17 cells in particular, on the way to migrate to the CNS (Figure 1). This causes the delay of EAE onset, although the mice eventually develop severe EAE as WT mice do¹¹. It should be noted that the delayed EAE onset is not due to defects in pathogenic T cell development because *Atg7* CKO mice have normal numbers of effector T cells and T cell expansion in the draining lymph nodes. EAE onset is also delayed when pathogenic WT Th17 cells were adoptively transferred in *Atg7* CKO recipients¹¹, suggesting that the delayed EAE onset is not caused by T cells. It is possible that elevated CCL20 levels in the inflamed lungs are involved, at least in part. CCL20 is a chemokine to attracts Th17 cells through its receptor, CCR6¹³. Lungs in *Atg7* CKO mice have enhanced *Ccl20* gene expression¹¹, which may explain the stalling of Th17 cells in the lung on the way to the CNS. Indeed, CCL20 is expressed and attracts Th17 cells in the entrance points for inflammatory cells into the CNS, the choroid plexus of the brain and the 5th lumbar of the spinal cord¹⁴⁻¹⁶. *Ccl20* expression is induced by intratracheal instillation of a low dosage of LPS, and inflammation in the lung can be induced¹¹. The LPS instillation delays EAE onset due to the accumulation of Th17 cells in the lung¹¹. Thus, lung inflammation stalls pathogenic T cell migration *en route* to the CNS during EAE development (Figure 1).

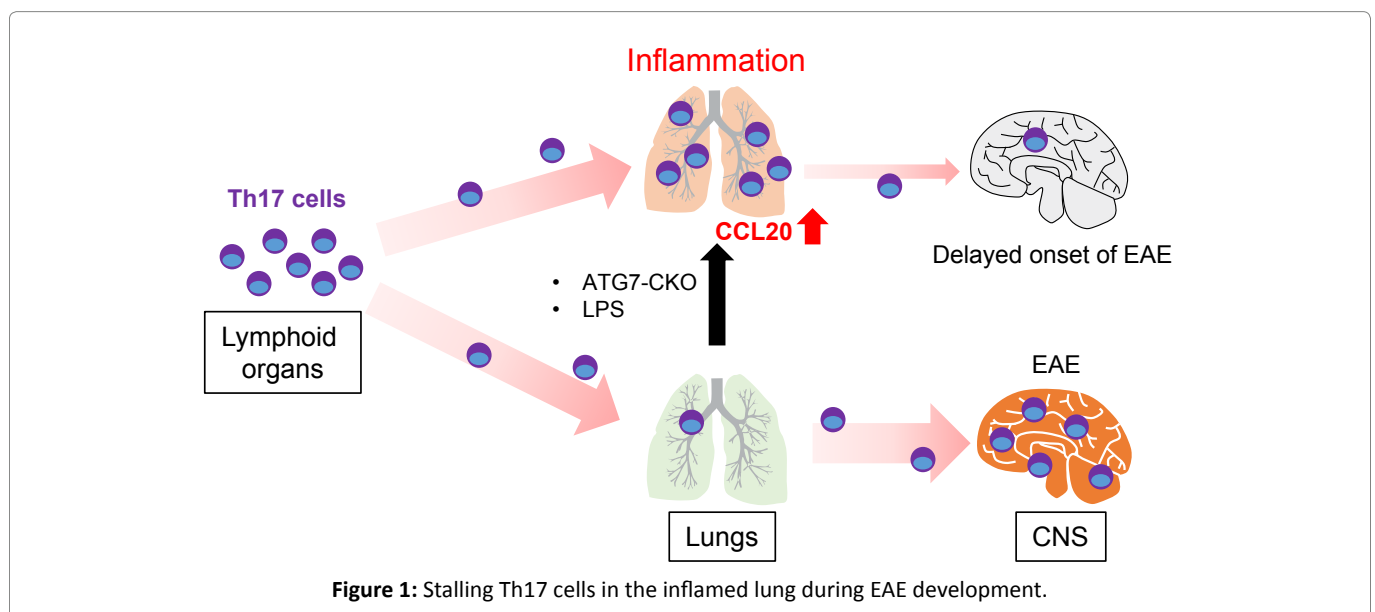


Figure 1: Stalling Th17 cells in the inflamed lung during EAE development.

Case 2 – Bacterial infection in the lung attenuating EAE progression

In the second article, Edwards *et al.* reported attenuated EAE severity with aerosol-inoculated respiratory bacterial infection with *Bordetella pertussis*⁸. Although the study did not mention the possible accumulation of pathogenic cells in the lung, the data showed significantly decreased infiltration of Th17 cells, neutrophils, and macrophages in the brain. The study suggests that the attenuation of EAE is due to IL-10-mediated suppression of T cell licensing in the lung, as well as downregulation of VLA-4 and LFA-1 expression on CD4⁺ T cells⁸. Therefore, the data also suggested the attenuation of the T cell-intrinsic ability to migrate to the CNS.

The two recent studies discussed above on EAE with lung inflammation or pulmonary infection did not show the same outcomes, particularly in disease severity. However, the studies revealed the pathogenic conditions in the lung have a significant impact on the development of the CNS autoimmune disease, and it will be of future interest to clarify what type of pulmonary inflammation is protective.

Impact of lung immune responses in pathogenesis of MS

Since we have discussed two reports on EAE, this section focuses on lung immunity and MS. Some reports suggested the connection between the lung and progression of human CNS inflammation in MS. For example, cigarette smoking has been known to increase a risk of MS^{17,18} and to decrease *Ccl20* expression in the lungs of human¹⁹. Together with our EAE results⁷, these human studies may implicate the decrease of *Ccl20* expression could shorten the period for Th17 cells to stay in the lung of smokers. At the same time, the period may be short but sufficient to license T cells to be encephalitogenic. In addition, upper respiratory infection with viruses is also a risk factor to trigger MS symptom in relapsing-remitting MS patients²⁰⁻²². In this case, virus infection is considered to trigger pathogenic Th1 responses in MS, as well as possible epitope spreading to trigger MS. That said, it does not necessarily mean that lung inflammation could delay or attenuate CNS autoimmunity as seen in EAE, but inflammation near the lung could simply trigger and enhance immune responses.

Concluding remarks

As we discussed in this review, the lung plays an important role as a hub of pathogenic T cells to migrate towards the CNS. The mechanism of T cell licensing in the lungs has not fully understood yet, and inflammation in the lung and proximal tissues could either ameliorate or exacerbates CNS autoimmune diseases. However, if the mechanism becomes clear, it might be possible to manipulate pathogenic T cell migration to the CNS through

the lung. Treatment by drug inhalation from the mouth is not invasive and an effective route to modify immune responses in the lung. Controlling CNS autoimmune diseases, such as MS, by modifying the lung immune system may be considered to be a new approach to treat the diseases.

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