

# HMGB1: a potential target of controlling pulmonary inflammation in people living with HIV

## Opinion

The Acquired immunodeficiency syndrome (AIDS) is commonly known as the result of human immunodeficiency virus (HIV) infection. HIV attacks the human immune system, including CD4+ T lymphocytes, macrophages and dendritic cells, etc. The clinical manifestations after HIV infection are the continuous decrease of CD4+ T lymphocytes, which eventually leads to the deficiency of human immune function, leading to various opportunistic infections and the occurrence of tumors.<sup>1</sup> According to the annual UNAIDS World AIDS Report in Geneva, Switzerland, an estimated 37.9 million people worldwide are living with HIV (about five out of every 1,000 people are infected with HIV), only 23.3 million are receiving antiretroviral therapy and 770,000 die from HIV-related diseases in 2018. Therefore, HIV/AIDS remains an important public health problem that poses a serious threat to human health.

AIDS combined with pulmonary infection is one of the most common diseases in opportunistic infections, accounting for 50%-69.6% of opportunistic infections.<sup>2</sup> The pathogenic microorganism includes bacteria, fungi, *Pneumocystis carinii*, *Mycobacterium*, cytomegalovirus (CMV), etc. CD4+T lymphocytes of HIV-infected patients are progressively reduced or even disappeared, leading to cellular immune deficiency and increasing the probability of lung infection. Pulmonary opportunistic infections were rarely seen in patients with CD4+T lymphocytes >500/mm<sup>3</sup>. When CD4+T lymphocytes were >350/mm<sup>3</sup>, the clinical symptoms were similar to those of ordinary pulmonary tuberculosis patients. However, when CD4+T lymphocytes <200/mm<sup>3</sup>, they were susceptible to *Pneumocystis carinii*, CMV, fungi, bacteria and mycobacterium atypia. There are many different kinds of lung infection, such as *pneumocystis carinii* pneumonia (PCP), CMV pneumonia, toxoplasma infection, tuberculosis, atypical mycobacteria disease and candida pneumonia etc. Among these infections, PCP and tuberculosis occur more frequently, they often exist as one or more pathogenic microorganism. These infections develop fast, bring to clinical diagnosis and treatment of great difficulties, to become one of the leading causes of death among AIDS patients.<sup>3,4</sup>

Previous studies<sup>3,4</sup> showed that AIDS complicated with pulmonary infection was closely related to T lymphocyte subsets, phagocytic function of alveolar macrophages, levels of TNF- $\alpha$ , IL-2 and the expression of TLR2 and TLR4 genes in lung tissue. These factors damage immune defense system of lung, leading to the recessions in the lung function of cilia clearance system, mucus gland secretion of the antimicrobial substances, serum complement components and pulmonary macrophage phagocytosis. Thus, pathogenic microorganisms are inhaled from the airway or ectopic focal infection pathogens are delivered through blood to alveolar, lung infection occurs.

High mobility group box 1 protein (HMGB1), named for its rapid migration in polyacrylamide gel electrophoresis, is a kind of DNA-binding non-histone protein with rich content in the nucleus. It is a new potential late-stage inflammatory mediator, which is involved in the pathogenesis of sepsis and an important late-stage inflammatory mediator of the lethal effect of endotoxin. It was reported to promote cell

activation and release of proinflammatory factors.<sup>5-9</sup> HMGB-1 activates multiple signaling pathways through RAGE (receptor for advanced glycation end products) and/or TLR-induced intracellular signaling pathways, such as MAPkinase and JNK pathways, and subsequent nuclear translocation of NF- $\kappa$ B, leading to the expression of various leukocyte adhesion molecules, pro-inflammatory cytokines, and chemokines.<sup>10,11</sup> It plays a key role in the process of sepsis, chronic obstructive pulmonary disease (COPD), lung infection, arthritis and gastrointestinal tumor. Moreover, it was also been found that signaling pathway of HMGB1/TLR4/NF- $\kappa$ B predominated in the pathogenesis of AIDS.<sup>12,13</sup>

Plasma HMGB1 level in people living with HIV was higher than that of HIV-negative control group, the mRNA expression level of HMGB1 and plasma HMGB1 level in AIDS patients with clinical symptoms were significantly higher than that of HIV-infected patients and HIV-negative control group. The mRNA expression level of HMGB1 and plasma HMGB1 level in AIDS patients with poor efficacy after HAART treatment were also significantly higher than those in the group with good efficacy. When CD4+T cell count was lower than 200/L, HMGB1 content and HMGB1 mRNA expression level in peripheral blood mononuclear cells (PBMCs) were negatively correlated with CD4+T cell count, suggesting that HMGB1 may play an important role in the onset and progression of HIV/AIDS.<sup>13</sup>

Base on the growing evidences that showed pulmonary inflammation in AIDS patients and important effects of HMGB1 in lung infection, we propose that HMGB1 might be a key target of controlling pulmonary inflammation in people living with HIV.

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## Conflicts of interest

The author declares that there are no conflicts of interest.

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