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Perspective:

HIV and paraquat poisoning: fighting fire with fire?*

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Ingestion by humans of paraquat (PQ), a high-efficiency herbicide, can cause extremely high mortality (60%–70%), since it undergoes cellular redox cycling, leads directly to cell damage and triggers uncontrollable inflammatory responses (Gunnell et al., 2007). Once PQ poisoning has occurred, the immune cells of different lineages are activated as major drivers of fibrosis (Fig. 1). Secondary lung fibrosis is the major cause of death.

Because of variable amounts of PQ exposure and individual differences, the outcome of present treatments such as haemoperfusion (HP), antioxidants, and immunosuppressive therapy is not stable and reliable (Zhang et al., 2012; Shao et al., 2015; Zhao et al., 2015; Wang et al., 2017). Some key questions need to be solved to improve clinical outcomes following PQ poisoning. We need to select or develop appropriate drugs based on the pathogenic mechanisms and characteristics of PQ. Thus, finding a suitable therapeutic target for PQ detoxification is a critical step.

It is known that a loss of $CD4^+$ T lymphocytes is the immune compromise caused by the human immunodeficiency virus (HIV). Only three cases of HIV patients with PQ poisoning are listed in PubMed (Ragoucy-Sengler and Pileire, 1996; Shang and Lu, 2015; Tsai et al., 2016). Fortunately, they all had excellent outcomes.

The first case was reported by Ragoucy-Sengler and Pileire (1996). This HIV-infected patient (with a serum concentration of 1.3 μg/ml PQ, five hours after exposure) survived after receiving lavage and diuresis, in spite of clinical and biological prognoses of death. Our team reported the second case of a 34-year-old man who had HIV infection and severe PQ poisoning (Shang and Lu, 2015). He survived with a good outcome despite a usually fatal serum concentration of PQ (2.17 μg/ml, ten hours after exposure) after receiving immunosuppressive therapy and HP. The latest case, published in 2016, involved an HIV patient with PQ poisoning (3.0 μg/ml, three hours after the exposure) who surprisingly survived without treatment (Tsai et al., 2016).

Though cases of HIV patients with PQ poisoning are rare, we found common features among these three cases. The recovered HIV patients tended to suffer much less lung injury than the general PQ-poisoned patients. In addition, they all had low $CD4^+$ T lymphocyte levels due to HIV infection (Ragoucy-Sengler and Pileire, 1996; Shang and Lu, 2015; Tsai et al., 2016). These low counts of $CD4^+$ T lymphocytes confirmed that the patients were in an immunosuppressed condition, which may be conducive to relieving the acute inflammation and lung fibrosis induced by PQ. The HIV-infected status appears to give a protective effect in PQ-poisoned patients. For this reason, immunosuppressive therapy for PQ poisoning seems to be appropriate. $CD4^+$ T lymphocytes might be a suitable target for immunosuppressive therapy (Fig. 1).

Consequently, we suppose the immunosuppressive drugs currently used for PQ detoxification are not optimal. Our next research step is to treat PQ-poisoned patients with $CD4^+$ T lymphocyte-targeted drugs and observe their effects. These drugs, including cyclosprone A, FK506 (tacrolimus), mycophenolate

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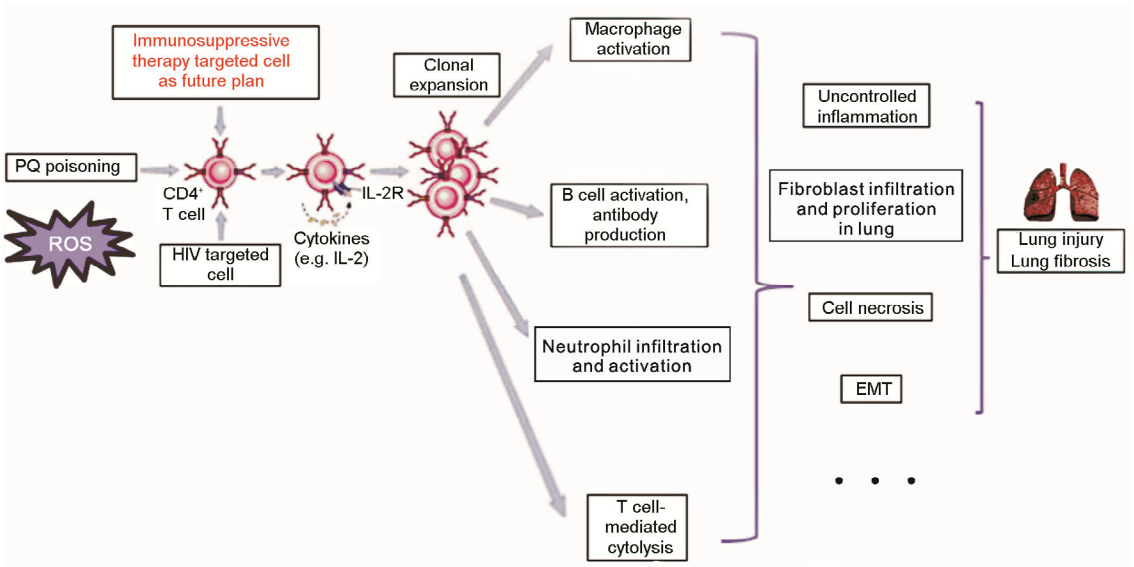

Fig. 1 Immune mechanism of pulmonary fibrosis after PQ poisoning (demonstrated partially via CD4$^+$ T cells)
EMT: epithelial-mesenchymal transition; HIV: human immunodeficiency virus; IL: interleukin; PQ: paraquat; ROS: reactive oxygen species

mofetil (MMF), muromonab CD3 (ortholone), and anti-thymocyte/anti-lymphocyte globulin (ATG/ALG), are commonly used in the treatment of allograft rejection. In the long term, the functional inactivation of a donor organ after transplantation is also a process of inflammation and fibrosis, in which CD4$^+$ T cells play a key role (Hügle, 2011). Therefore, the proposed use of CD4$^+$ T lymphocytes as a target to guide immunosuppressive therapy to improve the prognosis of PQ-poisoned patients could be feasible.

All inferences are uncertain, but science is derived from hypothesis. Herein, we share our ideas with peers, in the hope that we may receive some pertinent suggestions for future work.

Controversy

1. The first debate refers to the fact that the treatments used in these three cases were different. At present, there is no effective treatment for pulmonary fibrosis caused by PQ, and the clinical treatment strategy is yet to be agreed. Although the three cases in this essay had various treatments, my conclusion and inference were not affected. In particular, the two cured patients who did not receive immunosuppressive therapy demonstrated well the importance of the immune mechanism in PQ poisoning.

2. The second controversy surrounds whether the observed low CD4$^+$ T cell counts were due to HIV-1 disease progression or to a PQ poisoning effect. I would like to clarify that this short essay inferred only that CD4$^+$ T cells could be a target of PQ treatment. The low CD4$^+$ T cell counts in the three cases were caused by HIV infection or immunosuppressive treatment, indicating that the patients who survived were all in an immunosuppressive condition. Clinically, the cause of the low level of CD4$^+$ T cells is not a key point.

Compliance with ethics guidelines

Yuan-qiang LU declares that he has no conflict of interest.

This article does not contain any studies with human or animal subjects performed by the author.

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中文概要

题　目：HIV和百草枯中毒：以毒攻毒？

概　要：回顾性分析PubMed收录的仅有3例合并有HIV的急性百草枯中毒患者的救治经过及预后。探索急性百草枯中毒新的免疫治疗。提出采用$CD4^+$ T淋巴细胞作为急性百草枯中毒的免疫治疗精准靶点，可能改善预后，但需要进一步研究和临床实践。

关键词：百草枯；艾滋病病毒；免疫抑制治疗