CORRESPONDENCE

CD24Fc protects against viral pneumonia in simian immunodeficiency virus-infected Chinese rhesus monkeys

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Viral pneumonia is a major cause of mortality caused by both systemic and respiratory infections. The danger-associated molecular patterns (DAMPs) released during cell death in viral infection may cause a self-propagating inflammatory response with lasting lung damage. The CD24–Siglec 10/G interaction is an emerging immune checkpoint that regulates inflammation caused by DAMPs.[1–3] While we have demonstrated that fortifying this immune checkpoint can reduce inflammation in the colon,[4] joints[5] and central nervous system,[6] it is unclear whether CD24Fc can protect against pneumonia. To address this issue, we evaluated the lung pathology of simian immunodeficiency virus (SIV)-infected rhesus monkeys that received either normal saline (NS) or CD24Fc.

As diagrammed in Fig. 1a, 12 Chinese rhesus macaques were infected with SIVmac239 via intravenous infusion of 4000 50% tissue culture infective dose of SIVmac239 as previously described by Tian et al.[4] And then they were randomized into test and control groups that received three injections of CD24Fc or NS, respectively, on day 56 of infection. Five months later, another cycle of treatment was

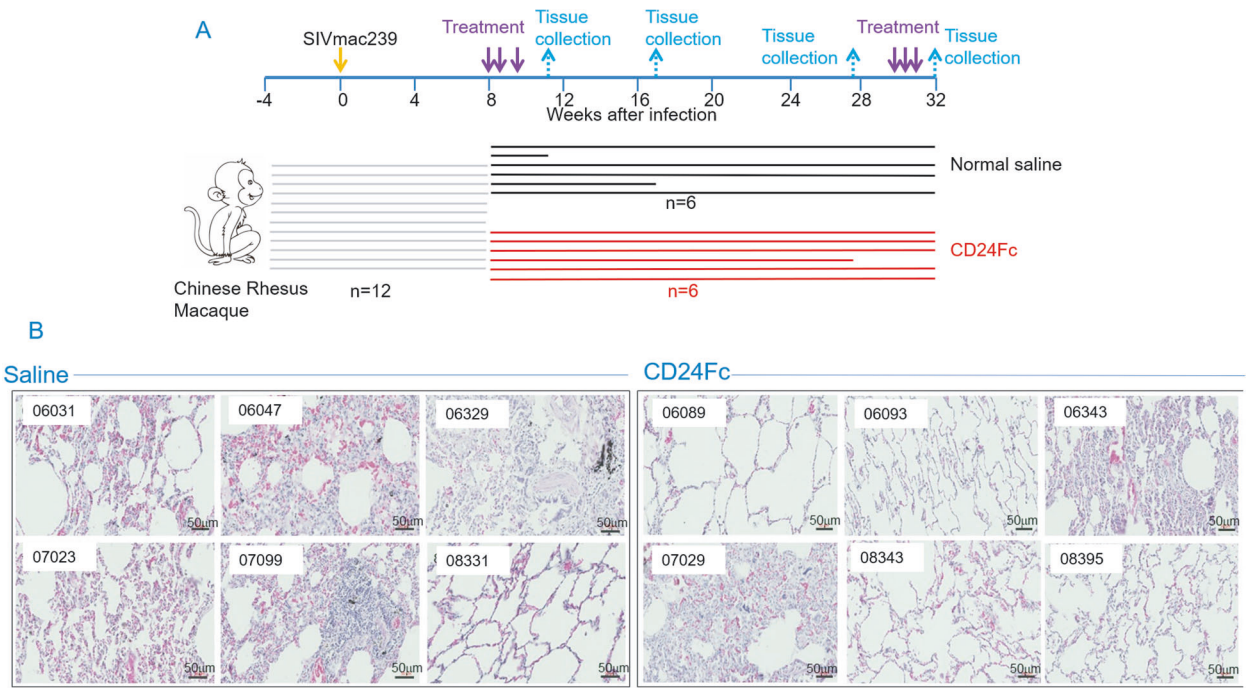

Fig. 1 CD24Fc protects SIV-infected Chinese rhesus monkeys from viral pneumonia. **a** Experimental protocol. The timeline of the study activities is shown at the top. The rhesus monkeys were randomized into two groups at 8 weeks after infection. Lung tissues were harvested either after premature death or at autopsy or necropsy at the termination of the study. Dark lines depict the survival of individual monkeys receiving normal saline, while the red lines depict the survival of monkeys receiving CD24Fc. **b** Representative images of pathological lesions in individual animals receiving normal saline (left) or CD24Fc. Scale bar: 50 μm

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given to the surviving monkeys, which were terminated 1 week after the last dosing for biomarker studies.[4] Lung sections from all randomized animals, regardless of whether they received all the injections, were included in the analysis, as detailed in Supplementary Table 1.

The lung sections obtained from either necropsy or autopsy were fixed with 4% paraformaldehyde and stained with hematoxylin and eosin (H&E). The H&E-stained sections were blinded and independently scored by two researchers for viral pneumonia. The blinded scoring revealed that 5/6 (83%) of control animals developed severe pneumonia, while 2/6 (33%) of CD24Fc-treated animals developed severe pneumonia, indicating a substantial reduction in pneumonia (Table S1, Fig. 1b). The most prominent pathology finding found in both groups of monkeys was interstitial pneumonia (06031, 06047, 06329 and 07099 in the NS group; 06343 and 07029 in the CD24Fc group, Fig. 1b).

In addition to the reduction in the incidence of pneumonia, substantial differences were observed in the pathological features of the NS- and CD24Fc-treated groups. Two control monkeys died within 9 weeks after completion of the first cycle of treatment with NS (Table S1). Both of these monkeys had pathological features of acute respiratory distress syndrome (ARDS), including hyaline membranes lining the alveolar walls in monkey no. 06047 (Supplementary Fig. S1) and alveolar hyaline formation and desquamation of pneumocytes in monkey no. 07099 (Supplementary Fig. S2). Since these features were not observed in the CD24Fc-treated group, our data suggest that CD24Fc may have protected monkeys against ARDS. Other features found in the control group but not in the CD24Fc-treated group included haemorrhage (06031, 06047 and 07023, Fig. 1b), giant cell formation (06047, Supplementary Fig. S3) and perivascular inflammation (06329 and 7099 in the control group).

Taken together, our data revealed that CD24Fc not only reduces the incidence of viral pneumonia but also qualitatively alters the nature of pathology in the lung. Previous studies have demonstrated that lung lesions developed within 2–4 weeks in SIV-infected rhesus monkeys. By 8 weeks, essentially all monkeys developed lung pathology, including perivascular inflammation, vasculitis, interstitial pneumonia and syncytial cells.[7] Since our treatment was initiated at 8 weeks after infection, our data demonstrate that CD24Fc has a therapeutic effect on SIV-induced lung inflammatory lesions. CD24Fc is an agonist of Siglecs and can fortify the CD24-Siglec innate immune checkpoint. In particular, we have shown that the CD24-Siglec pathway can protect against destructive inflammation triggered by cell death.[1] Since the death of pneumocytes is a prominent feature of COVID-19, and ARDS is a major cause of mortality due to COVID-19,[8] it would be of interest to test CD24Fc as a COVID-19 therapy.

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ADDITIONAL INFORMATION

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