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CD24 and Fc fusion protein protects SIVmac239-infected Chinese rhesus macaque against progression to AIDS

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ABSTRACT

Chronic immune activation and systemic inflammation are underlying causes of acquired immunodeficiency syndrome (AIDS). Products of virus replication and microbial translocation, co-infection or opportunistic pathogens, and danger-associated molecular patterns have been reported to contribute to chronic immune activation and inflammation in human immunodeficiency virus type-1/simian immunodeficiency virus (HIV-1/SIV) infection or other disease. To develop new strategies and therapies for HIV-1/AIDS, we tested if the CD24 and Fc fusion protein (CD24Fc), which interacts with danger-associated molecular patterns and sialic acid binding Ig-like lectin to attenuate inflammation, can protect Chinese rhesus macaques (ChRMs) with SIV infection. We found that CD24Fc treatment decreased weight loss, wasting syndrome, intractable diarrhea, and AIDS morbidity and mortality, while it was well tolerated by SIV-infected animals. Corresponding to the elimination of intractable diarrhea, CD24Fc significantly reduced the expression of IL-6 and indoleamine 2, 3-dioxygenase-1 in peripheral blood mononuclear cell and inflammation in the ileum, colon and rectum based on the reduction of inflammatory cells, pathological scores and expression of inflammatory cytokines. Furthermore, although CD24Fc did not restore $CD4^+$ T cell number or significantly change T cell subsets or $CD4^+$ T cell activation, it maintained low levels of plasma soluble CD14, $CD8^+$ T cell activation, viral load and proviral load in the peripheral blood mononuclear cells and marrow. These results suggested that CD24Fc confers protection to SIV-infected ChRMs against progression to AIDS. It was also implied that CD24Fc may be a potential therapeutic approach for the control of HIV-1/AIDS.

1. Introduction

Despite the revolutionary advances in anti-human immunodeficiency virus type-1 (HIV) therapy, HIV-1/acquired immunodeficiency syndrome (AIDS) remains one of the biggest threats in global health. Chronic immune activation is a strong independent

Abbreviations: CD24Fc, CD24 and Fc fusion protein; HIV, human immunodeficiency virus type-1; SIV, simian immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; DAMP, danger-associated molecular patterns; Siglec, sialic acid binding Ig-like lectin; ChRMs, Chinese rhesus macaques; cART, combination antiretroviral therapy; IDO, indoleamine 2, 3-dioxygenase-1; MPO, myeloperoxidase; PBMC, peripheral blood mononuclear cells

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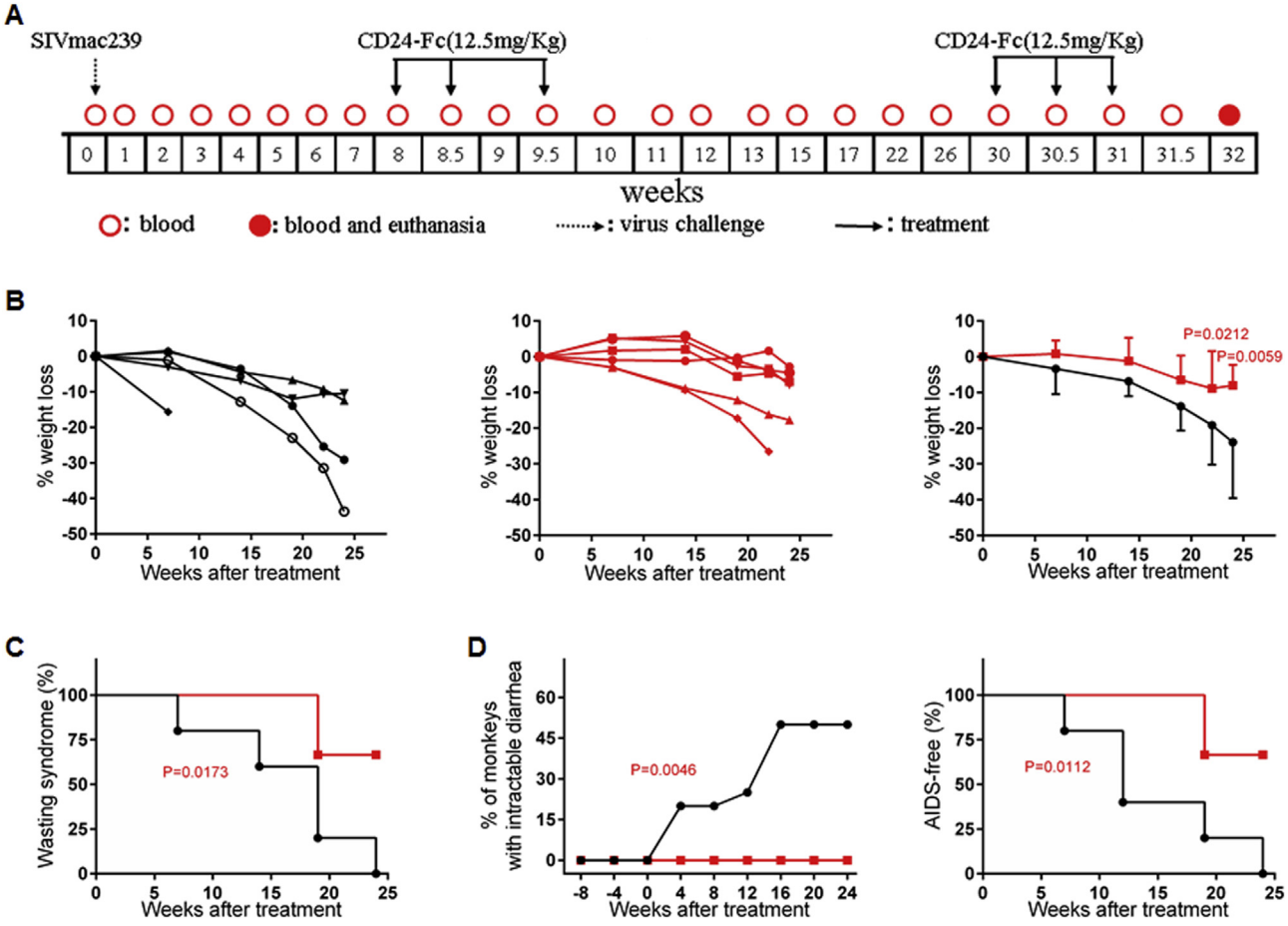

Fig. 1. CD24Fc protects Chinese rhesus macaque from AIDS caused by SIVmac239 infection. (A) Diagram of the experimental schedule. (B) Weight loss of SIVmac239-infected monkeys after vehicle (left) or CD24Fc treatment (middle). Summary data from the study are shown in the right panel. Data are presented as mean ± standard deviation (SD). (C–E) CD24Fc protects SIVmac239-infected monkey against wasting syndrome (C), diarrhea (D) and AIDS morbidity and mortality (E). Control group (circle, n = 5), CD24Fc treated group (square, n = 6). Single independent experiment/measurement was included for each animal at each time point.

predictor of disease progression and associated with impaired immune reconstitution in HIV-1-infected individuals in combination antiretroviral therapy (cART) (Pallikkuth et al., 2013). On the one hand, chronic immune activation leads to inflammation, and both immune activation and inflammation induce immunosenescence (Deeks, 2009). On the other hand, chronic inflammation causes tissue and organ damage (Rajasuriar et al., 2015; Younas et al., 2016), resulting in other non-AIDS complications, including cardiovascular, liver, and renal diseases (Deeks et al., 2013; Rajasuriar et al., 2015). Current approaches to attenuate chronic immune activation and inflammation include a combination of cART with inhibitors of cytokines and their receptors, anti-inflammatory drugs and immunosuppressants (Rajasuriar et al., 2013). In contrast, much less attention has been focused on addressing the underlying cause of inflammation. While inflammation can be caused by HIV infection and co-infection by other pathogens (Hunt et al., 2011; Kristoff et al., 2014; Paiardini and Muller-Trutwin, 2013; Sandler et al., 2014), the high frequency of AIDS patients with well-controlled viral infection, but poor immune reconstitution suggests that chronic inflammation propagates in the absence of overt viral replication.

Danger-associated molecular patterns (DAMPs) are intracellular components released during necrosis, pyroptosis, and secondary necrosis following apoptosis. By triggering Toll-like receptors and/or Nod-like receptors individually or in combination with other stimulators, DAMPs contribute to chronic immune activation and systemic inflammation (Chen et al., 2011; Lotze and Tracey, 2005), resulting in chronic inflammation and autoimmune disease (Kang et al., 2015; Shin et al., 2015; Venereau et al., 2016). Since necrosis and pyroptosis are prevalent during HIV infection and AIDS, DAMPs have been proposed to contribute to systemic immune activation (Troseid et al., 2011). Thus, in HIV-1 infected patients, it has been reported that increased levels of DAMPs, such as high mobility group box 1 and heat shock protein 70, are associated with the rapid loss of immune cells and rapid progression of AIDS (Agnew et al., 2003; Anraku et al., 2012; Espigares et al., 2006; Kocsis et al., 2003; Kuwata et al., 2009; Rawson et al., 2007; Troseid et al., 2010).

Although cART might reduce the levels of DAMPs, they did not eliminate the initial elevation of DAMPs after effective control of viral replication (Anraku et al., 2012; Nowak et al., 2007). It is therefore intriguing to explore if one can improve the outcome of AIDS therapy by targeting the host response to DAMPs. In this context, Chen et al. reported that CD24 interacts with DAMPs and forms a trimolecular complex with sialic acid binding Ig-like lectin G (Siglec G) in the mouse and Siglec 10 in primates. The CD24-Siglec G/10 pathway negatively regulates host response to DAMPs, while abrogation of either CD24 or the Siglec G gene in the mouse greatly exacerbates the inflammatory response to tissue injuries (Chen et al., 2011). More recently, it has been demonstrated that CD24 and Fc fusion protein (CD24Fc), a soluble CD24 fusion protein that interacts with both DAMPs and Siglecs (Chen et al., 2009, 2011), attenuates the host response to DAMPs and protects mice against rheumatoid arthritis and graft vs host disease (Toubai et al., 2014). It is therefore intriguing to test whether CD24Fc may