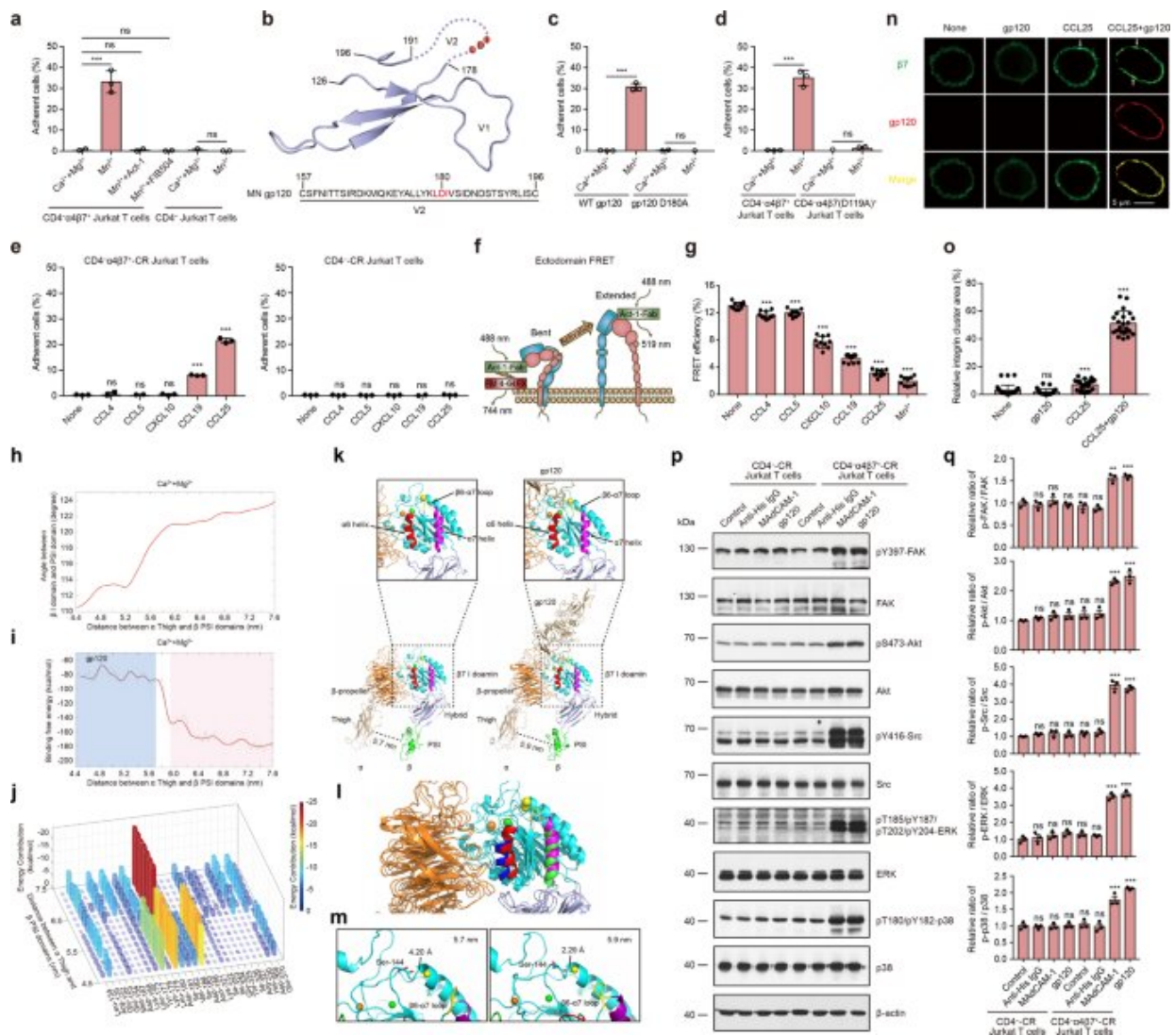


Treatment with anti- $\alpha 4\beta 7$ monoclonal antibody efficiently reduces transmission of SIV

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Distinct chemokines selectively induce HIV-1 gp120-integrin $\alpha 4\beta 7$ binding via

triggering conformer-specific activation of $\alpha 4\beta 7$. a Adhesion of CD4– Jurkat T cells or CD4– $\alpha 4\beta 7+$ Jurkat T cells to immobilized gp120 in 1 mM Ca²⁺/Mg²⁺ or 0.5 mM Mn²⁺. b A diagram of the V1 and V2 domains of gp120 was drawn based on the crystal structure of BG505 SOSIP.664 gp120 (PDB: 3J5M). Light red shadow indicates integrin $\alpha 4\beta 7$ binding site in the V2 loop. Dashed lines indicate the location of gp120 V2 loop. The sequence of the V2 domain of MN gp120 was provided at the bottom and the potential integrin $\alpha 4\beta 7$ binding motif in gp120 is highlighted in red. c Adhesion of CD4– $\alpha 4\beta 7+$ Jurkat T cells to the immobilized gp120 or gp120 D180A in 1 mM Ca²⁺/Mg²⁺ or 0.5 mM Mn²⁺. d Adhesion of CD4– $\alpha 4\beta 7+$ Jurkat T cells and CD4– $\alpha 4\beta 7$ (D119A)+ Jurkat T cells to immobilized gp120 in 1 mM Ca²⁺/Mg²⁺ or 0.5 mM Mn²⁺. e Adhesion of CD4–CR Jurkat T cells or CD4– $\alpha 4\beta 7+$ -CR Jurkat T cells to the immobilized gp120 in 1 mM Ca²⁺/Mg²⁺ with and without chemokine stimulation. f Experiment setup for measuring FRET efficiency between integrin $\alpha 4\beta 7$ β I domain and the plasma membrane (Ectodomain FRET). A composite of all molecules used is depicted. g FRET efficiency of CD4– $\alpha 4\beta 7+$ -CR Jurkat T cells before and after treatment with 0.5 μ g/ml chemokines or 0.5 mM Mn²⁺. h Relationship of the distance between integrin α Thigh and β PSI domains and the angle between β I domain and PSI domain in Ca²⁺/Mg²⁺. i Binding free energy profiles of integrin $\alpha 4\beta 7$ headpiece to gp120 in Ca²⁺/Mg²⁺ during the conformational transition. j Per-residue free energy decomposition of the residues at the interface of integrin $\alpha 4\beta 7$ headpiece and gp120 complex from the MM/GBSA. The residues of gp120 with energy contributions stronger than –1 kcal/mol along the conformational path of $\alpha 4\beta 7$ headpiece are illustrated. The color bar is set in the range of –25–0 kcal/mol. k Snapshot of integrin $\alpha 4\beta 7$ headpiece with a distance of 5.7 or 5.9 nm between $\alpha 4$ Thigh and $\beta 7$ PSI domains. The $\alpha 6$ and $\alpha 7$ helices of the $\beta 7$ I domain are colored in red and purple, and SyMBS, MIDAS, and ADMIDAS metal ions are colored in orange, green, and yellow spheres, respectively. l Superposition of integrin $\alpha 4\beta 7$ headpiece with a distance of 5.7 or 5.9 nm between $\alpha 4$ Thigh and $\beta 7$ PSI domains. The $\alpha 6$ and $\alpha 7$ helices of the $\beta 7$ I domain were shown in red and purple in 5.7 nm structure, and in blue and green in 5.9 nm structure. m The change of the distance of ADMIDAS metal ion to the backbone carbonyl of Ser-144 located at $\beta 1$ - $\alpha 1$ loop region and the movement of the $\beta 6$ - $\alpha 7$ loop (yellow colored) during the transition from 5.7 to 5.9 nm between $\alpha 4$ Thigh and $\beta 7$ PSI domains. n Confocal microscopy visualization of the integrin clustering on the plasma membrane of CD4– $\alpha 4\beta 7+$ -CR Jurkat T cells. Integrin $\beta 7$, green;

gp120, red. White arrowheads indicate the representative integrin clusters. Scale bar, 5 μm . o The relative integrin cluster area was calculated as the percentage of the fluorescence intensity of integrin clusters in relation to that of the entire cell surface. p, q CD4⁺CR Jurkat T cells or CD4⁺ α 4 β 7⁺-CR Jurkat T cells were pre-treated with CCL25 (0.5 $\mu\text{g}/\text{ml}$, in HBS with 1 mM Ca²⁺/Mg²⁺) for 15 min at room temperature. Then cells were stimulated with anti-His IgG (100 $\mu\text{g}/\text{ml}$), MAdCAM-1 (100 $\mu\text{g}/\text{ml}$) or gp120 (500 $\mu\text{g}/\text{ml}$) for 30 min at 37 °C, respectively. The expression and phosphorylation of FAK, Akt, Src, ERK, and p38 were determined by immunoblot analysis (p). The relative ratios of p-FAK/FAK, p-Akt/Akt, p-Src/Src, p-ERK/ERK, and p-p38/p38 were normalized to the values of CD4⁺CR Jurkat T cells without stimulation (Control) (q)

A research group led by Prof. Li Guohui from the Dalian Institute of Chemical Physics (DICP) of the Chinese Academy of Sciences (CAS), in collaboration with Prof. Chen Jianfeng's group from Shanghai Institute of Biochemistry and Cell Biology of CAS, revealed the regulation mechanism of integrin α 4 β 7 mediated human immunodeficiency virus 1 (HIV-1) infection.

This study was published in *Signal Transduction and Targeted Therapy* on July 16.

Integrin α 4 β 7, an important cell surface adhesion molecule, is responsible for mediating lymphocytes from [blood circulation](#) into the intestine and central nervous system. The abnormality of its function is closely related to human autoimmune diseases.

Previous studies have shown that intestinal homing CD4⁺ T [cells](#) expressing [integrin](#) α 4 β 7 are the early targets of HIV-1 virus [infection](#), which plays an important role in the pathogenesis of HIV-1 infection.

The binding between the envelope [protein](#) gp120 located on the surface

of the HIV-1 virus and the receptors on the surface of CD4+ T cells is a key step for HIV-1 to infect T cells.

In this study, the researchers investigated the interaction between integrin $\alpha 4\beta 7$ and gp120. They found that specific intestinal chemokines could stimulate integrin $\alpha 4\beta 7$ in a relatively stretched condition, leading to a highly activated conformation state, and it enabled integrin $\alpha 4\beta 7$ to bind the HIV-1 envelope protein gp120. While, the inactive integrin $\alpha 4\beta 7$ exhibited no binding ability with HIV-1 envelope protein gp120.

Moreover, they indicated that the interactions between the metal ion-dependent adhesion site (MIDAS) in the integrin $\beta 7$ subunit and the highly conserved tripeptide LDI in the HIV-1 envelope protein gp120 were the key site for integrin $\alpha 4\beta 7$ mediated HIV-1 infection.

In addition, they also found that the interactions between integrin $\alpha 4\beta 7$ and HIV-1 envelope protein gp120 might activate multiple intracellular signaling pathways, which further regulated HIV-1 virus replication and T cell function.

"This study would provide new strategies and ideas for the prevention and treatment of HIV-1 infection and the screening of related drugs," said Prof. Li.

More information: Shu Wang et al, Distinct chemokines selectively induce HIV-1 gp120-integrin $\alpha 4\beta 7$ binding via triggering conformer-specific activation of $\alpha 4\beta 7$, *Signal Transduction and Targeted Therapy* (2021). [DOI: 10.1038/s41392-021-00582-8](https://doi.org/10.1038/s41392-021-00582-8)

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