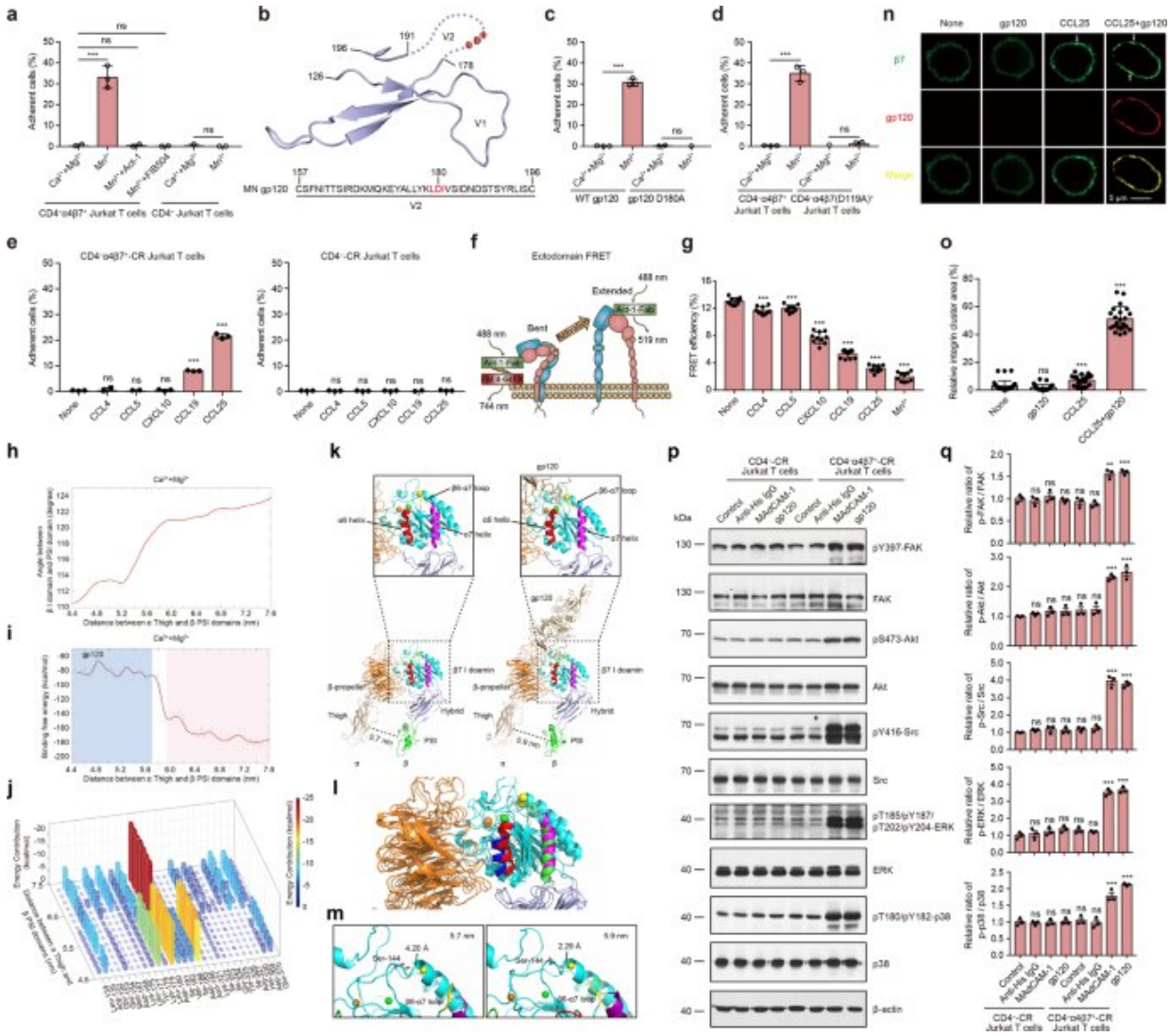
Medical Xpress

Treatment with anti-α4β7 monoclonal antibody efficiently reduces transmission of SIV

July 20 2021, by Li Yuan



Distinct chemokines selectively induce HIV-1 gp120-integrin α4β7 binding via

triggering conformer-specific activation of α4β7. a Adhesion of CD4– Jurkat T cells or CD4–α4β7+ 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 α4β7 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 α4β7 binding motif in gp120 is highlighted in red. c Adhesion of CD4–α4β7+ Jurkat T cells to the immobilized gp120 or gp120 D180A in 1 mM Ca2+/Mg2+ or 0.5 mM Mn2+. d Adhesion of CD4–α4β7+ Jurkat T cells and CD4–α4β7(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–α4β7+-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 α4β7 β I domain and the plasma membrane (Ectodomain FRET). A composite of all molecules used is depicted. g FRET efficiency of CD4–α4β7+-CR Jurkat T cells before and after treatment with 0.5 μg/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 α4β7 headpiece to gp120 in Ca2+/Mg2+ during the conformational transition. j Per-residue free energy decomposition of the residues at the interface of integrin α4β7 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 α4β7 headpiece are illustrated. The color bar is set in the range of −25–0 kcal/mol. k Snapshot of integrin α4β7 headpiece with a distance of 5.7 or 5.9 nm between α4 Thigh and β7 PSI domains. The α6 and α7 helices of the β7 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 α4β7 headpiece with a distance of 5.7 or 5.9 nm between α4 Thigh and β7 PSI domains. The α6 and α7 helices of the β7 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 β1-α1 loop region and the movement of the β6-α7 loop (yellow colored) during the transition from 5.7 to 5.9 nm between α4 Thigh and β7 PSI domains. n Confocal microscopy visualization of the integrin clustering on the plasma membrane of CD4–α4β7+-CR Jurkat T cells. Integrin β7, 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–α4β7+-CR Jurkat T cells were pre-treated with CCL25 (0.5 μg/ml, in HBS with 1 mM Ca2+/Mg2+) for 15 min at room temperature. Then cells were stimulated with anti-His IgG (100 μg/ml), MAdCAM-1 (100 μg/ml) or gp120 (500 μg/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 α4β7 mediated human immunodeficiency virus 1 (HIV-1) infection.

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

Integrin α4β7, 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 α4β7 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 α4β7 and gp120. They found that specific intestinal chemokines could stimulate integrin α4β7 in a relatively stretched condition, leading to a highly activated conformation state, and it enabled integrin α4β7 to bind the HIV-1 envelope protein gp120. While, the inactive integrin α4β7 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 β7 subunit and the highly conserved tripeptide LDI in the HIV-1 envelope protein gp120 were the key site for integrin α4β7 mediated HIV-1 infection.

In addition, they also found that the interactions between integrin α4β7 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 α4β7 binding via triggering conformer-specific activation of α4β7, *Signal Transduction and Targeted Therapy* (2021). DOI: 10.1038/s41392-021-00582-8

Provided by Chinese Academy of Sciences