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Structural Basis for Specific Membrane Targeting by the HIV-1 Gag Protein.[1]

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In HIV-1 infected cells, newly synthesized retroviral Gag polyproteins are directed to specific cellular membranes where they assemble and bud to form immature virions. Membrane binding is mediated by Gag's matrix (MA) domain, a 132-residue polypeptide containing an N-terminal myristyl group that can adopt sequestered and exposed conformations. Membane specificity was recently shown to be regulated by phosphatidylinositol-(4,5)-bisphosphate (PI(4,5)P2), a cellular factor abundant in the inner leaflet of the plasma membrane (PM). We now show that phosphoinositides, including soluble analogs of PI(4,5)P2 with truncated lipids, bind HIV-1 MA and trigger myristate exposure. The phosphoinositol moiety and one of the fatty acid tails binds to a cleft on the surface of the protein. The other fatty acid chain of PI(4,5)P2 and the exposed myristyl group of MA bracket a conserved basic surface patch implicated in membrane binding. Our findings indicate that PI(4,5)P2 acts as both a trigger of the myristyl switch and as a membrane anchor, and suggest a structure-based mechanism for the specific targeting HIV-1 Gag to PI(4,5)P2-enriched membranes.

[1]In collaboration with Jamil S. Saad, Jaime Miller, Janet Tai, Andrew Kim, and Ruba H. Ghanam, University of Maryland Baltimore County.