Structural Basis For Host Trna Control Of HIV-1 Gag Localization

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The HIV-1 Gag polyprotein drives and coordinates all steps in viral particle assembly. Indeed, the sole expression of Gag in human cells is sufficient to form virus-like particles that are nearly indistinguishable from immature virions (1). The N-terminal matrix (MA) domain of Gag specifies viral particle assembly sites by a direct interaction between its highly basic region (HBR) and phosphatidylinositol-4,5-bisphosphate (PIP2), a plasma membrane resident phospholipid (2,3). Surprisingly, crosslinking immunoprecipitation sequencing (CLIP-seq) analyses revealed that MA strongly associates with a subset of host tRNA in infected cells (4). In vitro experiments suggested that tRNA could competitively inhibit MA binding to membranes and liposomes (5,6). However, the nature, specificity, and biological function of the observed MA-tRNA interactions remain unknown.

To understand how Gag recognizes tRNA, we report a co-crystal structure of HIV-1 MA bound to human tRNALys3 at 3.15 Å resolution (7). The structure and attendant mutational, fluorescence, NMR, and CLIP-seq analyses revealed that MA specifically recognizes the "elbow" structure, a defining surface feature of cytosolic tRNAs, using a preorganized set of basic and aromatic residues of the HBR. The observation that MA uses the same interface to interact with either PIP2 or tRNA explains their mutually exclusive binding. The precise manner by which MA recognizes tRNA elbow borrows and blends strategies employed by both protein and RNA machines of the host, in a remarkable case of viral mimicry, elaboration and evolution.

Further, we identify a single amino-acid substitution that selectively abolishes MA-tRNA binding (K32A), which caused striking redistribution of Gag to the plasma membrane and significantly reduced HIV-1 replication. Together, this work reveals that HIV-1 has evolved an extraordinary dual parasitism of host tRNAs, which are exploited not only as primers of reverse transcription, but also as regulators of Gag protein subcellular localization and, thus, viral particle assembly.

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