Structural Basis of Drug-Induced Aggregation of HIV Integrase

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The major effect of allosteric HIV integrase (IN) inhibitors (ALLINIs) is observed during virion maturation, where ALLINI treatment results in IN aggregation and the formation of aberrant particles. Previously, to investigate the mechanism of action of ALLINIs, we crystallized full-length HIV IN bound with an ALLINI and determined the structure of this complex at 4.4 Å resolution. We have extended these ongoing structural studies to include new crystallographic structures with additional ALLINIs and complexes with resistance mutations. The structures reveal the formation of an open polymer, with dimers of IN interacting in a head-to-tail manner. An interface between the catalytic core domain of one dimer with the C terminal domain of an adjacent dimer forms around the ALLINI, which is deeply buried by IN surfaces. These surfaces are rich in residues that convey resistance to ALLINIs, as identified by serial viral passage experiments. Escape mutants were found to decrease drug-induced aggregation, and crystallographic studies of escape mutants support a model where ALLINIs disrupt virion maturation by inducing the formation of the polymer observed in the IN-ALLINI crystal structure. Biophysical analyses informed by these structures and using SEC-SAXS and CG-MALS suggest a novel structural model for IN oligomerization, supported by transmission electron microscopy examination of ALLINI-induced IN aggregates. Characterization of the higher order IN-ALLINI complexes and resulting escape mutants provides important data for optimizing ALLINI drug design and understanding mechanisms of resistance.