

Molecular Dynamics Evidence for Enzymatic Enabling of the Re-Conformation of the HIV-1 Coat Glycoprotein gp120

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Problem statement

- Each year since 2000, $\sim 0.02N$, where N is the number of years since 2000, of newly diagnosed HIV-1 cases escape ([8]) the conventional therapeutic regimen (protease- and reverse-transcriptase-inhibitor “cocktail”; [9]). At this escape rate, $\sim 30\%$ of newly diagnosed AIDS cases will be untreatable in 15 years.
- The law of independent probabilities ([12], p. 322) implies we need a drug arsenal that attacks a more comprehensive range of independent targets in HIV-1 than the conventional regimen does

Selecting a target

- gp120, an HIV-1 coat glycoprotein essential to fusion with the host cell membrane ([1]), is known to exist in at least two kinetically stable conformations. The first of these re-conforms to the second during transport (“PDB” = [16]):
 - a non-antigenic conformation (exemplar: PDB 2BF1 ([1], [10]), simian, unliganded), which cannot fuse with the cell membrane
 - an antigenic conformation (exemplar: PDB 1GC1 ([2], [10]), human, complexed with CD4 and Fab), which can fuse with the cell membrane
- If $\Delta G < 0$ for the gp120 re-conformation, it is plausible that the transition is facilitated by an enzyme ([5], p. 293). *This enzyme would be a candidate target for a new drug.* Else, it is unlikely that there is any immediate enzymatic mediation of the transition

Method

- Empirical force-field molecular dynamics (MD) simulation (NAMD2, [3]) was applied to the alignable regions of 2BF1 and 1GC1 (“G” chain only) and to regions of difference in the primary structures (*in isolation*) to generate conformations at 300 K, assuming
 - non-periodic boundary
 - CHARMM22 force definitions
 - 12 Å smooth non-bonded interaction cutoff
 - 13.5 Å pairlist distance
 - TIP3 water specification
 - missing coordinates “guessed” (by [3])
 - 20K steps
 - all else defaulted
- Alchemical free energy perturbation methods ([4]; [7], pp. 564 ff.) were applied to the above results to compute ΔG for the re-conformation

Results

- The calculations yield $\Delta G \cong -2 \text{ kcal/mol}$ for the re-conformation
- Considered in isolation, the contributions to ΔG arising from differences in the primary structures of the exemplars are less than 10% of the ΔG for the re-conformation
- $\Delta G \cong -2 \text{ kcal/mol}$ lies in the nominal range of ΔG values for enzymatically facilitated, non-metabolic, biological reactions ([6], pp. 129-130)
- Therefore, it is plausible that an enzyme facilitates the re-conformation of gp120. Such an enzyme is a candidate target for a new drug.
- Several caveats apply ([7], pp. 577 ff.); at the least, other MD setups/methods should be used to check these results; collaboration is welcome

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