A Novel Approach to Solve Target Mutation-Induced Drug Resistance for HIV-1 Fusion Inhibitors with the Hopfield Neural Network

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The formation of a hairpin core structure by the human immunodeficiency virus type 1 (HIV-1) transmembrane glycoprotein gp41 is the critical event that triggers viral fusion to the host cell. Fusion inhibitors are drugs that prevent the formation of a hairpin core by binding with the gp41 N-terminal Heptad Repeat (NHR). However, mutations on the NHR can cause some fusion inhibitors to lose their effectiveness at binding to the NHR, which results in a potency loss; this leads to HIV-1 drug resistance. This research analyzed the stability of the NHR-inhibitor complex and rigorously solved for the energy state of this complex by developing an energy function from the Hopfield neural network. By analyzing how induced mutations affect the stability of the complex, the fusion inhibitors that would still be effective against certain mutations were identified. Computational results were shown to be consistent with experimental results. After the validation of the energy function, randomly generated HIV-1 mutations in a much larger complex pool were tested by the mean-field theory approximation of the function itself in order to efficiently capture mutations that could cause a large percentage of potency loss. Once identified, these newly discovered mutations were then tested rigorously using the energy function again to validate if these mutations indeed caused a significant amount of inhibitor potency loss. This research not only identifies which drugs are effective against which mutations, but also identifies new mutations that should be considered when designing an HIV-1 fusion inhibitor.

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