THE USE OF AI AND ADVANCED COMPUTER SYSTEMS TO DEVELOP DRUGS AGAINST NEW EMERGING THREATS

Leveraging Ai And Experimental Approaches To Identify Short Linear Interacting Motifs (slims) For Antiviral Therapeutics

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Many cellular processes are regulated through the formation of protein-protein interactions that rely on interfaces formed by short linear interaction motifs (SLiMs). Interestingly, SLiM sequences are found in many viral proteins, and several SLiMs mimic the function of SLiMs found in host proteins. This suggests that targeting cellular pathways regulated by interactions involving SLiMs is a common mechanism used by viral proteins during infections. Continuing and unpredictable infections by hemorrhagic fever viruses (HFVs) poses a global health risk, especially from those viruses for which there is a lack approved drugs. Our hypothesis is that there are conserved host pathways regulated by interactions involving SLiMs that are exploited by HFVs that can be targeted for developing broad spectrum therapeutics. Therapeutics that target host proteins that are essential for HVF replication represent an attractive therapeutic option, as these molecules tend to have broad-spectrum antiviral activity and are less likely to lead to the formation of resistant strains.

To develop a pipeline for identifying therapeutic targets, we are combining biochemical, bioinformatics, and structural biology with artificial intelligence (AI) based modeling to identify SLiMs within viral proteins that mediate key host-viral protein interactions. As an initial example, we are investigating the LIR (LC3-interacting region) motif, a SLiM found in regulatory factors that interact with LC3-family proteins to regulate autophagy. Importantly, LIRs are over-represented in viral proteins and the autophagy pathway is a known target of several different HVFs. To initiate our methodology, phage display analysis was performed to identify 16-mer peptides that bound with high affinity and specificity to the six human LC3-family proteins (LC3A, LC3B, LC3C, GABARAP, GABARAPL1 and GABARAPL2). Structural models of the selected 16-mer peptides in complex with their target LC3 protein were then generated using AlphaFold and analyzed by FoldX to characterize the binding interfaces. In addition, the human genome and the genomes from several HFVs were analyzed to identify proteins that contain LIRs with high sequence similarity to the peptides identified in the phage display. Select sequences from the human and viral proteins are then evaluated biophysically (Isothermal Titration Calorimetry) and structurally (X-ray crystallography) to characterize their binding with their LC3 targets. We will present our experimental results and demonstrated how they are being incorporated into machine learning protocols to identify key LIR motifs in host and viral proteins that could serve as targets for developing broad-spectrum therapeutics against HVFs.

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