

Targeting Intrinsically Disordered Regions (IDRs) in Viral Proteins via Molecular Recognition Features (MoRF) Analysis

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In order to replicate, viral proteins hijack the host machinery. They interact with numerous viral proteins using molecular recognition features (MoRFs- induced folding upon binding) located inside intrinsically disordered regions (IDRs) during the infection cycle [1, 2]. IDRs are widely distributed in viral genomes and are often found to be associated with the pathogenicity and oncogenicity caused by the viruses [3]. This study looked into the IDRs/MoRFs found in the emerging viral diseases Human parainfluenza 4A virus (HPIV-4A) and Chandipura virus (CHPV). A rare infection, HPIV-4A, produces a milder respiratory disease. CHPV, on the other hand, is linked to encephalitic illness. In previous studies, Measles morbillivirus virus (MeV) and Vesicular stomatitis virus (VSV) were chosen as representative family viruses of HPIV-4A and CHPV, respectively, because they are densely ornamented with IDRs [4, 5]. Since phosphoprotein is highly disordered and needed for replication and transcription, it could be a promising drug target [6]. The IDRs/MoRFs found in phosphoprotein were targeted using conserved domain analysis and molecular docking. The compounds used in this docking study were then divided into three categories: phytochemicals, repurposed drugs, and antiviral drugs. To summarise, when compared to anti-viral drugs, repurposed drugs (derived from plants) and phytochemicals are the most effective inhibitors of MeV phosphoprotein. Antiviral approaches have so far been used to target viral structural proteins such as polymerase and protease [7]. Unfortunately, pharmacological inhibition of these structural proteins is sometimes surprisingly ineffective due to drug resistance. Inhibiting conserved MoRFs is a novel alternative to this strategy.

References:

- [1] Disfani FM, Hsu WL, Mizianty MJ, Oldfield CJ, Xue B, Dunker AK, Uversky VN, Kurgan L. MoRFPred, a computational tool for sequence-based prediction and characterization of short disorder-to-order transitioning binding regions in proteins. *Bioinformatics*. 2012 Jun 15;28(12):i75-83.
- [2] Chica C, Diella F, Gibson TJ. Evidence for the concerted evolution between short linear protein motifs and their flanking regions. *PLoS One*. 2009 Jul 8;4(7):e6052.
- [3] Xue B, Williams RW, Oldfield CJ, Goh GK, Dunker AK, Uversky VN. Viral disorder or disordered viruses: do viral proteins possess unique features? *Protein Pept Lett*. 2010 Aug;17(8):932-51.
- [4] S. Longhi, V *et al*. The C-terminal domain of the measles virus nucleoprotein is intrinsically disordered and folds upon binding to the C-terminal moiety of the Phosphoprotein. *J. Biol. Chem*. 278, 18638–18648 (2003).
- [5] Leyrat C *et al*. The N(0)-binding region of the vesicular stomatitis virus phosphoprotein is globally disordered but contains transient α -helices. *Protein Sci*. 2011;20(3):542-556. doi:10.1002/pro.587
- [6] R. Cox, R. K. Plemper, The paramyxovirus polymerase complex as a target for next generation anti-paramyxovirus therapeutics. *Front. Microbiol*. 6, 459 (2015).
- [7] Kiser JJ, Flexner C. Direct-acting antiviral agents for hepatitis C virus infection. *Annu Rev Pharmacol Toxicol*. 2013;53:427-49.