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Discovery of promising functional motifs as key candidates for multi-antiviral therapy

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Motivation and Aim: In the realm of infectious diseases, the rise of diverse viruses like Zika, Dengue, Enteroviruses (EV-C2, EV71, CA16), SARS-CoV-2, and Chikungunya underscores the need for adaptable antiviral strategies. Each virus presents unique challenges, from severe birth defects associated with Zika and Dengue [1–3] to the global impact of SARS-CoV-2 [6, 7] and the prolonged symptoms caused by Chikungunya [4, 5].

Current antiviral approaches often target specific viruses, leaving a gap in developing interventions effective across various infections [8–10]. Recent advances in understanding RNA-RNA interactions have prompted exploration into shared intervention regions across different viruses. The SPLASH method, known for its comprehensive study of RNA-RNA interactions, offers a practical avenue for this exploration.

Methods and Algorithms: In our pursuit of adaptable antiviral strategies, we employed a multifaceted methodology to identify potential targets for versatile antiviral therapy applicable across various viral infections (Fig. 1). The search began by assigning orthogroups to cluster host transcripts, aiming to identify shared orthogroups across at least five viruses. This step allowed to delineate transcript clusters essential for subsequent analysis. Subsequently, we delved into functional annotation and molecular network interactions using the STRING database. This phase involved annotating host transcripts within orthogroups and exploring their interactions within cellular networks, providing insights into potential intervention regions. To identify significant viral RNA motifs with multi-viral therapeutic potential, we employed advanced sequence analysis techniques. This included GC content Markov Chain Monte Carlo simulations and multiple-sequence global alignment, enabling us to detect highly significant RNA motifs amidst the genomic complexity. Following motif identification, highly probable motifs were estimated by using position-specific score matrix and genome scanning. This step allowed us to pinpoint motifs with the highest likelihood of exhibiting broad-spectrum efficacy against diverse viral infections.

Results: We identified orthogroup-specific viral motifs, notably OG0002480 and OG0009649, exhibiting promising characteristics for broad-spectrum antiviral interventions. These motifs demonstrated specificity across diverse viral genomes, including Dengue, SARS-CoV2 Delta, and Zika (Brazilian strain) viruses for OG0002480 motif, and Zika (Brazilian, Singaporean strains) and SARS-CoV2 (wt and Delta strains) viruses for OG0009649 motif. Pairwise intersections between unrelated

viruses and genome scanning allowed us to identify regions of high confidence in RNA interactions. With strain-specific genomic origin, highlighting the nuanced diversity in viral infection mechanisms, even among closely related viruses. Exploration into the cellular mechanisms associated with these motifs provided crucial insights into viral infection dynamics, particularly highlighting their involvement in actin binding and focal adhesion through ACTN1, ACTN4, VCL and FLNC1 FLNC3 transcripts, consequently.

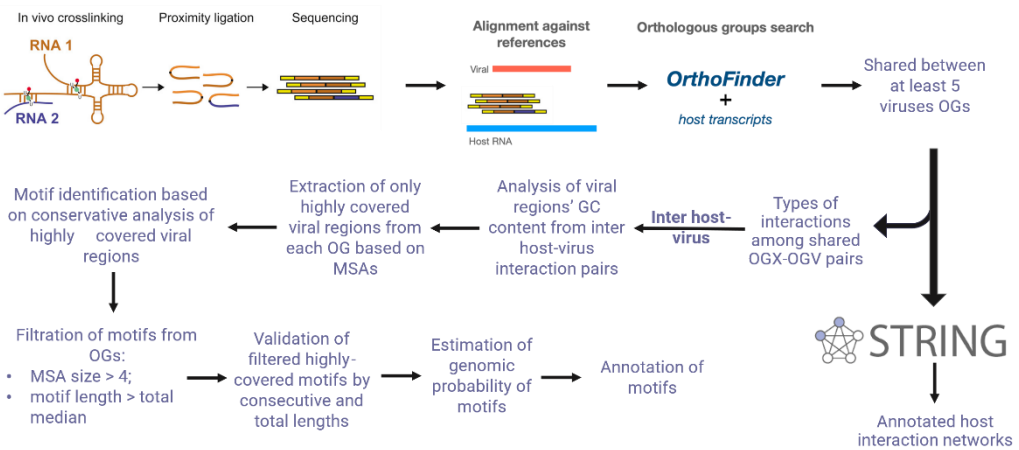

Fig. 1. Pipeline of the identification and analysis of potential motifs as multiple antiviral therapy targets. Step 1. SPLASH data analysis. Step 2. Orthogroups assignment and search for conservative ones. Step 3. Inter-host-viral interactions filtration and potential motifs identification. Step 4. Validation of identified motifs via genome scanning. Step 5. Annotation of identified motifs and host interaction network analysis

Conclusion: The applied analysis of SPLASH interactions between viral and host RNA laid a robust foundation for antiviral therapy development. The identification of orthogroup-specific motifs underscores promising avenues for therapeutic intervention, potentially offering broad-spectrum effectiveness. As we continue to unravel the intricacies of viral-host interactions, the prospects for developing effective, multi-viral therapies appear increasingly promising. Moving forward, further exploration of shared RNA motifs and validation of potential therapeutic targets will be crucial for advancing the field of antiviral therapy development and combating emerging viral threats effectively.

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