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Broad-spectrum antiviral activity of Ranalexin-1G against respiratory viruses.

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Introduction:

Respiratory viral infections represent a major global health burden, particularly in infants, older adults, immunocompromised individuals, and patients with underlying conditions. Despite their clinical impact and the continuous emergence of respiratory viruses, effective broad-spectrum antiviral strategies remain limited. Antimicrobial peptides (AMPs) are emerging as promising antiviral candidates due to their ability to interfere with multiple stages of the viral life cycle. Amphibian skin secretions are particularly rich in AMPs, which contribute to the natural defense of these animals against diverse pathogens. Several amphibian-derived peptides have already demonstrated antiviral activity against clinically relevant respiratory viruses.Ranalexin-1G is a cationic 20-amino-acid peptide belonging to the ranalexin family, previously characterized mainly for its antibacterial and antifungal properties. However, its antiviral potential remains largely unexplored. In this study, we investigated the antiviral activity of ranalexin-1G against a panel of clinically relevant respiratory viruses, including human coronavirus 229E (HCoV-229E), respiratory syncytial virus (RSV), human parainfluenza virus type 3 (HPIV-3), and measles virus (MeV).

Materials and Methods:

Cytotoxicity of ranalexin-1G was evaluated in Vero76, Vero/hSLAM, and human bronchial epithelial BEAS-2B cells by MTT assay and in human erythrocytes by hemolysis assays. Its antiviral activity was assessed against HCoV-229E and MeV by plaque reduction assay, and against RSV, poliovirus type 1 (PV-1), and HPIV-3 using tissue culture infectious dose ($TCID_{50}$) assay. Experiments included both simultaneous treatment of cells with virus and peptide (co-treatment) and pre-incubation of virus with the peptide (virus pre-treatment), with viral inhibition quantified as the reduction in plaque numbers or cytopathic effects relative to untreated infected cells. In addition, HCoV-229E replication was quantified by real-time quantitative PCR targeting the S and RdRp genes, to confirm the antiviral activity at the molecular level.

Results:

Ranalexin-1G showed selective antiviral activity against enveloped respiratory viruses, with minimal cytotoxicity and no significant hemolytic activity, indicating a favorable in vitro safety profile (Fig. 1). Strong inhibition was observed against HCoV-229E and MeV (Figs. 2-3), while the peptide was inactive against the non-enveloped PV-1 (Fig. 4), suggesting a role for direct interactions with the viral envelope. RSV showed moderate susceptibility, with the strongest activity at the two highest concentrations tested (50 and 25 µM) in the pre-virus assay, while in the co-treatment assay activity was mainly observed at 50 µM. HPIV-3 was only affected at 50 µM in both assays (Fig. 5). Notably, qPCR confirmed a significant reduction in HCoV-229E viral RNA, supporting inhibition of viral replication (Fig. 2).

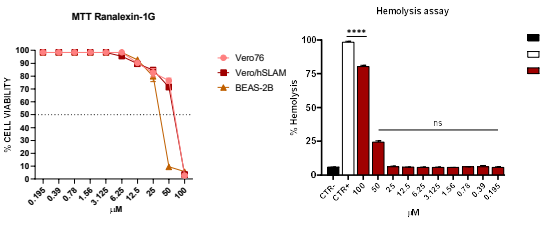


Figure 1. MTT assay on Vero76, Vero/hSLAM, and BEAS-2B cells and hemolysis assay of ranalexin-1G. Triton X-100 (20%) was used as the positive control (CTRL+), while untreated erythrocytes served as the negative control (CTRL−).

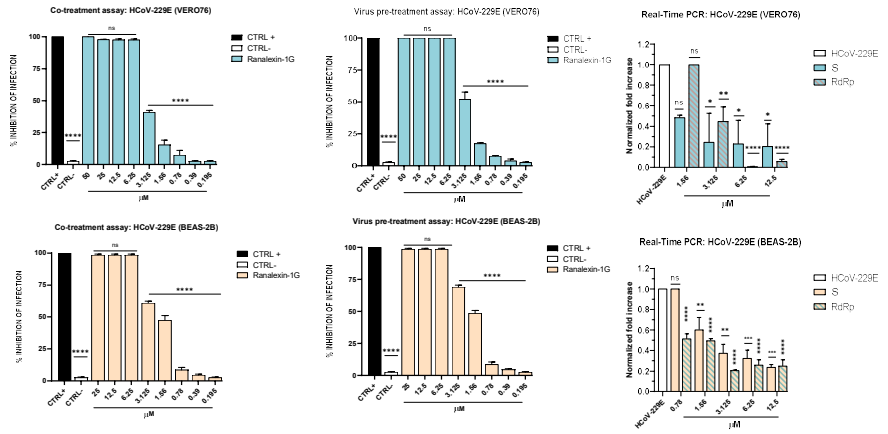


Figure 2. *Antiviral activity of ranalexin-1G against HCoV-229E in Vero76 and BEAS-2B cells, assessed by plaque reduction assay under co-treatment and virus pre-treatment conditions, and confirmed by RT-qPCR targeting the S and RdRp genes. Hylin-a1 (25 µM) was used as the positive control (CTRL+), while uninfected cells served as the negative control (CTRL−).*

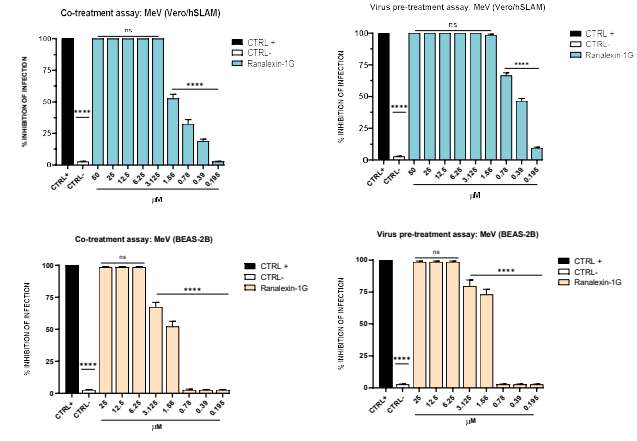


Figure 3. *Antiviral activity of ranalexin-1G against MeV in Vero76 and BEAS-2B cells, assessed by plaque reduction assay under co-treatment and virus pre-treatment conditions. Hylin-a1 (25 µM) was used as the positive control (CTRL+), while uninfected cells served as the negative control (CTRL−).*

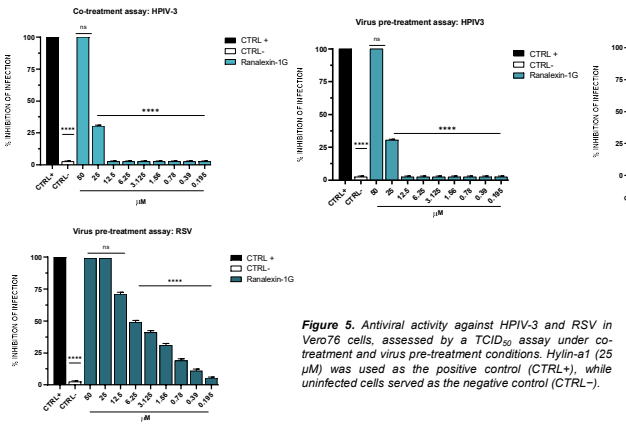


Figure 5. *Antiviral activity against HPIV-3 and RSV in Vero76 cells, assessed by a $TCID_{50}$ assay under co-treatment and virus pre-treatment conditions. Hylin-a1 (25 µM) was used as the positive control (CTRL+), while uninfected cells served as the negative control (CTRL−).*

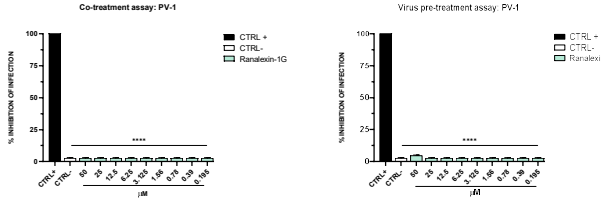


Figure 4. *Antiviral activity against a non-enveloped virus in Vero76 cells, assessed by a $TCID_{50}$ assay under co-treatment and virus pre-treatment conditions. The data showed that the peptide did not inhibit viral replication in either treatment. Pleconaril (2 µg/mL) was used as the positive control (CTRL+), while uninfected cells served as the negative control (CTRL−).*

Discussion and Conclusion.

Ranalexin-1G exhibits a selective, virus-dependent antiviral profile. Its strong activity against HCoV-229E and MeV, coupled with inactivity against non-enveloped PV-1, supports a role for direct interactions with the viral envelope. The reduction of HCoV-229E RNA confirms inhibition of viral replication, while the limited activity against RSV and HPIV-3 highlights virus-specific susceptibility. Together with its favorable safety profile, these findings support ranalexin-1G as a promising antiviral peptide candidate. Further studies will evaluate its activity in BEAS-2B cells against RSV and HPIV-3, while efforts will focus on identifying ranalexin-1G analogues or modified peptides with improved cytotoxicity and antiviral activity.