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Abstract Title

Respiratory Syncytial Virus Induces GSDMD and GSDME-mediated Bronchial Epithelial Cell Pyroptosis

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Background

Accounting for over 2% of all deaths of children under 5 years old, respiratory syncytial virus (RSV) poses a significant burden to global pediatric health. Despite extensive research efforts, there is still a lack of effective treatments against RSV for children. The gasdermin (GSDM) family members GSDMD and GSDME are pore-forming proteins that serve as terminal executioners pyroptosis, a form of lytic cell death that can play double-edged roles in host responses to viral infections.

Objective

This study aims to determine the mechanisms and roles of airway epithelial cell pyroptosis induced by RSV.

Methods

Immortalized human bronchial epithelial cells (HBEC-3KT) were infected with RSV-GFP. Infection was visualized using fluorescence microscopy and viral replication was quantified with plaque assay. LDH release was measured to assess cell lysis. GSDMD and GSDME expression and activation were determined by Western blotting. GSDMD activity was inhibited using pharmacological inhibitor LDC7559. GSDMD and GSDME expression were silenced by siRNA-mediated knockdown.

Results

RSV infection of HBEC3-KT cells induced activation of GSDMD and GSDME at different timepoints. GSDMD inhibitor LDC7559 significantly reduced RSV-induced LDH release by 15.84% and RSV infection rate by 48.75% compared with RSV-infected control cells ($p<0.0001$). siRNA-mediated knockdown of GSDMD significantly reduced RSV-induced LDH release by 10.75% ($p=0.0202$), while GSDME inhibition significantly reduced LDH release by 10.41% ($p=0.0239$). Importantly, siRNA-mediated knockdown of GSDMD and GSDME significantly decreased RSV release from infected cells by 6.10 and 5.58 folds respectively ($p<0.0001$).

Conclusion

RSV infection induces LDH release, GSDMD and GSDME activation in human bronchial epithelial cells, indicating active pyroptosis. Interestingly, both GSDMD and GSDME are involved in RSV release from infected epithelial cells. These findings suggest that GSDMD and GSDME are plausible targets for host-directed therapy against RSV infection.