WEBINAR 6 HIGHLIGHTS

AIRWAY SMOOTH MUSCLE CELL DYSFUNCTION IN RSV INFECTION

ReSViNET
RESPIRATORY SYNCYTIAL VIRUS NETWORK
FOUNDATION

SUMMARY

On June 30th 2021, the 6th ReSViNET webinar was held with guest speaker, Dr. Giovanni Piedimonte (Pediatrics, Biochemistry & Molecular Biology, Tulane University, New Orleans, Louisiana, USA) and co-host Prof. Larry J. Anderson (Department of Pediatrics, Emory University, Atlanta, Georgia, USA).

This webinar focused on the unique ability of RSV to dysregulate the location, abundance, and function of key receptors modulating the concentration of calcium ions in airway smooth muscle cells.

INTRODUCTION

- The most common etiology of viral lower respiratory tract infection children is RSV;
- Despite many similarities with asthma, several studies have failed to demonstrate any consistent benefit from the use of β2AR agonists in the setting of viral bronchiolitis. Furthermore, virus-infected asthmatic children have a higher risk of treatment failure during acute exacerbations;
- TRPV1 channels are expressed & functional in human bronchial epithelial & smooth muscle cells, and play a role in airway disease.

AIMS

Discuss effect of RSV on:

- β2ARs in airway smooth muscle; [1]
- TRPV1-mediated calcium entry into airway smooth muscle and epithelium. [2,3]

KEY FINDINGS

RSV infection results in:

- Increased phosphorylation of β2ARs, & the loss of β2ARs from the cellular plasma membranes & intracellular proteasomal degradation;
- Increased Ca2+ signaling, promoting contractility upon stimulation with Gαq-stimulating agonists;
- Increased expression & activation of TRPV1 channels as a consequence of increased signaling through the NGF-TrkA axis;
- TRPV1-mediated increase in Ca2+ influx into airway smooth muscle & epithelial cells can originate from extra- or intracellular Ca2+, depending on the presence of replicating RSV & the genetic predisposition to the asthma of the host. RSV-induced increase in intracellular Ca2+ mediated by TRPV1 activation can contribute to clinical manifestations of asthma, including increased synthesis & release of TH2 cytokines, mucus overproduction, breakdown in barrier permeability, & increased bronchoconstriction.

1. Harford, T.J. et al., *Science Signaling* (2021);
2. Harford, T.J. et al., *J. of Allergy and Clin. Immunol.* (2018);
3. Harford, T.J. et al., *Am. J. of Physiol-Lung C.* (2021).

DISCUSSION

- Data suggest RSV replication in smooth muscle cells of children's airways generates pro-contractile phenotype by increasing the intra-cellular Ca2+ concentrations while inducing the inactivation, degradation, and loss of receptors mediating bronchodilation.
- Loss of functional β2ARs can account for lack of clinical response of RSV-infected patients to β-agonists in the clinical settings of acute bronchiolitis and virus induced asthma exacerbations.
- Upregulation of TRPV1 expression and activity , as well as the potentiation of Gaq-stimulating agonists, leads to stronger and prolonged airway smooth muscle contraction, as well as other hallmarks of airway obstruction like cough, mucus production, and mucosal edema.

TAKE HOME MESSAGE

Human airway smooth muscle cells are susceptible to RSV infection, which leads to profound alterations in the abundance, location, and function of receptors controlling intracellular calcium concentrations and consequently the airway tone and reactivity.

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NEXT WEBINAR

NEXT WEBINAR: SEPTEMBER 17TH, 2021

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