ATS 2025 Highlights
Respiratory Structure and Function Early Career Professionals

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Get to know members of the RSF Assembly

Is your research clinical, basic science or translational?

Basic science.

Tell us about your research?

My research area focuses on the interaction between airway inflammation and organelle stress. Emerging evidence from our own laboratory and others suggests the role of Tumor Necrosis Factor alpha (TNFA) on airway smooth muscle (ASM) hyper-reactivity and force generation, with an increase in metabolic demand. I am studying the molecular mechanisms underlying TNFA–mediated mitochondrial remodeling, which encompasses the changes in mitochondrial structure, dynamics and function, to meet enhanced energy demand; while maintaining a homeostatic response.

Where do you see yourself in 5 years?

In next 5 years, I envision myself as an Independent Academic Researcher, with independently funded research projects focusing on the acute and chronic inflammation mediated molecular changes in airway, and how the cellular homeostasis machinery is altered in the context of airway diseases.

What do you find is the major benefit of RSF Assembly Membership?

The RSF Assembly Membership provides the unique opportunity to create professional networking with the leading basic science researchers and clinicians working in the field of airway biology across the globe.

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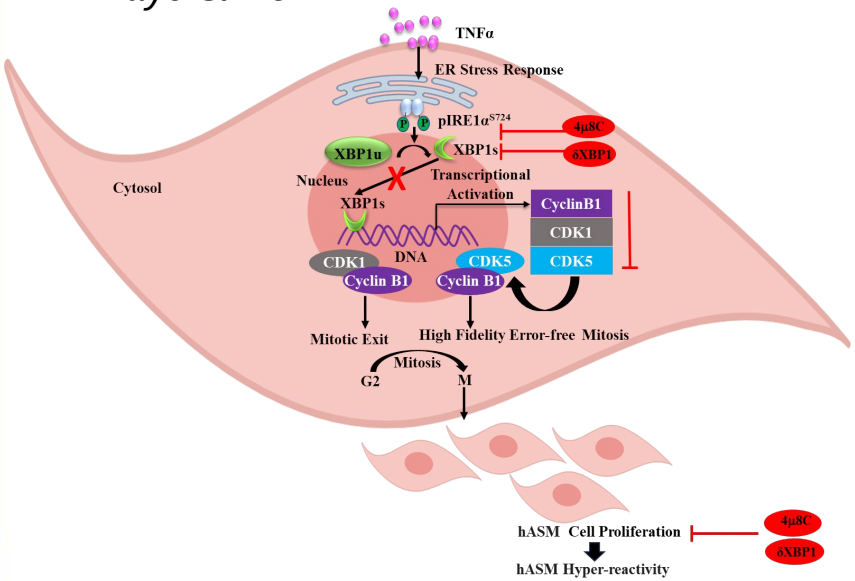

TNFA induced pIRE1A^{S724}/XBP1s-ER stress pathway promotes CDK1, CDK5 and Cyclin B1 genes activation, associated with an increase in ASM cell proliferation. Inhibition of pIRE1A^{S724}/XBP1s pathway reduced the effect of TNFA on ASM cell proliferation.

Signaling Pathway Underlying TNFA-Induced Proliferation of Human Airway Smooth Muscle Cells

Objective: The effects of acute airway inflammation are mediated by pro-inflammatory cytokines such as tumor necrosis factor alpha (TNFA) and associated with airway remodeling, characterized by airway smooth muscle (ASM) hyperreactivity and proliferation. The molecular mechanism underlying TNFA-induced ASM cell proliferation is not fully understood. Previous studies from our lab demonstrated that TNFA exposure induces reactive oxygen species (ROS) formation and the accumulation of unfolded proteins in the endoplasmic reticulum (ER). This triggers an unfolded protein response (UPR^{ER}) that involves autophosphorylation of inositol requiring enzyme 1 alpha at Serine 724 (pIRE1A-mediating alternative splicing of X-box binding protein 1 (XBP1s) mRNA. XBP1s, a ubiquitous transcription factor in ASM cells, targets cyclin-dependent kinases (CDK1 and 5) and Cyclin B1. In the present study, we hypothesized that TNFA promotes XBP1s mediated transcriptional activation of the CDK1, CDK5 and Cyclin B1 gene, which play a significant role in promoting proliferation of ASM cells.

Methods: Human ASM cells were dissociated from bronchiolar tissue samples collected during lung surgery from female and male patients (34 to 60 years of age) with no history of chronic respiratory diseases or current smoking. Isolated ASM cells from the same patient were serum-deprived for 48 h and separated into two groups: 1) untreated controls, and 2) treated with TNFA (20 ng/ml) for 6 h. Two loss of function experiments involved 1) transfecting ASM cells with a non-spliceable XBP1 mutant, and 2) treating the cells with 4u8C, a pharmacological inhibitor for IRE1A mediated XBP1 splicing. ASM cell proliferation was measured using MTS assay and BrdU incorporation assay. The binding of XBP1s to the CDK1, CDK5 and Cyclin B1 promoters were confirmed by chromatin immunoprecipitation (ChIP) assay. Expression of CDK1, CDK5 and Cyclin B1 was determined by qRT-PCR and Western blot. Results were analyzed by paired t-tests.

Results: TNFA treatment increased ASM cell proliferation. The ChIP assay revealed that XBP1s binds to the promoter region of the CDK1, CDK5 and Cyclin B1 genes, and the binding affinity was increased in TNFA-treated ASM cells. Consistent with these results, we found that TNFA treatment increased both mRNA and protein expressions of CDK1, CDK5 and Cyclin B1 in ASM cells. Inhibition of XBP1 splicing reduced ASM cell proliferation and the expression of CDK1, CDK5 and Cyclin B1 in ASM cells.

Conclusion: TNFα induces an UPR^{ER} response that activates the pIRE1a^{s724}/XBP1s ER stress pathway. XBP1s transcriptionally targets CDK1, CDK5 and Cyclin B1 expression mediating an increase in ASM cell proliferation.

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