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Novel signaling mechanisms for airway remodeling and hyper-responsiveness in chronic obstructive pulmonary disease (COPD)

Statement of the Problem: COPD is the fourth leading cause of mortality in the world and will be the second leading cause of death by 2020. However, the molecular processes for this devastating disease remain largely unknown, and current treatments are limited.

Purposes: This study was to test a novel hypothesis that the reciprocal crosstalks between ion channel-mediated calcium signaling and transcriptional factor-dependent inflammatory signaling are essential for COPD. The current study also sought to determine whether specific genetic and pharmacological targets for these signaling molecules would become effective therapeutics for COPD.

Methodology: Ion channel expression and activity were assayed using RT-PCR, Western blotting and patch clamp recordings; airway remodeling and hyper-responsiveness examined using *in-situ* immunohistological staining and both *in-vivo* and *in-vitro* muscle contraction measurements; and targeted molecule activities changed using virus-based genetic modifications.

Findings: Among 7 known different gene-encoded classic transient receptor potential (TRPC) channel members, only the TRPC3 channel shows a predominant activity and expression in airway smooth muscle cells (ASMCs). This channel is significantly upregulated in COPD patient ASMCs. Mice with nicotine-induced COPD also show largely increased TRPC3 channel expression and activity in ASMCs. *In-vivo* lentiviral shRNA-mediated TRPC3 channel knockdown abolishes airway remodeling and hyper-responsiveness in COPD. The channel blocker Pyr3 produces similar effects. The TRPC3 channel promoter has binding sites for NFκB, an important inflammatory transcription factor. NFκB expression and activity are increased in COPD ASMCs. Genetic NFκB function gain and loss, respectively, increases and blocks TRPC3 channel promoter activity and expression. Vise verse, TRPC3 channel gain and loss, downregulates and upregulates NFκB activity and expression.

Conclusion & Significance: Reciprocal crosstalks between TRPC3 channel-mediated calcium signaling and NFκB-dependent inflammatory signaling are essential for airway remodeling and hyper-responsiveness in COPD. Specific lentiviral TRPC3 channel shRNAs and channel blockers may become novel and effective treatments for COPD.

Biography

Yong-Xiao Wang has been a Full Professor in Albany Medical College (USA) since 2006. He has had extensive research experience in basic, translational and drug research concerning pulmonary hypertension, asthma, chronic obstructive pulmonary disease, diabetes, and cardiac arrhythmia for over 30 years. As the Principal Investigator, he has received numerous NIH R01 research awards, like AHA Established Investigator Award, and various other grants, where he holds 2–3 NIH R01 grants with other awards each year. As the Corresponding Author, First Author and Key Contributor, he has numerous publications in highly peer-reviewed journals including *Antioxid. Redox Signal* (Impact Factor: 8.209), *Proc. Natl. Acad. Sci. USA* (9.432), *Nature* (34.480), *Circ. Res.* (9.214), etc. He has been the Editor of academic books in the field including one entitled by, "*Redox Signaling in Health and Disease Pulmonary Vasculature*" that has been confirmed for publication by Springer (New York). He has also served as the Editorial Board Member and/or Section Editor for the *Clinical and Translational Medicine, Pulmonary Circulation* and several other journals.

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