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| **Enhancing ER-protein folding capacity restores steroid sensitivity in severe asthmatic airways** |
| Prabuddha S. Pathinayake1, Alexandra C. Brown2, Richard Y. Kim2,6, Jay C. Horvat2, and Peter A.B. Wark1,3,4,5 |
| *1School of Medicine and Public Health, The University of Newcastle and Hunter Medical Research Institute, Newcastle, NSW, Australia**2School of Biomedical Sciences and Pharmacy, The University of Newcastle and Hunter Medical Research Institute, Newcastle, NSW, Australia**3Department of Respiratory and Sleep Medicine, John Hunter Hospital, New Lambton Heights, New South Wales, Australia*4 School of Medicine, Monash University, Melbourne, Victoria, Australia.5 AIRMED Alfred Health, Melbourne, Victoria, Australia.6University of Technology Sydney, School of Life Sciences, Sydney, Australia |
| **Introduction/Aim:** People with severe steroid-resistant asthma show poor disease control, progressive loss of lung function and need to use high doses of inhaled and systemic corticosteroids. Glucocorticoid Receptor (GR)-Heat shock protein 90 (HSP90) multiprotein heterocomplex formation is important for efficient steroid signalling. Upregulated endoplasmic reticulum (ER) stress and protein folding defects could interfere with this process. Here we show that facilitating ER protein folding capacity using chemical chaperones enhances steroid sensitivity in experimental models of severe asthma.**Methods:** Primary human bronchial epithelial cells (pBECs) were treated with a Th1/17 cytokine mix 10ng/mL IL-17A, 5ng/mL IFN-ɣ and 1ng/mL TNF-α for 48hrs to induce steroid insensitivity(n=3). Cells were then treated with 100nM dexamethasone (Dexa) with or without chaperone (2mM 4-PBA) for 12hrs. The expression of canonical corticosteroid-responsive genes and pro-inflammatory genes was measured by qPCR. To demonstrate that protein misfolding directly interferes the steroid responsiveness, pBECs were treated with ERS inducers; 2ug/mL tunicamycin or 1mM thapsigargin with or without Dexa and steroid responsive genes expression was measured. Infection-induced severe, steroid-resistant (SSR) asthma mice model (Chlamydia and OVA) was also treated with Dexa with or without 4-PBA and the inflammation and airway hyperresponsiveness (AHR) was measured(n=5).**Results:** Th1/17 cytokine mix significantly downregulated steroid-responsive HSD11B2 and FKBP5 (p=0.04) genes and upregulated proinflammatory IL-6 and IL1β genes (p=0.02). Dexamethasone alone did not change these gene expressions. Interestingly, Dexa together with 4-PBA significantly upregulated the expression of steroid-responsive genes (p=0.0023) and downregulated proinflammatory genes(p=0.02). ER stress inducers also significantly downregulated steroid-responsive genes(p=0.002). In our steroid-resistant mouse model, dexamethasone together with 4-PBA significantly reduced both airway inflammation(p=0.01) and AHR(p=0.03) while Dexa alone did not.**Conclusion:** Resolving ER-protein misfolding enhances steroid sensitivity in asthmatic airways. |