“Role of mitochondria in the development of airway remodeling in severe asthma”

Dr. Rakhee K. Ramakrishnan

Graduated student of the first batch of Ph.D. program in Molecular Medicine, University of Sharjah, Sharjah, United Arab Emirates

Abstract:

Subepithelial fibrosis is a characteristic feature of airway remodeling in asthma which correlates with disease severity. Current asthma medications are ineffective in treating fibrosis necessitating a deeper understanding of the mechanism, particularly in severe asthmatics that represent a distinct phenotype with their mixed pattern of neutrophilic-eosinophilic inflammation and glucocorticoid insensitivity making them refractory to currently available therapies. In this study, we aimed to investigate the mitochondrial phenotype in fibroblasts isolated from airway biopsies of non-asthmatic and severe asthmatic subjects by examining their mitochondrial quality control machinery as a mechanism contributing to fibroblast persistence in severe asthma. We hypothesized that severe asthmatic fibroblasts exhibit mitochondrial damage resulting in their aberrant pro-fibrotic phenotype. Firstly, we provide evidence of increased activation of mitophagy and mitochondrial biogenesis in severe asthmatic fibroblasts as a result of significantly reduced mitochondrial membrane potential at baseline compared to non-asthmatic controls. Interestingly, these fibroblasts displayed neither an apoptotic nor senescent phenotype, but an adaptive survival mechanism triggered by increased AMPKα phosphorylation. Cytokines, such as IL-17A, TGF-β1 and IL-13 are enriched in severe asthmatic airways and are important regulators of airway remodeling in asthma. We, therefore, hypothesized that these cytokines impair mitochondrial function in severe asthmatic fibroblasts contributing to the development of fibrosis. To our knowledge, this is the first study to demonstrate that IL-17, TGF-β and IL-13 accelerated mitochondrial dysfunction in bronchial fibroblasts, but to a greater extent in severe asthmatic fibroblasts when compared to non-asthmatic controls. IL-17, in particular, intensified the mitochondrial dysfunction but impaired the mitochondrial quality control machinery in the non-asthmatic and severe asthmatic fibroblasts. Moreover, IL-17 augmented a pro-fibrotic and anti-apoptotic response in both group of fibroblasts. Inhibition of autophagy using bafilomycin-A1 restored the IL-17 mediated changes in mitophagy to their basal levels. Bafilomycin-A1 also reversed the IL-17 associated fibrotic response in these fibroblasts, suggesting a role for autophagy in the induction of fibrosis by IL-17 in bronchial fibroblasts. Bcl10 is a well-known mediator of the canonical NF-κB pathway, which is key to airway inflammation in asthma. Therefore, we also studied Bcl10-mediated NF-κB activation as a potential pathway regulating fibrotic signaling in severe asthmatic fibroblasts. This is the first report providing evidence of elevated protein expression of Bcl10 in the pathogenesis of severe asthma. We also identified the participation of Bcl10-mediated NF-κB pathway in LPS-induced activation of IL-8 in bronchial fibroblasts, where an exaggerated response was noted in severe asthmatic fibroblasts when compared to controls. This work finds its importance in describing the role of mitochondria and autophagy in the development of subepithelial fibrosis in severe asthma. Our results demonstrated that the enhanced turnover of mitochondria in bronchial fibroblasts may

contribute to their increased survival and pro-fibrotic phenotype observed in severe asthma. Interestingly, the cytokine-mediated induction of mitochondrial dysfunction appears to be associated with the activation of autophagy highlighting the pathological role of autophagy in severe asthma. Our study also provided insights into a potential pathological pathway involving Bcl10 that contributed to fibrotic signaling in severe asthmatic airways revealing the therapeutic potential of targeting autophagy and Bcl10 signaling in ameliorating fibrosis, particularly in severe asthmatic individuals.

Supervisor & Co-Supervisor names:

- University of Sharjah:
  - Main Supervisor: Prof. Qutayba Hamid
  - Co-Supervisor: Dr. Rifat Hamoudi, Dr. Bassam Mahboub
  - Mentor: Prof. Rabih Halwani
- Lubeck University: Prof. Saleh Ibrahim

Publications from the PhD thesis:

1. Poon AH, Choy DF, Chouiali F, Ramakrishnan RK, Mahboub B, Audusseau S, Mogas A, Harris JM, Arron JR, Laprise C, Hamid Q. (2017) Increased Autophagy-Related 5 Gene Expression is Associated with Collagen Expression in the Airways of Refractory Asthmatics. Frontiers in Immunology. doi: 10.3389/fimmu.2017.00355.

2. Ramakrishnan RK, Mahboub B, Hamid Q. (2018) Asthma-chronic obstructive pulmonary disease overlap: A distinct pathophysiological and clinical entity. In: Asthma, COPD, and Overlap: A Case-Based Overview of Similarities and Differences, 1st Edition, edited by Bernstein J, Boulet LP, Wechsler M. Boca Raton: CRC Press. Chapter 4

3. Ramakrishnan RK, Al Heialy S, Hamid Q. (2019) Role of IL-17 in asthma pathogenesis and its implications for the clinic. Expert Review of Respiratory Medicine. doi: 10.1080/17476348.2019.1666002

4. Ramakrishnan RK, Bajbouj K, Al Heialy S, Mahboub B, Ansari AW, Hachim IY, Rawat S, Salameh L, Hachim MY, Olivenstein R, Halwani R, Hamoudi R, Hamid Q. (2020) IL-17 induced autophagy regulates mitochondrial dysfunction and fibrosis in severe asthmatic bronchial fibroblasts. Frontiers in Immunology. doi: 10.3389/fimmu.2020.01002

5. Ramakrishnan RK, Bajbouj K, Hachim MY, Mogas A, Mahboub B, Olivenstein R, Hamoudi R, Halwani R, Hamid Q. Enhanced mitophagy in bronchial fibroblasts from severe asthmatic patients. PLOS ONE (Under Revision).