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| Decline of Unfolded Protein Response with Age Increases Susceptibility to Infection and Inflammation |
| Thishan Illankoon1,2, Alexandra Mueller1,2, Haressh Sajiir1,2, Kuan Yau Wong1,2, Sumaira Z. Hasnain1,2,3 |
| *1.Translational Research Institute – Mater Research Institute, Brisbane, Australia;*  *2.University of Queensland, Faculty of Medicine, Brisbane, Australia;*  *3.Princess Alexandra Hospital, Brisbane, Australia.* |
| **Introduction/Aim:**  Protein misfolding in the Endoplasmic Reticulum (ER) can be induced by various endogenous and exogenous triggers, leading to the formation of insoluble protein aggregates. This disrupts protein homeostasis and causes cellular stress, which if either acutely severe or chronically unresolved, can result in cell death. Consequently, eukaryotic cells have evolved a regulatory network termed the unfolded protein response (UPR) that mediates protein folding to uphold homeostasis.  **Method:**  We aim to identify whether this age-related senescence of the UPR at lung mucosal sites is a contributing factor to the increase in respiratory infection and severity reported in aged individuals. Using respiratory biobank biopsy samples from healthy individuals across a wide age range (20-30 to >65 years old), we will perform qPCR, RNAseq, metabolic assessments, histological techniques, and explore epigenetic markers. In order to identify changes in aspects of the UPR with age, which will be confirmed using primary murine and human respiratory organoids.  **Results:**  Using qPCR in mouse organoids of varying ages (6, 12, 19, 24 weeks old), we identified that GRP78 and XBP1 both decline with age, whereas CHOP and IRE1 increase. Additionally, there was a reduction in autophagasome formation and LC3 expression in aging. Indicating a shift in the UPR with age to favour apoptosis over homeostasis recovery, with impaired autophagy action.  **Conclusion:**  This suggests an age-related impairment and decline in appropriate UPR, potentially causing the increase in infection susceptibility and severity with age.      **Key Words:**  **Nomination for New Investigator Award**    **Grant Support:** |