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Category: Postdoc
Name: Thivanka Muthumalage
PI: Irfan Rahman
Title: Selective ablation of telomere protection protein 1 (TPP1) in lung epithelium induce an age-dependent augmentation of the inflammatory response by tobacco smoke exposure
Abstract: Inflammation, aging, and altered respiratory mechanics are important processes in the pathogenesis of chronic obstructive pulmonary disease (COPD) wherein exposure to cigarette smoke (CS) is a critical etiological factor. Our lab has previously shown that telomere protection protein 1 (TPP1) is involved in CS-induced telomeric DNA damage and cellular senescence. TPP1 is one of the subunits of shelterin complex proteins, POT1, TRF1, TRF2, Tin2, Rap1, and POT1, that mediates telomere length homeostasis and integrity. However, the interplay between aging and CS-exposure affecting TPP1 mediated telomere protection is unclear. We hypothesized that TPP1 protects against induced telomere DNA damage via the shelterin complex in an age-dependent manner. TPP1-flox and TPP1-CreCC10 (Club cell-specific TPP1 deletion) mice (2-6 months old) were exposed to CS (1-month, 100 mg/m3 TPM). Mice of the same genotype at mature (2-5 months) and older (5-15 months) ages were exposed to mainstream smoke (3-months, 200 mg/m3 TPM). Differential cell counts in the bronchoalveolar lavage (BAL) fluid and inflammatory cytokines were analyzed by flow cytometry and ELISA/Luminex assay, respectively. Additionally, respiratory mechanical properties were evaluated by Flexivent (Scireq). Further, protein abundance of DNA damage, shelterin complex, and cellular senescence markers in the lungs were determined by immunoblotting and histological analyses. In CS exposed mice, a significant lung infiltration of leukocytes, neutrophils and T-lymphocytes, were observed in both TPP1-CreCC10 compared to TPP1-flox mice compared to their unexposed counterparts. Lung mechanics were not significantly altered, albeit evident differences in compliance, elastance, and resistance in the TPP1-CC10Cre group in both age groups. CS exposure affected inflammatory cytokines with increased lung levels of TNFα, IFNγ, IL-5, IL-6, MIP-1β, MCP-1, eotaxin, IL-4, IL-9, G-CSF, KC, and IL-12p70 in TPP1-CreCC10 compared to TPP1 flox air and CS exposed mice. CS exposed TPP1-flox and TPP1-CreCC10 mice showed altered expression of DNA damage (γH2AX), shelterin complex (TPP1 and TIN2), and cellular senescence (p21 and p16) markers. The severity of these alterations was enhanced in the older mice compared to the younger group in both floxed and CreCC10 group, suggesting that aging increases susceptibility to pulmonary inflammation and injury. Conclusion: These data suggest an increased lung inflammation caused by CS exposure resulted in altered differentiation of naïve T cells and the regulation of T-lymphocyte response in TPP1-CreCC10. We conclude that TPP1 plays a protective role against CS-induced inflammation and cellular senescence processes in an age-dependent manner. Supported by the NIH R01 ES029177 and R01 HL137738.