Lung Biology Research & Trainee Day
June 7, 2021

Category: Postdoc
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Title: p16-3MR mouse model: Role for Studying Cellular Senescence in vivo
Abstract: Authors: Gagandeep Kaur1, Isaac Sundar1, and Irfan Rahman1 Cellular senescence and lung aging are associated with the pathogenesis of chronic obstructive pulmonary disease (COPD).Cellular senescence is defined as the state of irreversible cell cycle arrest in response to intrinsic (DNA damage) or extrinsic stressors (oxidative stress). It plays a critical role in causing cigarette smoke (CS)-induced premature lung aging. However, the role of cellular senescence in this process in not fully understood due to the lack of a suitable model. In view of this, we chose a novel mouse model-p16-3MR- characterized by a trimodality reporter fused to p16INK4a gene promoter that enables detection, isolation, and selective elimination of senescent cells. To determine the suitability of this model in CS-mediated lung pathologies, we exposed young (12-14 months) and old (17-20 months) p16-3MR mice to 30 day mainstream CS exposure. We studied; (a) tissue luminescence and fluorescence using IVIS imaging to detect and identify senescent tissues, (b) expression of senescent genes (p16, p21, and p53) and SASP-associated markers (MMP9, MMP12, PAI-1, and FN-1), and (c) SA-β-Gal activity in air- and CS-exposed mouse lungs. Our results showed a significant increase in the lung tissue luminescence (3-fold; $p<0.05$) and fluorescence (4-fold, $p<0.001$) in CS-exposed young p16-3MR mice, thus illustrating an upregulation in the cellular senescence on CS exposure. qPCR and immunoblotting results demonstrated an increase in the expression of senescence markers (p16, p21 and p53) and SASP-associated genes (IL-6, MMP12, IL-1α, and CCL2) in CS-challenged p16-3MR mice. Furthermore, we showed a significant (~2-fold, $p<0.05$)) rise in SA-β-Gal activity in the lung homogenates from CS-exposed young p16-3MR mice as compared to the air controls. Overall, we showed that p16-3MR is an effective model to study cellular senescence in age-related lung pathologies. In future, p16-3MR reporter mouse model can be used as a disease model for understanding the pathobiology of cellular senescence and other underlying mechanisms involved in COPD and fibrosis. Supported by the NIH 1R01HL135613, ES029177, HL137738 and HL133404 Citation: Kaur, G.; Sundar, I.K.; Rahman, I. p16-3MR: A Novel Model to Study Cellular Senescence in Cigarette Smoke-Induced Lung Injuries. Int. J. Mol. Sci. 2021, 22, 4834. https://doi.org/10.3390/ijms22094834