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Topic Category: 4083-ASIP Lung - inflammatory, immunologic and fibrosing pulmonary diseases (non-infectious)

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Presentation Preference: Indifferent

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Sponsor's Society: Pathology - American Society for Investigative Pathology (ASIP) - Host Society
Keywords: 1. TERT 2. Pulmonary fibrosis 3. Myeloid cell

Telomerase Expression in Myeloid Cells is Essential for Pulmonary Fibrosis

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Shortened telomeres and mutations in telomerase reverse transcriptase (TERT) or its RNA component (TERC) have been reported in some patients with fibrotic interstitial lung disease, such as idiopathic pulmonary fibrosis (IPF). However telomerase is induced in lung fibroblasts from such patients without evidence of telomere shortening, and selective TERT deficiency in mesenchymal cells significantly reduced pulmonary fibrosis in an animal model. Moreover TERT in the bone marrow (BM) is essential for fibrosis in the same model. However, the precise cellular source of TERT in the BM is unknown. The objective of this study was to elucidate further the identity and the role of the TERT-expressing BM-derived cells in the injured lung by evaluating the effects of selective TERT deficiency in myeloid (LysM⁺ cells) on bleomycin (BLM) induced pulmonary fibrosis. The myeloid cell specific TERT knockout mice (LysM-TERT KO) were created by crossing floxed TERT mice with LysM-Cre mice. The results showed that BLM induced significant TERT expression in BM-derived CD45⁺ cells in lungs of control (WT) mice, which was not observed in the LysM-TERT KO mice. This was also associated with the loss of TERT expression in whole lung tissue in LysM-TERT KO mice while TERT expression in the BM was reduced by >80%. Interestingly, BLM-induced TERT expression in lung CD45⁺ cells in WT mice was also abolished by myeloid cell TERT deficiency in LysM-TERT KO mice. The myeloid cell specific TERT deficiency caused significant reduction in pulmonary fibrosis along with diminished lung expression of pro-fibrotic cytokines. Additionally, LysM-TERT KO mice showed diminished numbers of c-kit⁺ lung hematopoietic progenitor cells (LHPC) after BLM treatment in comparison with WT controls. Taken together these findings suggest a pro-fibrotic role for the induction of TERT in myeloid cells.

Support or Funding Information

This study is supported by NIH grants HL052285 and HL112880.