Synopsis of Original Research Paper

Biological Role of Klotho Protein in Ageing of Connective Tissue and Its Therapeutic Application to Skin Diseases

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Homozygous mutant klotho ($KL^{-/-}$) mice exhibit multiple phenotypes resembling human aging. In the present study, we focused on examining the pathology of the lungs of klotho mice and found that it closely resembled pulmonary emphysema in humans both histologically and functionally. Histology of the lung of $KL^{-/-}$ mice was indistinguishable from those of wild-type littermates up to 2 wk of age. The first histological changes appeared at 4 wk of age, showing enlargement of the air spaces accompanied by destruction of the alveolar walls, and progressed gradually with age. In addition to these changes, we observed calcium deposits in type I collagen fibers in alveolar septa and degeneration of type II pneumocytes in 8- to 10-week-old $KL^{-/-}$ mice. Pulmonary function tests revealed prolonged expiration time in $KL^{-/-}$ mice, which is comparable with the pathophysiology of pulmonary emphysema. The expression level of messenger RNA for type IV collagen, surfactant protein-A was significantly increased in $KL^{-/-}$ mice, which may represent a compensatory response to alveolar destruction. The starvation of human lung fibroblast cells (MRC-5) for 96 hours decreased their 3H-thymidine uptake up to 75%. The transfection of the klotho gene into MRC-5 cells using adenovirus vector, however, prevented their decline in 3H-thymidine uptake. These results implied that connective tissue including fibroblasts played an important role in the pathogensis of pulmonary emphysema in $KL^{-/-}$ lung.