

Department of Pathology

Research in Progress Seminar

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"Potential Role of IGFBP-3 in Cellular Senescence"

Little is known about the molecular mechanism that drives cells into a senescent state. The senescent state is marked by functional and morphological changes including the production of senescence-associated β -galactosidase (SA- β -Gal). Recent studies demonstrate that IGF binding protein-3 (IGFBP-3) expression correlates with the progression of senescence in normal human fibroblasts. Further studies identified a positive transcription regulatory element, IGFBP-3 enhancer element, which contributes to the up-regulation of IGFBP-3 during cellular senescence, suggesting that IGFBP-3 may play a role in the induction of senescence in normal human fibroblasts.

To characterize a functional role of IGFBP-3 in cellular senescence, we used a progressive replicate senescent human lung fibroblast system; young early passage cells as population doubling (PD) 17, pre-senescent cells as PD 24 and senescent cells as PD 30. Morphological changes characteristic of senescence, an

enlarged, flattened appearance and large nuclei are observed in PD 30, while PD 24 shows early senescence-associated changes, and PD 17 exhibits normal morphology. The SA- β -gal assay indicates a staining of greater than 75% for PD30, 30% staining for PD 24 and less than 3% for PD 17, indicating increased senescence as replication increases. The expression of senescence-related genes, p53, p21 and p16, were increased as the PD increased, indicating this cell system may use a known molecular circuitry of senescence. Interestingly, IGFBP-3 expression also increased with the progression of senescence, however maximal expression was detected in PD 24 pre-senescent cells, suggesting IGFBP-3 may be necessary to induce senescence. With the overexpression of IGFBP-3 in PD 17, data showed an induction of senescent characteristics including an increase in SA- β -gal staining similar to PD 30. Further, suppression of endogenous IGFBP-3 using a retroviral IGFBP-3 siRNA construct in PD 24, resulted in a significant delay of senescence demonstrated by reduced SA- β -gal staining, confirming the effect of IGFBP-3 on induction of senescence in normal human fibroblasts.

Taken together, these results strongly support that IGFBP-3 plays an active role in cellular senescence. Further elucidation of specific underlying mechanisms will provide a better understanding for the physiological function of the IGF-IGFBP system in cellular senescence and aging.