ALTERED DNA METABOLISM IN AGED AND PROGERIC FIBROBLASTS

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Aspects of DNA metabolism in aged human fibroblasts and fibroblasts from patients with the Hutchinson-Gilford progeria syndrome have been compared to aneuploid and hybrid mammalian cells. We find the dynamics of DNA metabolism as measured by rejoining of radiation-induced DNA breaks and cyclic repair of DNA is decreased in the "old" cells and in certain progeric cells. Aged fibroblasts and strains of progeric fibroblasts EX-441 and AK are more susceptible to cell death as measured by endonucleolytic DNA degradation.

Hybrid mammalian cells evidence an extreme resistance to ionizing radiation as measured by colony formation, rejoin DNA breaks most rapidly and appear most resistant to cell death. Aneuploid cells, tumor cells and early passage (< 10 doublings) diploid fibroblasts appear to be equally sensitive as measured by these endpoints. Middle passage human fibroblasts (10 to 45 population doublings) repair DNA breaks less rapidly. Progeric strains LD and SJ repair still less rapidly than these cells and progeric strains KH and EX-17 are even more deficient. Senescent human cells evidence mixed populations with different repair capabilities.

To develop an animal model system, we have investigated DNA repair characteristics during the in vitro lifespan of Syrian hamster embryo cells. These cells evidence either senescence after 6 to 10 mean population doublings or grow exponentially for over 20 population doublings. These cells evidence reduced DNA repair as measured both by unscheduled DNA synthesis and rejoining of DNA strand breaks as they reach senescence.

Further, we have observed DNA repair capabilities are influenced by co-cultivation with competent cells. EX-17 and EX-441 are progeric strains which evidence different DNA metabolic deficiencies. However, when they are co-cultivated 2-8 hr both deficiencies are ameliorated and DNA metabolic activity returns to that of normal cells.

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