

THERAPY-INDUCED CELLULAR SENESCENCE AND TELOMERE DYSFUNCTION IN COLORECTAL CANCER

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BACKGROUND: Accelerated cellular senescence (ACS) is an emerging concept implicating sustained cell-cycle arrest of tumor cells in response to cancer treatment. Following exposure to chemotherapy, tumor cells enter a state of cell-cycle arrest or cellular senescence. Uncapping events occur at the telomere ends in response to DNA damage, including the dissociation of TRF2 protein from the telomere ends followed by rapid degradation of telomere length. Characteristically, senescent cells in irreversible cell-cycle arrest demonstrate massive loss of telomere length. However, small subsets of cells are able to bypass or escape senescence and reenter the cell-cycle resulting in tumor progression. These escape cells show either partial or total recovery of their telomere loss. We hypothesize that telomere dysfunction reinforces cellular senescence.

METHODS: Human colon adenocarcinoma lines were tested for ACS following exposure to chemotherapeutic agents by either b-galactosidase staining or morphologic changes. Using an adenoviral approach, we specifically blocked recapping at the uncapped telomere ends via expression of the dominant negative TRF2 allele in senescent tumor cells. Additionally, tumor cells were treated with telomerase inhibitors TMPyP4 and TAG-6.

RESULTS: We demonstrate ACS in 7 of 8 human colorectal tumor cell lines exposed to camptothecin and oxaliplatin. The selective expression of the mutant protein TRF2 blocked telomere capping and significantly reduced escape colony formation. Additionally, the application of pharmacologic telomerase inhibitors also reduced senescence reversal.

CONCLUSIONS: These results suggest that uncapping and loss of telomere length in response to DNA damage plays an important role in preventing escape from therapy-induced senescence, and regulation of telomere capping events following chemotherapy may represent a novel approach to colorectal cancer treatment.