

S010 Targeting telomeric DNA as a therapeutic strategy

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The extreme 3' ends of eukaryotic telomeres comprise 100-200 nucleotides of single-stranded DNA together with multiple copies of the single-stranded binding protein POT1. In human cancer cells POT1 is involved in the regulation of the catalytic and end-capping functions of the specialized reverse transcriptase telomerase, which serves to maintain telomere integrity in these cells.

The tandem TTAGGG repeats of telomeric DNA can be induced to fold up into four-stranded quadruplex structures under the influence of appropriate small molecules, which can do this in cells, by displacing bound POT1 and telomerase from the single-stranded overhang. This in turn elicits rapid senescence and cell death, as a consequence of 1. exposing telomeric ends, and 2. inhibiting telomerase catalytic function, with those cells having short telomeres being especially sensitized to senescence.

The quadruplex approach to selectively targeting cancer cell telomeres will be illustrated by examples in several cancer cell lines and xenografts.