TSPYL5 prevents POT1 degradation in cells with an alternative mechanism of telomere maintenance

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An estimated 10% of cancer cells maintain their telomeres with a telomerase-independent mechanism known as Alternative Lengthening of Telomeres, or ALT, for which no specific molecular target has been identified yet. Here, we unraveled novel roles for TSPYL5 (Testis Specific Y-encoded-Like Protein 5) in preventing proteasomal degradation of the shelterin component POT1 in ALT^+ cells, but not in telomerase-expressing cells or normal fibroblasts. We found that TSPYL5 is a novel PML body component and protects ALT^+ cells from telomere deprotection and cell death by titrating away the USP7 deubiquitinase, a TSPYL5-inhibited and PML body-associated protein, from the POT1 interaction partner, TPP1. Co-localization of ALT telomeres with PML bodies is responsible for the sensitivity to TSPYL5 depletion as PML depletion fully rescued POT1 loss. Our discovery that TSPYL5 is required for ALT^+ cell viability by keeping POT1 offers novel therapeutic perspectives for ALT^+ cancers.