Identification of telomere dysfunction in Friedreich ataxia

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In Friedreich ataxia (FRDA), GAA repeat expansion within the first intron of the frataxin (*FXN*) gene leads to downregulation of *FXN*, resulting in oxidative stress, mitochondrial iron accumulation and neuronal atrophy. We hypothesised that telomere length might be shortened as a result of oxidative damage in FRDA. To investigate telomere function in FRDA, we initially assessed the telomere length in human and mouse FRDA fibroblasts and we found that both cell types had chromosomes with relatively longer telomeric repeats compared to controls. In contrast, we noted a significant telomere shortening in FRDA leukocyte cells compared to control cells. Consequently, we screened the FRDA fibroblasts for expression of telomerase activity and we identified that the telomerase activity was not present in these cells. We then assessed the co-localisation of PML bodies with telomeres and frequencies of telomere sister chromatid exchange (T-SCE) in these cells. Our results showed significantly higher co-localised PML foci with telomeric DNA and substantially higher T-SCE levels in the FRDA cell lines relative to the controls suggesting activation of an alternative lengthening of telomeres (ALT)-like mechanism. Analysis of growth curve and population doubling times of these cells revealed that the FRDA fibroblast cultures underwent growth arrest with higher cumulative population doubling compared to the controls. However, further analysis of telomere length at different passage numbers revealed that the telomere length in the FRDA cells shortened faster than the controls. Finally, we detected a significantly higher frequency of γ-H2AX foci and telomere dysfunction-induced foci (TIF) in the FRDA cells compared to the controls, suggesting induced telomere dysfunction in these cells. In conclusion, our results demonstrate a telomere dysfunction phenotype and accelerated telomere shortening in FRDA cells. In addition, the results suggest that intertelomeric recombination was initiated in the FRDA cells but was not capable of preventing accelerated telomere shortening.