

**Consequence of single break near telomere in human cells**

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Low dose radiation effects remain an open question, mainly due to the lack of models that permit to address it. Using human cells tagged with a plasmid integrated on end of a "marker" chromosome, we demonstrated that a single break near the telomere has dramatic consequences on the genome stability, inducing the panel of chromosomal instability detected in cancer cells including gene amplification and large chromosome imbalances (LOH up to 100 Mb), Sabatier et al, Mol Cancer Res 2005. One of the consequences of the chromosome instability induced by a single telomere loss is to let emerge cells with high proliferative advantages. An increase of the tumorigenicity of these cells is observed when transplanted on nude mice. Such cell models would be very informative to characterize the role of the modulation of DNA damage repair (NHEJ and HR) in the consequence of single chromosome break. First we tested the feasibility of using replicative small interfering vectors for efficient and long term silencing in human cells. We silenced NHEJ protein -DNAPK, LigIV, and XRCC4- and HR protein -Rad51/Rad52/Rad54- in HeLa cells. Our data suggested that the major effect of NHEJ on telomere maintenance is indirect via misrepaired breaks in subtelomeric and telomeric whereas the major effect of HR on telomere maintenance is direct via telomere replication and telomere recombination. We are working on the in-validation of DNA repair genes in telomere tagged models. Having demonstrated that a single break near telomere could have such consequences we now address the question of radiation-induced chromosome breaks that will occur at low doses (25 mGy -> 1DSB per cell), studying clonogenic survival and the emergence of resistant clones due to chromosome breakage.