

DIFFERENT PATTERNS OF CHROMOSOMAL EVOLUTION BETWEEN TELOMERASE POSITIVE AND ALT CELL LINES

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Clonal evolution of cancer cell populations and immortalized cell lines is characterized by continuous emergence and disappearance of numerical and structural chromosomal aberrations. To investigate any differences between the patterns of genomic evolution in telomerase expressing cancers versus telomerase negative tumors and cancer cell lines, we constructed snapshots of karyotypic evolution in vitro, by comparing randomly selected GTG and/or inverted DAPI or FISH-aided karyotypes, from the telomerase positive (TA) human cancer cell lines K-HOS, SW480, HeLa, and MCF-7, and the telomerase negative human osteosarcoma cell lines U2OS, and SaOS-2, from subsequent passages and different sources. Short term cultures of two ovarian cancer metastases tested negative and positive respectively for telomerase expression by TRAP, were also examined. Despite maintenance of a signature Karyotype, chromosomal evolution and continuous genomic instability was observed in both types of telomere restoration. Telomerase positive cancer cell lines showed increased rates of numerical and structural chromosomal instability. In contrast, and opposing current opinion, ALT cell lines retained remarkable numerical and structural chromosomal stability. Fission, fusion and telomere capping of constitutive heterochromatin was observed only in the ALT+ cell lines and is reported for the first time. This dynamic process that was more pronounced in the U2OS cell line led to the generation of minute chromosomes and could be associated to the ALT recombinatorial mechanism (s). ALT cell lines showed a 5-10 fold increased rates of whole genome duplication compared to ALT(-). Polyploidization in the form of whole genome duplication was considered as an artifact of continuous growth. Transduction with hTERT dramatically suppressed genome duplication in the absence of telomerase activity. The presence of large blocks of interstitial telomeres in several recombinant chromosomes encountered in both types of immortal growth, indicated that other recombination sites and conditions beyond "shortest telomeres" could drive structural rearrangements and karyotypic evolution. In the numerically "pseudo stable" low TA SW-480 cell line, chromosomal losses were compensated by continuous non-disjunctions. Telomeric length discrepancies of disjoined identical homologues support a complementary mechanism of telomere restoration operating through inter-chromatid telomere recycling and continuous aneuploidy.