

Letter to the Editor

Neoplasia, ageing, and genetic instability due to defective caretaker genes*

Sir,

In all human populations, cancer prevalence and genomic instability increase as a function of age, suggesting that loss of genetic homeostasis contributes to carcinogenesis. Loss of genetic homeostasis is reflected by the accumulation of chromosome damage and DNA alterations which result from age-dependent decrease of efficiency and fidelity of our genomic maintenance systems. Chromosomal rearrangements reflect errors of recombinational types of DNA repair which, in a variety of leukemias and lymphomas, give rise to chimeric proteins with altered functions. A number of cancer prone conditions are caused by biallelic inactivation of caretaker genes, e.g. *TP53*, *WRN*, *ATM*, *BLM* and the *FANC* family of genes, including *BRCA2*. At the cellular level, inactivation of caretaker genes leads to chromosomal instability, reflecting inability to properly recognize and/or repair genetic damage caused by exogenous (e.g. ionizing radiation, chemicals) or endogenous (e.g. reactive oxygen species) agents. Chromosomal alterations are strikingly different among caretaker gene syndromes, indicating involvement of the respective genes in different genomic maintenance functions (e.g. NER, HR, NHEJ, etc.). While *ATM* defects yield specific chromosomal rearrangements involving chromosomes 7 and 14, *BLM* defects result in sharply increased sister chromatid exchange rates, and *WRN* helicase defects cause “variegated translocation mosaicism” (VTM [1–3]). VTM is characterized by the emergence of multiple chromosomal rearrangements in a clonal fashion, mostly side by side with diploid cells. During propagation in vitro, a given VTM cell clone may expand or disappear over time (clonal succession and clonal attenuation). The phenomenon of VTM may contribute to the early occurrence of mostly mesenchymal tumors in Werner syndrome patients.

A highly instructive example of the adverse effects of genetic instability is Fanconi anemia (FA), a can-

cer prone multisystem disorder caused by biallelic mutations in one of at least 13 different genes, including *BRCA2*, *PALB2* and *BRIP1* [4]. FA patients display a variable pattern of congenital anomalies, but also a myriad of progeroid features (pigmentary changes, premature occurrence of endocrine dysfunction, osteoporosis, squamous cell carcinomas of the aerodigestive tract and the anogenital region). FA cells show a characteristic pattern of spontaneous and induced chromosomal instability (chromatid-type lesions and multiradial exchanges between non-homologous chromosomes), while primary aneuploidy is rare. As a consequence of impaired homologous recombination repair, FA cells are defective in the removal of DNA-interstrand crosslinks and stalled replication forks. This renders FA cells exquisitely sensitive towards DNA-crosslinking agents and, most notably, to the DNA-damaging effects of reactive oxygen species. Exposing FA cells to hypoxia all but eliminates their chromosomal instability and restores cell cycle progression and cell growth to near normal [5]. Thus, FA may represent the only human model of the “free radical” theory of ageing [6]. Somatic reversion events (due to intragenic crossover, gene conversion, back mutation, or compensating second site mutations) have all been observed in patients with Fanconi anemia and in patients with Bloom syndrome. Somatic reversions are highly instructive experiments of nature since a single mutational event suffices to restore the genetic instability cellular phenotype to completely normal [4]. The phenomenon of somatic reversion confirms that single gene mutations cause chromosomal instability, thereby increasing the likelihood of genomic imbalance and, subsequently, the likelihood of neoplastic cell growth.

Abbreviations

NER: Nucleotide excision repair
HR: Homology directed repair
NHEJ: Non-homologous end joining

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