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Letter to the Editor

The "aneuploidy–modified mutator-phenotype" theory of malignant tumors *

To the Editor,

Aneuploidy is thought to be involved in tumor formation for many reasons including (i) its commonness, especially among malignant neoplasms; (ii) cell lines with specific karyotypic changes can be grown from certain types of tumors; and (iii) many immortal tumor cell lines are hyperploid. Mutations are thought to be involved in tumor formation for reasons including (i) tumor cells transmit their abnormalities to their descendants; (ii) many hereditary predispositions to tumor types are associated with specific germ-line mutations (iii) many carcinogens are mutagens. In addition to these mechanisms, acquired somatic cell replicative infidelity of DNA ("mutator phenotype") may be a mechanism of tumor formation, because more somatic genomic events are found in malignant tumor cells than could arise either by repeated exogenous mutagenic insults or by aneuploidy alone. Nevertheless, lines of living organisms with "mutator phenotype", sooner or later, might be expected to die out through the accumulation of lethal mutation loads. Despite this, all cases of cancer seem to contain at least some lines of cells which are immortal.

In an earlier somewhat parallel consideration, Muller [1] in the 1960s suggested that populations of living organisms which reproduce asexually are likely to die out because of accumulations of germ-line mutations ("Muller's ratchet"). He further suggested that in sexually-reproducing organisms, two aspects of meiosis – recombination of chromosomes and "crossing-over" – might allow for the formation of occasional gametes in which the accumulated deleterious mutations are significantly reduced by accidental distribution of the majority of such mutations to other gametes. He argued that this would have the effect that at least some progeny of the species do not continue to carry all of the mutation load(s) of their parents.

The present author [2–4] has suggested that in tumor cells – which reproduce asexually – aneuploidy might act in a way analogous to the features of meiosis to correct excess mutational loads caused by "mutator phenotype". A scheme could be: (i) a mutation affects genomic elements for control of growth, and for replicative fidelity of DNA, leading to "mutator phenotype". Then (ii) aneuploidy could develop when "mutator phenotype" results in mutation of genomic elements for mitotic-and-chromosomal stability. And then (iii) an asymmetric mitosis (in the course of the aneuploid phase) could produce occasional cells in which the "bad copy" is lost (or an extra "good copy" is gained) of the original genomic element which had been mutated to provide the "mutator phenotype". The resulting cells would have significantly restored fidelity of replication of DNA, and hence could give rise to populations which are relatively genomically stable, hyperploid and immortal despite having large numbers of alterations in their DNA.

Alternative schemes, for example in which a chromosomal lesion – analogous to the formation of the Philadelphia chromosome – starts the "mutator phenotype" condition, could apply to some tumor types.

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