

## Letter to the Editor

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### Meiotic-like division to a aneuploidy: Chromosomal instability (CIN), cell-senescence and cancer\*

To the Editor,

An understanding of cancer cell heterogeneity requires knowledge of mechanisms for somatic cell variation. For plant (galls) and animals alike, such genetic cell differences can arise from mutations, somatic crossing over, segregation mistakes and from certain viral infection. This latter route for some DNA-viruses is an early virus-induced change to polyploid cells which is also increasingly being recognized in neoplastic-risk associated lesions [3]. Indeed, division of polyploid cells by multipolar spindles is one favorite route to cancer cell diversity [6]. But, these abnormal divisions do not occur for primary, human diploid cells where a cancerous process has to start.

However, the polyploid issue in tumorigenesis goes back more than a century when there was mention of a gonadal-like division in the origin of aneuploidy [1]. Such divisions of polyploidy would separate whole chromosomal complements from each other and reduce the genomic content of for example an octoploid cell to four G1 tetraploid cells. Supportively, some works have shown polyploid-segregations into whole genomic sets in mitosis (e.g.,  $4n$  into  $2n-2n$ ;  $2n-1n-1n$ ;  $1n-1n-1n-1n$ ), but the explanation was multipolar mitosis [5]. This division, if present, would distribute the chromosomes randomly.

These possibilities of somatic cell variation from a meiotic-like division of polyploid cells have lately become a reality [7–10]. This process has now been shown to occur for two different human, diploid fibroblast cell-strains. The recognition of this genome reductional division was based on the fact that the polyploid cells were a special type: endopolyploid from several DNA-synthetic periods not intervened by mitosis [2]. In regular mitosis these polyploid cells contained diplochromosomes which are units of two sister chromosomes forming a four-chromatid complex.

These cells underwent two bipolar mitoses in succession which firstly separated the sister pairs from each other and secondly divided the bichromatid chromosomes into single chromatid nuclei (e.g.,  $4n/8C$  to  $2n/4C$  bichromatids to  $2n/2C$  single chromatids) [8]. The “four-strand” stage and the two bipolar divisions in succession resulting in cells with reduced genomic content are indeed, gonadal/meiotic-like.

But, unanswered is: what triggered endopolyploidization in the two cell-strains? Commonly, endopolyploidy arises from cell cycle arrest-escaped G2/M cells with genomic damage which skip mitosis and re-replicate into diplochromosomes [2]. For cells with short telomeres, approaching senescence, there is specific occurrence of chromosomal instability (CIN) from heterochromatinization [9]. It causes genomic damage by clumping of chromosomes from changed gluey-chromatin with the result of breakage/miss-segregations in mitosis. Consequently, meiotic-like division of endopolyploid cells derived from CIN-cells, can result in aneuploidy associated with chromosomal aberrations which is a hallmark in tumorigenesis. Hence, epigenetic changes causing CIN with potential for endopolyploidy and further division to aneuploidy are special cell senescence-associated events. In non-healing wounds as in chronic lesions, cell replication to senescence occurred over time with the result of similar CIN and polyploidy [4]. Thus, potential neoplastic development from such “end-of-lifespan”-genetic variability are therefore, age-related which agrees with prevalence of cancers in advanced age.

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**References**

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