Title
Does aneuploidy destabilize karyotypes automatically?

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LETTER

Reply to Duesberg: Stability of peritriploid and triploid states in neoplastic and nonneoplastic cells

We thank P. H. Duesberg for his interesting comments (1) on our recently published report that aneuploidy in itself does not cause chromosomal instability (2). The topic of aneuploidy in cancer cells has been surprisingly little debated publicly, despite the fact that it is a prevalent phenomenon that remains enigmatic from many viewpoints. We welcome this opportunity to discuss our data further, with a particular focus on chromosomal instability at triploid and near-triploid levels.

P. H. Duesberg is indeed correct that in our paper (2) there was a slight trend of increased aneusomy index (AI) in the group of aneuploidy syndromes compared with controls. However, except for cases with triploidy, this increase was not significant using stringent statistical testing. Both triploid cases in our study died in utero, which is in fact the most common outcome for triploid pregnancies. Furthermore, triploid pregnancies typically are very small for gestational age, have multiple anatomical defects, and partial mole development of the placenta. Survival of live-born pure triploids rarely extends beyond a week. Taking these data together, this implies that triploidy confers dramatic alterations in gene expression, arguing against Duesberg's statement that "the balance of chromosomes in congenital triploids is the same as that in normal cells" (1). This statement also contradicts previous original data reported by Duesberg's team in 1998, which showed that near-triploid cancer cells ($n = 71$) were more unstable than highly hypodiploid and highly hypertetraploid cancer cells (3).

Duesberg's hypothesis of a dose-dependent relationship between the degree of aneuploidy and the rate of chromosomal instability has some parallels to data from yeast, which has led to a model where the more a cell's karyotype deviates numerically from a multiple of the haploid set, the more chromosomally unstable it becomes (4). However, one should be careful in applying this finding to primary human cells. In fact, the model agrees poorly with several details in our recently published study (2). First, if such a proportionality existed, our triploid cases should have had lower AI than the hyperdiploid cells with single and double trisomies. In fact, we found the opposite. Second, one would also expect the pseudodiploid DLD-1 colon cancer cell line to have lower AI than the double and single trisomy cells. However, this was not the case (2). Finally, one must predict that our two cases with double trisomies would be more unstable than the single trisomics. Such a difference was not found. Taking these data together, we find that the main difference in chromosomal instability in our study was between cancer cells and noncancer cells, irrespective of karyotype.

We would finally like to stress that because it has been well established that chromosomal instability causes aneuploidy, one must be extra careful when claiming that the reverse statement is true. Care in interpretation is also warranted when extrapolating data from artificial models of aneuploidy to primary human cells, because many of these cell systems are themselves generated through a process including chromosomal instability. Hence, they are far from ideal tools for studying the causal relationship between aneuploidy and genome instability.

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2 Valind A, Jin Y, Baldetorp B, Gisselsson D (2013) Whole chromosome gain does not in itself confer cancer-like chromosomal instability. *Proc Natl Acad Sci USA* 110(52): 21119–21123.
3 Duesberg P, Rausch C, Rasnick D, Hehlmann R (1998) Genetic instability of cancer cells is proportional to their degree of aneuploidy. *Proc Natl Acad Sci USA* 95(23):13692–13697.
4 Zhu J, Pavelka N, Bradford WD, Rancati G, Li R (2012) Karyotypic determinants of chromosome instability in aneuploid budding yeast. *PLoS Genet* 8(5):e1002719.

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The authors declare no conflict of interest.

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