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Tetraploidy and CIN: a dangerous combination

Comment on: Kuznetsova AY, et al. Chromosomal instability, tolerance of mitotic errors and multidrug resistance are promoted by tetraploidization in human cells. Cell Cycle 2015; 14(17):2810-20; PMID: 26151317; http://dx.doi.org/10.1080/15384101.2015.1068482.

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Chromosomal instability (CIN) is a hallmark of cancer, and is associated with both poor prognosis and drug resistance.[1] Tetraploidy has also been frequently observed in human cancer despite being a relatively rare occurrence in somatic cells. Experimentally induced tetraploidy has been shown to result in an increase in numerical and structural chromosome aberrations. Recent bioinformatics analyses have shown a significant proportion of solid tumors (11–64%) show evidence of a whole genome duplication event, and this is associated with higher rates of copy number alterations,[2] suggesting that tetraploidy is a common route to genome instability in cancer. We recently showed that tetraploid cells are better able to tolerate chromosome missegregation events than diploid cells, resulting in the evolution of CIN in tetraploid cells over extended periods of time in laboratory culture.[3] In this issue of Cell Cycle, Storchova and colleagues confirm these results, and elegantly extend their analysis to search for a mechanistic basis for CIN tolerance in tetraploid cells.[4]

In this study, the authors investigate genome stability in tetraploid clones derived from HCT-116 and hTERT-RPE1 cells. Intriguingly, tetraploidy resulted in a CIN+ phenotype (increased chromosome missegregation, aneuploidy, and segregation error tolerance) in all HCT-116 tetraploid clones, but in only one of 3 hTERT-RPE1 tetraploid clones. This analysis of both cancer and immortalised non-transformed cell lines suggests that CIN is a common, although not obligatory, result of tetraploidisation.

Intriguingly, the tetraploid clones that exhibited a CIN+ phenotype showed a similar deregulation of p53 signaling after drug induced chromosome missegregation, with a lack of nuclear p53 accumulation and absence of p53 stabilization. These data suggest that the ability of tetraploid clones to proliferate after chromosome missegregation could be due to changes in p53 regulation. It is interesting however, that despite a basal increase in mitotic errors, tetraploid clones do not show changes in p53 regulation under normal, untreated conditions.

To examine the role of p53 regulation further, the authors carried out analysis of the expression of 388 p53 interacting genes. Among a list of 7 genes up regulated in all tetraploid clones were 2 anti-apoptotic genes. This finding supports data suggesting that tetraploidisation induces apoptosis,[5] and begins to shed light upon a mechanism through which tetraploid cells can avoid this fate. Further, specifically in CIN+ clones, 2 genes were up-regulated that are involved in the response to stress (FOXO1 and NDRG1). It will be interesting to investigate whether these genes function in the acquisition of the CIN+ phenotype in tetraploid cells, for example whether they are involved in modulating cell fate after segregation errors. Whether these changes in gene expression result in alterations at the protein level remains to be established. Furthermore, it will be crucial to investigate whether genes that are altered in tetraploid cells are also de-regulated in human polyploid cancers.

Finally, the authors showed that tetraploid clones tended to be more resistant to a range of drug treatments. Although some of the increases in relative resistance are fairly modest, this may still important have clinical implications, especially as the assays used were only short-term and the duration of cytotoxic therapy in the clinic is measured in months rather than days.

This paper by Storchova and colleagues adds to the now growing body of evidence showing that tetraploidy is an important driver of CIN in cancer.[4] For the first time CIN is shown to arise in immortalised non-transformed human cells after tetraploidisation, raising intriguing questions about when this phenotype might arise in the transition from pre-invasive to malignant disease in patients. Intriguingly, the presence of extra centrosomes does not seem to influence the level of chromosome missegregation in tetraploid cells. This result is surprising, as extra centrosomes are a major cause of numerical CIN in tetraploid cell lines.[6] The cellular mechanisms responsible for increased chromosomal instability in tetraploid cells remain to be elucidated; data provided in this paper shed light on potential approaches to define such mechanisms. Given the association between genome duplication and poor patient prognosis.[3,7] together with the tolerance of segregation errors as a major route to CIN, this promises to be a fruitful area for further research.

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