Tetraploidy and tumor development

In tumorigenesis, aneuploidy is frequently preceded by tetraploidy. Major issues include how tetraploidy arises and how cells can effectively respond to this state. Two recent papers address these issues. Shi and King demonstrate that nondisjunction of chromosomes in mitosis frequently results in tetraploidy through mitotic cleavage failure. Fujiwara et al. demonstrate that p53 null tetraploid cells are highly competent to induce tumors in nude mice. Together, these papers emphasize the unique hazard of tetraploidy and the fact that p53 status has an intrinsic capacity to eliminate tetraploid cells and suppress tumorigenesis. This p53-dependent elimination may represent a checkpoint control.

Tetraploidy, the presence of twice the normal number of chromosomes, is an ominous state in mammalian tissues. In many human carcinomas, cells with tetraploid DNA content arise as an early step in tumorigenesis and precede the formation of aneuploid cells (Margolis et al., 2003). Aneuploidy and chromosomal instability in turn are characteristic of the great majority of human cancers (Cahill et al., 1999) and are linked to the progressive development of high-grade, invasive tumors. The mechanism by which tumor cells proceed through a tetraploid intermediate to aneuploidy, often with prolonged tetraploid precancerous status, is therefore of central importance to cancer research. It is of equal importance to understand why tetraploidy represents such a danger, and how normal cells evade development of tetraploid status.

Two fascinating recent papers (Fujiwara et al., 2005; Shi and King, 2005) have addressed different aspects of this important issue, and the recent work has emphasized the significance of tetraploidy in tumor development.

The paper by Shi and King showed that in cell lines with relatively high spontaneous rates of chromosome nondisjunction in late mitosis, the fate of the majority of cells with segregation errors is to become tetraploid. Surprisingly, tetraploidy arises because the majority of cells that exit mitosis with chromosome nondisjunction revert to a single binucleate tetraploid cell though furrow regression, a late event recorded by video microscopy.

The paper by Fujiwara et al. looked at downstream events after the creation of tetraploid cells. In this work, the tetraploid cells were created by brief exposure of p53 null mouse mammary epithelial cells to an actin assembly inhibitor that interferes with cell cleavage. Tetraploid cells were then isolated by cell sorting, and their fate followed. It is of substantial interest that tetraploidy status proves to be relatively stable but leads to a marked increase in chromosome translocations in vitro and to high levels of tumorigenesis when p53 null tetraploid cells are introduced into nude mice, by comparison to p53 null diploid cells sorted from the same initial population.

The Shi and King paper raises two important issues. How does missegregation induce tetraploidy, and more importantly, what is the value to the cells in becoming tetraploid? With respect to the mechanistic aspect, the authors appear to rule out the obvious, that furrow failure is the product of chromosome bridges. Furrow failure occurs even in cells with no evident bridging, and thus raises the issue whether it occurs by design rather than mechanical failure.

If by design, the value of a mechanism to induce tetraploidy following missegregation may be that mammalian tissues seem to have an intrinsic capacity to eliminate tetraploid cells. This may take the form of a tetraploidy checkpoint, by which p53-competent cells are prevented from proceeding to further cell cycles. Experimental observations have suggested the existence of such a tetraploidy checkpoint (Margolis et al., 2003), but this remains controversial (Uetake and Sluder, 2004; Wong and Stearns, 2005). Tetraploid cells may also be subject to Darwinian selection, since tetraploid cells do not invariantly produce tetraploid progeny but instead produce, with some frequency, highly aneuploid daughter cells that are eliminated (Borel et al., 2002; Meraldi et al., 2002). The reason that tetraploid cells produce aneuploid progeny is that they have inherited twice the normal complement of centrosomes, which will frequently establish multipolar spindles and generate random chromosome segregation in subsequent divisions (Meraldi et al., 2002; Borel et al., 2002; Fujiwara et al., 2005). An intrinsic capacity to eliminate tetraploid cells is in evidence in both the Shi and King and the Fujiwara et al. papers. In this process, evidence would seem to favor specific checkpoint controls as opposed to Darwinian selection, as in both papers elimination of tetraploid cells is p53 dependent.

Difficulty in the ensuing mitosis is not the sole reason for elimination of tetraploid cells. In Shi and King (2005), the majority (60%) of p53-competent hTERT-immortalized cells do not proceed to the next division when tetraploid, whereas the authors show that p53-suppressed HeLa cells, by comparison, almost universally divide when tetraploid. Of the tetraploid hTERT cells that divide, 35% form multipolar spindles and thus must become highly aneuploid. By the reasoning of the authors, these downstream missegregation events should also cause furrow regression, resulting in further ploidy increase, rather than aneuploidy. This possibility was not pursued. Given that the majority of hTERT cells did not proceed to the subsequent mitosis, is this a checkpoint? If a tetraploidy checkpoint were responsible, it would appear to be leaky in these cells. This would not be the first cell cycle checkpoint that has proven to be leaky. In the end, perhaps a statistical suppression of tetraploid cell growth would be sufficient to prevent maintenance of a tetraploid population in normal tissue, thus suppressing the attendant risk for tumor development. As hTERT-immortalized cells frequently lack important elements of cell cycle checkpoint control (Dickson et al., 2000), it is worth asking whether early passage primary cells would perform better when tetraploid.

In Fujiwara et al., the emphasis was on the analysis of the outcome when p53 null mouse mammary epithelial cells become tetraploid. The cells continue to proliferate and maintain approximate tetraploid status, with increasing incidence of nonreciprocal translocations. The aneuploid cells that arise from multipolar mitosis are clearly subject to rapid elimination. Comparable to p53 null cells, paired littermate p53wt cells also proceed to 8N with some frequency after induction of tetraploidy, but unlike the p53 null cells, the large majority strikingly fail

to proliferate by 72 hr. Again, this is consistent with the possible existence of a tetraploidy checkpoint.

A tetraploidy checkpoint would be of obvious utility to the prevention of tumor progression. If a tetraploidy checkpoint were tissue or condition dependent, then it would be imperative to determine its limitations. If it does not exist despite having such obvious survival value, the question is: why not? One possibility is that, like the inability to respond to DNA damage during mitosis (Skoufias et al., 2004), the cell may simply lack the machinery to read tetraploidy or to respond to it.

In both papers, something is preventing the majority of p53-positive cells from proliferating when tetraploid. On the other hand, the capacity to arrest when tetraploid appears to be leaky. In both cases, the general issue is whether the suppressed growth is indeed a p53-dependent tetraploidy checkpoint. Time will tell. The nature of potential controls in tetraploid cells will only be resolved once a molecular mechanism explains the evident p53-dependent suppression of cell proliferation in the presence of tetraploidy status.

Taken together, the two articles by Shi and King and by Fujiwara et al. suggest that chromosome nondisjunction results in tetraploidization, and that the tetraploid state is associated with a predisposition to tumorigenesis in the absence of functional p53.

Thus, the spindle assembly checkpoint, and proper regulation of sister chromatid cohesion, are likely to play important roles in preventing the tetraploid state, which is in turn an evident precursor to tumorigenesis.

Ultimately, understanding why p53-compromised tetraploid cells have an increased propensity for genetic instability may be a key to understanding the process of tumorigenesis.

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Selected reading

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