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Very CIN-ful: Whole Chromosome Instability Promotes Tumor Suppressor Loss of Heterozygosity

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Mechanisms by which whole chromosome instability lead to tumorigenesis have eluded the cancer research field. In this issue of *Cancer Cell*, Baker et al. show that CIN induced by a defective mitotic checkpoint, under certain genetic and tissue contexts, leads to accelerated loss of heterozygosity of a tumor suppressor gene.

Chromosomal instability (CIN) resulting from the failure to correctly segregate sister chromatids during mitosis has long been proposed to drive the tumorigenic process. An abnormal chromosome complement, or aneuploidy, is frequently observed in tumors, and a number of in vivo models of induced aneuploidy lead to tumor formation or accelerate tumorigenesis in a variety of settings (Perez de Castro et al., 2007).

However, a simple mechanistic explanation linking CIN to tumorigenesis has eluded the cancer biology field for years. One possibility is that CIN favors loss of heterozygosity of tumor suppressor genes by accelerating the missegregation of the wild-type allele-carrying-chromosome. In a study in this issue of *Cancer Cell*, the van Deursen lab shows that in *p53* heterozygous mice, CIN driven by a weak mitotic checkpoint leads to the loss of heterozygosity of the *p53* locus and acceleration of lymphomagenesis (Baker et al., 2009).

Defects in the mitotic checkpoint, a molecular mechanism that ensures correct chromosome segregation during mitosis, have been causally implicated in CIN by a number of different studies. Both partial loss of function of key mitotic checkpoint genes (e.g., *bub1*, *bubR1*, *cenpE*, *mad2*, *mad1*) as well as overexpression of some of these gene products (e.g., Mad2, Hec1) lead to CIN and, in many cases, to spontaneous tumor onset (Perez de Castro et al., 2007). In the current study, Baker et al. focus on whether reduced Bub1 levels, which were known to generate aneuploidy (Jeganathan et al., 2007), could accelerate loss of heterozygosity of known tumor suppressor genes and, by so doing, accelerate tumor onset. While their results clearly show that LOH can be accelerated by CIN in certain cases, as discussed below, they also underscore the importance of context in subsequent tumor formation.

p53 heterozygous animals typically develop sarcomas and a low frequency of thymic lymphomas (Jacks et al., 1994). Mice with reduced levels of Bub1 ($bub1^{-/H}$) showed a greatly accelerated incidence of thymic lymphomas in the context of p53 heterozygosity, and lymphoma cells from these animals showed numerical and structural chromosome abnormalities. Moreover, all lymphomas analyzed had lost the remaining wild-type copy of p53. Remarkably, tumor cells had also duplicated the mutant allele as seen by spectral karyotyping and allele-specific PCR. This duplication is likely a result of mis-segregation or mitotic nondisjunction given the presence of $bub1^{-/H}$ induced CIN and the fact that informative SNP markers are also duplicated distal to the *p53* locus, ruling out mitotic recombination and gene conversion.

The observation of loss of heterozygosity of the wild-type tumor suppressor allele and duplication of the mutant one was also seen with *bub1* hypomorphism in the context of the $APC^{min/+}$ model of colon adenocarcinoma. $APC^{min/+}$ animals normally develop small intestinal adenomas at complete penetrance but develop colon adenocarcinomas at low frequency (Luongo et al., 1994). When crossed to $bub1^{-/H}$ animals, colon tumor incidence was increased 3-fold. In all cases analyzed, allele-specific PCR confirmed loss of heterozygosity of the *APC* wild-type allele and FISH showed duplication of the mutant one. Unlike with the *p53* lymphomas, however, whether the duplication of the mutant APC^{min} allele was a result of chromosome duplication, mitotic recombination or gene conversion was not established given the lack of informative SNP markers in the studied strain.

LOH and duplication of the mutant chromosome in the context of mitotic CIN raises the question of whether this mechanism is specific for mitotic checkpoint defects. Apparently not. Studies by others have already shown that in $p53^{+/-}$ animals, tumors induced by irradiation (Tanaka et al., 2002), as well as spontaneous tumors (A. Balmain, personal communication), also lose the wild-type chromosome and duplicate the mutant one. Hence, the CIN imparted by *bub1* hypomorphism is not introducing a new mechanism for tumor progression but accelerating one that is already commonly seen in this setting.

In contrast to the observations seen with *p53* and *APC*, $bub1^{-/H}$ failed to accelerate the appearance of pituitary adenomas in $Rb^{+/-}$ animals and did not significantly affect prostate lesions in the context of *PTEN* heterozygosity. In fact, in the $PTEN^{+/-}$ setting, though *bub1* hypomorphism had no effect on the incidence of advanced stage IV prostatic intraepithelial neoplasia (PIN IV), there was a reduction in the number of less aggressive PIN II and PIN III lesions. The observations in the *Rb* and *PTEN* systems suggest that the role of CIN in accelerating tumorigenesis is very much context dependent. In fact, even in the *p53*

heterozygous animals, which normally develop sarcomas at a higher incidence than lymphomas, *bub1* partial loss of function had no effect on sarcoma incidence. Though $APC^{min/+}$ colon tumor incidence was similarly increased in the $bub1^{+/-}$ setting, no change was seen in the incidence of small intestinal tumors, which are also seen in this strain. The mechanistic basis for this context dependence will require further studies. Technologies to carefully measure rates of aneuploidy and LOH in early neoplastic lesions will undoubtedly aid in this analysis.

Previous studies have already suggested that CIN might, in some contexts, act as a tumor suppressor (Garcia-Higuera et al., 2008; Rao et al., 2005; Weaver et al., 2007). Baker et al.'s study reinforces the notion that whether CIN favors or prevents tumor formation and progression is very much subject to the setting under which it occurs. Certain cell types may be particularly sensitive to abnormal chromosome complements and be eliminated in early lesions. Whether non-cell-autonomous effects are at play in such suppression has not yet been analyzed. Aneuploidy in cells of the tumor microenvironment, for example, may contribute in some tissue types to tumor suppression. Conditional models of CIN will be required to address this issue.

The finding that, in the setting of *p53* or APC^{min} heterozygosity, the mutant allele is similarly duplicated strongly suggests that there is selective pressure to maintain two copies of the chromosome harboring the tumor suppressor that undergoes LOH. Haploinsufficiency of genes on this chromosome likely decreases the fitness of cells that have undergone such a loss, and these cells are rapidly outcompeted in the population.

The results presented in this issue by Baker et al. provide the first evidence for a potential mechanism by which CIN can lead to tumorigenesis by linking aneuploidy to loss of heterozygosity of tumor suppressor genes. As so often happens with important advances in cancer biology, more questions are now raised. Could CIN favor the duplication of chromosomes harboring oncogenic mutations at the same time as it accelerates the loss of tumor suppressors? Does CIN occur prior to the loss of tumor suppressors and is it generally present in early preneoplastic lesions as one might predict from the current analysis? Does such a mechanism of mutant chromosome retention occur in human cancers?

Nonetheless, this study uncovers an important mechanistic insight into how LOH is accelerated by defects in the mitotic checkpoint pathway and paves the way for a deeper understanding of the role of CIN in cancer initiation and progression.

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Proliferation and Tumor Suppression: Not Mutually Exclusive for Eph Receptors

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Eph receptors are important but controversial regulators of cancer development. A recent study reported in *Cell* reveals that in the intestinal epithelium, EphB2 enhances proliferation through a kinase-dependent pathway and inhibits migration independent of its kinase activity. These separate pathways simultaneously promote proliferation but suppress invasive growth of intestinal adenomas.

Extensive evidence implicates the Eph receptor family of tyrosine kinases in cancer development, but it remains incompletely understood how these receptors affect cancer progression. Opposite tumor-promoting and tumor-suppressing effects have been described, sometimes for the same Eph receptor in the same type of cancer (Pasquale, 2008). Switching