Cell Cycle 13:9, 1370–1370; May 1, 2014; © 2014 Landes Bioscience

Is aneuploidy deciding your fate?

Comment on: Clemente-Ruiz M, et al. Cell Cycle 2014; 13:1450–55; PMID:24626182; http://dx.doi.org/10.4161/cc.28417

Konstantina Rowald and Rocio Sotillo*; Mouse Biology Unit; European Molecular Biology Laboratory (EMBL); Monterotondo, Italy;
*Email: sotillo@embl.it; http://dx.doi.org/10.4161/cc.28753

Fighting cancer is like fighting evolution. Its variant genetic background and its easy adaptability made it an exasperating case for science. Today we know that one of the reasons behinds its genetic flexibility is the occurrence of errors during chromosome segregation, a phenomenon also known as chromosome instability (CIN). Until today, it remained unclear if CIN stands at the origin or is a consequence of tumorigenic transformation. To study the role of CIN in cells' fate, several model systems have been implemented targeting the expression of proteins involved in the spindle assemble checkpoint (SAC). Although spontaneous tumor formation has been shown in some cases, other studies also described deleterious or no effects on tumorigenesis.[1,2]

In this issue of *Cell Cycle*, Milan's group brought new fire to the controversy around the role of aneuploidy in cancer, suggesting that a minimum threshold of aneuploidy is required to drive tumors.[3] This argues in contrast to recent findings of Morais Da Silva and colleagues, where depletion of SAC function and the consequent aneuploidy were not sufficient to cause hyper-proliferation.[4] Both studies used *Drosophila* cancer models in which SAC genes in the wing primordia were knocked down causing aneuploidy, cell delamination, and consequent cell death. By additional blockage of apoptotic pathways, delaminating cells activate a JNK-dependent transcriptional program that triggers the expression of MMP1 and Wg, causing tissue overgrowth. The depletion of Bub3, Mad2, and BubR1 in *Drosophila* wing epithelial cells unable to undergo apoptosis leads to increased levels of aneuploidy and neoplastic growth. However, when perturbing mitosis via CENP-E (a kinesin motor protein that helps the attachment of microtubules to kinetochores) and Nsl1 knockdown (that mediates kinetochore targeting of Bub3), Morais da Silva and colleagues did not observe tumors despite cells being aneuploid. This led to the conclusion that an unknown cytosolic tumor suppressor function of checkpoint proteins stands at the origin of the observed cell transformation. As this result stood in contrast to previously described findings of mitotic gene depletion causing CIN and tumor growth after inhibition of cell death in *Drosophila*,[5] Milan's group revisited these experiments. Interestingly, knockdown of CENP-E and Nsl1 in their model induced a tumorigenic response in terms of cell delamination, basement membrane degradation, and tissue proliferation.[3] The authors attributed these opposing results between the 2 laboratories to the higher levels of aneuploidy, suggesting that a minimum level of aneuploidy is needed to activate tumorigenic response pathways. A similar concept highlighting the importance of moderate aneuploidy levels has also been proposed after collective data from murine models.[2] Yet here, depending on the targeted gene, similar percentages of aneuploidy display different tumor predisposition. The necessary levels of aneuploidy might consequently vary with the cell type, the function of the individual gene, and/or the targeting strategy. In this context, it will be interesting to analyze if different knockdown levels of CENPE and Nsl1 also correlate with differing results.

Fact remains that, while patients scored in the highest quartile of CIN signatures have improved disease outcome, intermediate levels are associated with increased tumor malignancy and poor patient prognosis.[2] The degree of mitotic aberrations therefore certainly plays a role in cancer development and therapeutic response. Nonetheless, this correlation rather highlights CIN as a mediator of the selective advantage rather than a pure driver of tumorigenesis. This is also underlined by the fact that additional permissive changes in the signaling context like the inhibition of programmed cell death is needed to allow transformation of aneuploid cells. The involvement of SAC-independent functions of the targeted proteins in the cancer-initiating events in current CIN models can therefore also not be excluded. To clarify this controversy, further studies on the role and the interactions of SAC proteins during interphase and outside of mitosis are needed.

References

1. Schvartzman JM, et al. Nat Rev Cancer 2010; 10:102-15; PMID:20094045; http://dx.doi.org/10.1038/nrc2781
2. Zasadil LM, et al. Semin Cell Dev Biol 2013; 24:370-9; PMID:23416057; http://dx.doi.org/10.1016/j.semcdb.2013.02.001
3. Clemente-Ruiz M, et al. Cell Cycle 2014; 13; PMID:24626182
4. Morais da Silva S, et al. J Cell Biol 2013; 201:385-93; PMID:23609535; http://dx.doi.org/10.1083/jcb.201210018
5. Dekanty A, et al. Proc Natl Acad Sci U S A 2012; 109:20549-54; PMID:23184991; http://dx.doi.org/10.1073/pnas.1206675109