Comment Re: HMGA2 Is a Negative Regulator of DNA-PK Pathway

To the Editor: Recently, Li and colleagues (1) have presented evidence for the impairment of nonhomologous and joining repair (NHEJ) of DNA damage by the chromatin binding protein HMGA2. In this interesting article, the cytogenetic stability of fibroblasts transfected by a construct encoding HMGA2 was analyzed as a hallmark of deficient NHEJ. Twenty-five metaphases of these fibroblasts were karyotyped and compared with the 25 metaphases transfected with the vector alone. Whereas the wt-38/vector cells displayed no cytogenetic abnormalities, except for "three cells showing minimal instability of a single break in the centromeric region," five cells transfected with the HMGA2 vector showed a near-tetraploid karyotype. Furthermore, the latter cells are reported to display a variety of structural chromosome abnormalities. In the transduced cells, the presence of HMGA2 was shown by Western blot analysis, whereas it was not detectable in the vector-alone cells. The number of metaphases analyzed for the cytogenetic evaluation is low, if not too low. Furthermore, for cytogenetic evaluation, quite different types of chromosomal aberrations are mixed. In particular, tetraploidy is not rare in fibroblast cultures. We are wondering if tetraploidy can be considered a hallmark of NHEJ. Generally, the possible interaction between the capacity of a cell to repair DNA damage and its HMGA2 level remains a question of high interest, but it seems difficult how to explain genotoxic effects caused by a protein that is abundant during embryonic life (2, 3). In particular, during that phase, strong proliferative activity necessarily has to coincide with proper maintenance of genetic integrity.

Hence, it is tempting to speculate if HMGA2 interferes with DNA repair at unphysiologically high concentrations only. Fibroblasts kept in culture with fetal bovine serum express high levels of HMGA2 that are well comparable to those seen in embryonic tissues and fibroblasts that have been used by Li and colleagues as controls. These controls expressed much lower HMGA2 levels than the transfected fibroblasts. Therefore, it seems plausible to assume that the cytogenetically unstable cells displaying sporadic translocations or dicentrics are those with strong overexpression of the recombinant HMGA2 in a range usually not found during embryonic development.

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References


Published OnlineFirst 2/9/10. ©2010 AACR.
doi: 10.1158/0008-5472.CAN-09-3081
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Cancer Res 2010;70:1742. Published OnlineFirst February 9, 2010.

Updated version
Access the most recent version of this article at:
doi:10.1158/0008-5472.CAN-09-3081

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