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Regulation of DNA damage responses by mismatch repair

Anatoly Zhitkovich

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DNA mismatch repair (MMR) is a major genome maintenance system that is responsible for correction of replication errors. Many human cancers exhibit very high rates of spontaneous mutagenesis and a microsatellite instability (MIN+) phenotype, which are characteristics of inactive MMR. This raises important questions regarding the nature of selection processes leading to the loss of functional MMR during malignant transformation and what it means for the use of specific chemotherapeutic agents. One of the unusual cases of a very high MIN+ incidence (>80%) is lung tumors caused by occupational exposure to carcinogenic hexavalent chromium (Cr-6). Evidence from different cellular models will be presented to demonstrate a critical role of MMR in processing of relatively innocuous DNA phosphate-Cr adducts into highly toxic DNA double-stranded breaks and subsequent activation of stress signaling and apoptosis. MMR-mediated DNA breakage requires a passage of Cr-damaged DNA through S-phase and an unprecedented sequential assembly and activation of both MSH6 and MSH3 branches at S/G2 border. MSH6, a single base mismatch detecting protein, is a sensor of Cr-DNA damage, which subsequently recruits downstream MLH1-PMS2 dimer followed by activation of the MSH3 branch. Inactivation of any of several MMR proteins prevents chromosomal breakage and cytotoxicity by Cr-6. Based on these results, we propose that a chronic exposure to Cr-6 selects for resistant cells with deficient MMR, leading to the outgrowth of populations with a mutator phenotype conferring high transformation potential. Thus, one origin of MIN+ cancers could involve selective pressure imposed by prolonged exposures to specific carcinogens to inactivate MMR. We will also present biochemical and genetic evidence that shed light on the mechanistic basis of differences in sensitivity of MIN+ cancer cells to alkylating chemotherapeutic agents.

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Correspondence: anatoly_zhitkovich@brown.edu
Department of Pathology and Laboratory Medicine, Brown University, Providence, RI, USA

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