

MISMATCH REPAIR, MICROSATELLITE INSTABILITY AND CANCER

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In 1993, the autosomal dominant syndrome hereditary non-polyposis colon cancer (HNPCC) was linked to germline defects in genes encoding postreplicative mismatch repair (MMR) proteins. Since that time, MMR defects, which are most easily detectable as microsatellite instability (MSI), have been identified in many other types of tumours, including skin cancers. Interestingly, although seven human MMR genes, *hMSH2*, *hMSH3*, *hMSH6*, *hMLH1*, *hMLH3*, *hPMS1* and *hPMS2*, have been identified to date, the vast majority of HNPCC families carries mutations in only two: *hMSH2* and *hMLH1*. In sporadic tumours, the MMR defect is generally unconnected to sporadic mutations in *MMR* genes; the MSI phenotype is most often linked to a transcriptional silencing of the *hMLH1* gene by cytosine methylation. We are now trying to understand why mutations in the *hMSH2* and *hMLH1* genes give rise to cancer, while defects in *hPMS2*, which bring about similar biochemical defects in MMR, are detected in only a small minority of tumours with MSI. Most recently, we have developed a cell line, in which the MMR defect is inducible. Using this strictly isogenic cell pair, we have been able to show that the MMR system is not only involved in mismatch repair and in the control of genetic recombination, but also in DNA damage signalling. Thus, MMR-deficient cells are up to 100-fold more resistant to treatment with the methylating agents MNNG or Temozolomide than their MMR-proficient counterparts. Our data show that these methylating agents activate a cell cycle arrest in the G2/M phase, which leads in most cell types to apoptosis. The arrest is triggered by the ATM/ATR and Chk1/Chk2 kinases, which phosphorylate a large number of downstream targets, among them the tumour suppressor protein p53 and the phosphatase cdc25. Interestingly, downregulation of expression of the *MMR* genes *hMSH2* and *hMLH1* that does not affect MMR efficiency can attenuate the signalling response. This implies that cells expressing suboptimal levels of MMR proteins will not have a MSI phenotype, but that they might not undergo apoptosis upon DNA damage. This might lead to further mutations and transformation and, finally, to cancer.