Inherited defects in the DNA glycosylase MYH cause multiple colorectal adenoma and carcinoma

Sankar Mitra

University of Texas Medical Branch, Sealy Center for Molecular Science, Department of HBC&G, 6.136 Medical Research Building, Route 1079, Galveston, TX 77555, USA
Email: samitra@utmb.edu

Dr Cheadle has raised issue with a statement in our commentary that the lack of base excision repair enzymes has not so far been linked to cancer. While we should have cited the articles of Cheadle and his colleagues showing a linkage between MYH missense mutations and colorectal cancer in some families, our statement was based on the phenotype of null mouse mutants deficient in damaged base-specific DNA glycosylases. Several laboratories have generated knockout mouse strains lacking individual DNA glycosylases, including oxidatively damaged base-specific DNA glycosylases OGG1 and NTH1. Both published and unpublished results clearly show that, unlike in the case of mismatch repair-deficient mice, glycosylase-deficient mice do not show significantly enhanced susceptibility to cancer. We, therefore, wrote what is generally accepted: that these DNA glycosylases with overlapping substrate ranges provide back-up or redundant functions, so that the absence of one will be covered by another for the repair of a critical mutagenic lesion.

The work of Dr Cheadle and his collaborators strongly suggests a critical role for MYH in preventing carcinogenesis in humans. Further studies are needed to reconcile the apparent discrepancy between the human and mouse studies.

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