
Letter

In a recent issue of Cancer Research, Lin et al. (1) reported on the differential effects of the Msh2$^{G674A}$ mutation on DNA mismatch repair (MMR) and apoptosis functions. Their results using mice that carry the G674A missense mutation in the conserved ATPase domain confirm that Msh2-mediated apoptosis is an important component of tumor suppression. The implication of the report is that only the Msh2$^{G674A}$ mutation could cause DNA MMR deficiency but would not affect the DNA damage response function of Msh2. However, it appears to be misleading because there are many mutations in the Msh2 gene that would have the same effects as the Msh2$^{G674A}$ mutation on DNA MMR and apoptosis functions.

The differential effects of the hMSH2$^{K675A}$ mutation on DNA MMR and apoptosis functions were reported in the published study by Zhang et al. (2). An hMSH2 point mutation (hMSH2$^{K675A}$) that is deficient for MMR still induces apoptosis when overexpressed (2), indicating that the hMSH2$^{K675A}$ mutation uncouples DNA MMR and apoptosis. It is predictable that the Msh2$^{G674A}$ mutation and other missense mutations in the same motif within the conserved ATPase domain of the Msh2 protein would have the same effects on MMR and apoptosis as the hMSH2$^{K675A}$ mutation. The study by Lin et al. (1) confirmed the previous result of the hMSH2$^{K675A}$ mutation (2). Unfortunately, Lin et al. did not mention the published study about the hMSH2$^{K675A}$ mutation in their report.

The authors decided to generate a mouse line carrying the Msh2 missense mutation to assess its impact on MMR and apoptosis. Based on the published study (2), the region of the Msh2 protein responsible for inducing the apoptotic response (death domain) appears to be localized between amino acid residues 114 and 601. Since the Msh2$^{G674A}$ mutation is located outside of that region, it is unlikely to assess the impact of the Msh2$^{G674A}$ mutation on its response to DNA damage-induced apoptosis. If the authors had generated a mouse line carrying Msh2 mutation in between amino acid residues 114 and 601, they would have had a better chance to assess its impact on DNA damage-induced apoptosis. It will be very important to find mutations in the Msh2 protein that affect DNA damage-induced apoptosis but not MMR.

As mentioned in the published study (2), fine mapping of the domain responsible for the induction of cell death (apoptosis) in the hMSH2 protein should greatly facilitate our ability to identify protein partners participating in this response. Ultimately, this may lead to a better understanding of how hMSH2 protein controls apoptosis, which in turn will result in a better treatment of HNPCC patients.

Hong Zhang
Z-BIOMED Inc.
Rockville, MD 20855
References

