Letter to the Editor

Clinical Cancer Research

$BRAF^{V600E}$ Inhibitor Radiosensitizes Thyroid Cancer—Letter

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We read with great interest the article by Robb and colleagues (1), wherein they explored the mechanisms of radiosensitizing BRAF V600E–mutated thyroid cancers using the tyrosine kinase inhibitor vemurafenib. The authors describe a mechanism for the increased radioresistance of V600E-mutated thyroid cancers and support this with a significant amount of data. However, we feel that there may yet be some questions left unanswered.

After preincubation with vemurafenib and subsequent irradiation, the authors demonstrate a deficiency in DNA damage repair by means of increased γH2AX protein, residual 53BP1 foci, and comet assays in the V600E cancer cells. However, vemurafenib affects the cell cycle and causes a G_1 arrest specifically in V600E thyroid cancer cells (2). Thus, V600E-mutant cells may respond differently to irradiation after vemurafenib compared with wild-type cells, as the cell cycle determines the DNA damage repair pathway [homologous repair (HR) or non-homologous end joining repair (NHEJ)]. However, the authors then chose a different experimental setup for testing this effect of vemurafenib on HR and NHEJ, where cells were not preincubated with vemurafenib, but vemurafenib was added at the time of irradiation. This might attenuate any effect vemurafenib would have on the cell cycle prior to irradiation and, subsequently, the choice for a repair pathway.

Furthermore, the authors state that the mechanism for the deficiency in DNA damage repair is dependent on XLF. Without a doubt, XLF/NHEJ1 is a vital factor in the NHEJ pathway, as demonstrated using siRNA experiments. The authors attribute the increased repair efficiency of V600E to increased XLF expression. However, the authors did not describe why they selected XLF for analysis, as there was only a 1.17-fold difference in mRNA expression between wild-type and V600E cells, and this was comparable with other factors in the NHEJ pathway (Ku70, Ku80, and DNA-PK; Supplementary Table S2). Moreover, the fact that knocking down most XLF indeed affects DNA damage repair, does not support the hypothesis that the slight increase in XLF in V600E mutants would be responsible for the improved repair efficiency.

Thus, we commend the authors for their work, yet feel that exploration of the issues mentioned could shed light into vital mechanisms that affect the basic radiosensitivity of (thyroid) cancer cells.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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