

ANSWERING REVIEWERS

Reviewer's code: 03475830

COMMENTS TO AUTHORS

The authors have postulated a hypothesis, that BRAF inhibitor induced colonic polyps may arise due to activation of the serrated pathway. The writing is excellent and the paper is worthy of publication as a hypothesis generating work. I have two comments: 1. While the idea is interesting, the evidence supporting this presently limited. The paper would benefit from suggestions for future scientific investigation to confirm this hypothesis, rather than skipping this step to suggest molecular treatment. 2. The paper is very "gene heavy" and probably would be difficult for the general readership of the journal to read and understand. Nevertheless I think this paper should be published if the editor feels it is suitable.

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1. Future scientific investigation to confirm the hypothesis

A comprehensive compilation of a series of patients on BRAF inhibitor treatment of melanoma in whom colonic polyps arise is mandated. This will permit histological characterization as to whether these polyps are serrated or adenomatous. Bi-sulfite sequencing analysis of genes that are proposed to be epigenetically silenced by CpG island promoter methylation should inform on the relative merits of the epigenetic component of the iatrogenic disease model. DNA and RNA of the selected genes of interest is suggested. Lastly RNAi screening to assess the level of MAFG in these polyps, itself a silencer of p16^{INK4A} should provide evidence supporting the senescent tenet of the hypothesis