Reviewer’s report

Title: High-Resolution Analysis of HLA Class I Alterations in Colorectal Cancer

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Reviewer: Matthias Kloor

Reviewer’s report:

General

In the present manuscript, the authors describe alterations of HLA class I antigen expression in colorectal cancer. Among 21 specimens, alterations of the HLA class I phenotype were detected in 8 cases (38%). Loss of single HLA-A or B alleles were detected in 4 cases, whereas 4 tumors displayed total loss of HLA-A and B expression. HLA class I alterations were significantly more frequent in tumors exhibiting the MSI-H phenotype. The authors report interesting details about type and frequency of HLA class I alterations in colorectal cancer. The results are relevant, particularly in view of future immune therapeutic approaches and therefore should be published.

Major Compulsory Revisions

none

Minor Essential Revisions

1. A central statement of the paper is that the frequency of HLA class I alterations determined by using FCM in the present study is lower than reported in some previous studies. However, I feel this may be somewhat overstated. There are several potential reasons for this (low number of samples, sample taking issues a.o.) which are independent from the method applied for HLA class I antigen detection. These issues should also be discussed, e.g. the fact that the comparably high number of stage A/B patients (no stage D patients were recruited) may contribute to a lower number of HLA class I alterations.

2. Among 21 colorectal cancers, 11 are localized in the proximal colon. Is this the result of a preselection process? This should be discussed.

3. Paragraph 3 of Results is unclear and should be rewritten. The authors want to emphasize that the four MLH1-negative tumors are most likely sporadic. Instead of referring to "sporadic MSI-H cases" first, and then supporting the assumption, the section should begin with the statement that (1) the respective tumors show MLH1 loss, (2) have no clinical criteria indicative of HNPCC, and are thus most likely sporadic.

4. The conclusive paragraph (Conclusion, paragraph 2) appears to be inappropriate. Vaccination against colorectal cancer is not the scope of the study. Therefore, it is suggested to incorporate the last paragraph in the Discussion section. Moreover, the last sentence should be omitted, because there is still a considerable number of deaths related to sporadic MSI-H colorectal cancer each year which clearly indicate that there is a need for novel therapeutic approaches.

5. Reference 8 appears to be wrong. The cited results are from Cabrera et al. 1998, not 1996 (breast cancer).

6. In the text (Material and Methods, Flow Cytometry) it is stated that in 6 cases the HLA phenotype was not known prior to resection. In the corresponding table (Table 2) only 5 cases are marked by asterisks.

Discretionary Revisions

In general, I think that the most interesting finding of the paper is the detailed characterization of allele- and locus-specific losses in colorectal cancer and their association with the MSI-H phenotype. Therefore, I would suggest to strengthen this point rather than to focus on the difference between the observed
frequency of alterations in the present study and previous ones (Cabrera et al. 1998). Moreover, the first paragraph of the discussion appears to be self-contradictory, emphasizing the higher sensitivity of FCM compared with IHC and the enhanced detection of variations (in addition, the increasing use of FCM is not an argument in that context at all). To my opinion, this would rather argue in favor of a higher frequency of HLA class I alterations observed by this method.

**What next?:** Accept after minor essential revisions

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No

**Declaration of competing interests:**

I declare that I have no competing interests.