Reviewer's report

Title: Numbers of Mutations To Different Types of Colorectal Cancer

Version: 1 Date: 11 March 2005

Reviewer: Simo Schwartz Jr

Reviewer's report:

General

This manuscript determines by using a previously published bayesian algorithm the estimate number
of mutations required for a cell from the colon crypt to achieve malignant transformation and tumor
clonal expansion. The authors calculate that 6 mutations are enough for MSS tumors, and also that
the number of expected required mutations varies according to the MSI and germline nature of the
colon cancer. Hence, 5-6 mutations seem to be required for germline cases whereas 7-8 are
needed for its sporadic version, which suggest that at least one additional alteration besides the
inactivation of MLH1 by hypermethylation is needed. Further, they show that no differences are
found in the estimates when considering the cancer stages suggesting that mutations accumulate
before transformation and clonal expansion. They also argue about the tumor expansion and
multistage (adenoma-carcinoma sequence) models for tumorigenesis.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can
be reached)

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the
author can be trusted to correct)

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Discretionary Revisions (which the author can choose to ignore)

At the end of the methods section. Authors wrote “…numbers of oncogenic mutations (genetic or
epigenetic)…” I wouldn’t refer to the epigenetic alterations as mutations because is a bit misleading.
I will suggest to us the word “alterations” instead. “…numbers of oncogenic alterations (genetic
mutations or epigenetic alterations)…”

At the last paragraph of the Results section. The authors wrote “…engineered mice and rare
humans…” I would not use the word “rare” when referring to humans to avoid misinterpretation, but
a more specific one for the real meaning.

Along the discussion, authors argue about the two main models that can explain how mutations
accumulate before clonal expansion. The multistage model (from birth to transformation) and the
tumor progression (adenoma-carcinoma sequence) models. Both seem to perfectly well explain the
results found, but the authors seem to favor that mutations accumulate very early in life and thus, the
multistage model. It is not clear to me the reason why this model is favored and will ask the authors
to better clarify the reasons of their priorization.

Furthermore, although authors conclude that the most likely number of mutations required for cancer
in MSS cases is independent of the cancer stage at the time of diagnostic, numbers on table 1 show
small differences of 1-2 mutations between stages C and D (with estimates of 6 mutations each) and
cases A or B (with estimates of 7 and 8 respectively). I would like the authors to discuss further these
results because they seem to suggest that more advanced cancer cases have lower numbers of
required mutations than the less advanced ones.

**What next?:** Accept after discretionary revisions

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No

**Declaration of competing interests:**

I declare that I have no competing interests