

Review of: "The Stay-Or-Leave Dilemma of Cells in Punctuated Tumors"

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Potential competing interests: No potential competing interests to declare.

I think that the "stay-or-leave" model to understand tumor behavior, along with the use of game theory-based methods, is an interesting approach to studying tumor growth and progression. I have some comments/suggestions in order to help improve this short article.

1. In the abstract, it appears to note that hypoxic regions are restricted to the tumor bulk (".... adverse microenvironment, which is situated in the tumor interior, cells...."), but it is not totally true as it has been documented that the tumor microenvironment surrounding the tumor bulk could also exhibit hypoxia. Therefore, I would suggest avoiding the expression ".... which is situated in the tumor interior...." or changing it to "which is predominant but not limited to the tumor bulk."

2. The phrase ".... molecular level, which will enable them to escape the tumor, while others will not and will thus perish....." may be somewhat ambiguous and imprecise as cancerous cells cannot leave a tumor because they constitute the tumor by their own. Moreover, not all malignant cells that persist in the primary tumor mass will die. I would modify the phrase to ".... molecular level, which will enable them to escape the primary tumor mass, while some others will not and will perish under such selective conditions of hypoxia and nutrient deprivation....".

3. I think there is a little error in the following phrase ".... the fixation of a high-fitness clone in the early phases of tumor development^[2]. The accelerated growth of such clones soon makes them the major....". First, it seems to refer to a single tumor clone, but immediately after, it seems to refer to tumor clones in plural.

4. I am not sure about the meaning of the expression "chromosomal complexity" in the phrase ".... has shown that metastatic competence is achieved basically by chromosome complexity, and that 9p....". I think it rather means "chromosomal aberrations." Another example could be the sentence "...Along with high levels of chromosome complexity, punctuated tumors typically display....".

5. I am a bit confused by the appearance of opposite ideas. At the beginning of the article, the acquisition of greater fitness is associated with intratumor heterogeneity ("...i.e., will acquire greater fitness. This contributes to the development of new clones and/or subclones which will shape intratumor heterogeneity (ITH)...."). Then, punctuated tumors are related to a high fitness (".... The punctuated model of evolution is characterized by the fixation of a high-fitness clone in the...."). Nevertheless, then it is noted that punctuated tumors are characterized by a low (not high) intratumor heterogeneity (".... levels of chromosome complexity, punctuated tumors typically display low levels of ITH....."). I think authors should clarify

this.

6. I think it may not be correct to expose such direct statements like “... Here, the acquisition of metastatic capacities is a survival response....”. Considering that authors intend to emphasize a tumor “model” or “point of view”, I suggest the use of the conditional form “...Here, the acquisition of metastatic capacities could be considered as a survival response....”.

7. I am a bit confused by the sentence “... using the maximum tolerable dose in these patients needs to be rethought, as it is doomed to fail....”. I suppose that the idea exposed by the word “rethought” is something like “dosage readjustment” or “therapeutic strategy reformulation”. Furthermore, I would expose the same idea in an alternative way like “angiogenic-based therapies need to be reformulated as currently they are not effective in cancer management” rather than “they are doomed to fail”.

8. In the phrase “... modifies cell behavior, e.g. in glioblastoma tumor cells^[9] and other neoplasms....”, I would like to suggest authors avoid imprecise expressions like “other neoplasms”. Instead, I would add, if possible, other examples such as pancreatic cancer, hepatocellular carcinoma, lung cancer, colon cancer, melanoma, breast cancer, prostate cancer...etc. (I think that a total of 3 examples may be sufficient to represent the relevant nature of stroma-tumor cell collaboration in the context of the “stay-or-leave” idea.)

9. As a minor suggestion, the authors intend to establish a comparison between individuals/malignant cells and between ecosystems/tumors. In order to be a little more precise in the text, I would modify the phrase “.... inevitability, individuals (cells) in their respective ecosystems (tumors) attempt to develop different strategies to increase survival possibilities, e.g. by escaping....” toward something like “.... inevitability, individuals (malignant cells) in their respective ecosystems (tumor tissues) attempt to develop different strategies to increase their survival potential, e.g. by escaping....”.

10. As a minor suggestion, I would add a “title” in the Figure 1 description. Something like “Figure 1. Stay-or-leave dichotomy in tumor growth. The top panels show a ChatGPT idealization of the”.