Open Peer Review on Qeios

The Stay-Or-Leave Dilemma of Cells in Punctuated Tumors

Claudia Manini[1], Michele Infantino[2], Iker López-García[3], Jose Ignacio Lopez[4]

1 "San Giovanni Bosco" Hospital
2 ESCP Europe Business School
3 Universidad Internacional De La Rioja
4 Biobizkaia Health Research Institute

Funding: No specific funding was received for this work.

Potential competing interests: No potential competing interests to declare.

Abstract

Punctuated-type carcinomas are aggressive tumors in which large regions exist under hypoxia and nutrient scarcity. To survive in this adverse microenvironment, which is situated in the tumor interior, cells evolve under a stay-or-leave dichotomy where the acquisition of metastatic competences is understood as an attempt by cells to survive.

Claudia Manini[1], **Michele Infantino**[2], **Iker López-García**[3], and **José I. López**[4*]

[1] *Department of Pathology, San Giovanni Bosco Hospital, 10154 Turin, Italy.*

[2] *ESCP Europe Business School, 10134 Turin, Italy*

[3] *UNIR, International University of La Rioja, 26006 Logroño, Spain*

[4] *Biomarkers in Cancer, Biobizkaia Health Research Institute, 48903 Barakaldo, Spain.*

[*]Corresponding author (jilpath@gmail.com)

All biological systems, cancer included, evolve from birth to death on a temporal scale. Nothing in biology breaks this paradigm. Trying to overcome this inevitability, individuals (cells) in their respective ecosystems (tumors) attempt to develop different strategies to increase survival possibilities, e.g. by escaping the primary tumor under unfavorable contexts to reach better landscapes farther away. This behavior is a key issue in oncology because despite the enormous advances made in the last years, metastases are frequent in malignant tumors and are still responsible for most deaths in cancer patients.

Fitness is an ecological term which measures the ability of an individual to transmit their genetic background to their progeny. In oncology, fitness is a measure of tumor aggressiveness, i.e. the ability to invade and metastasize[1]. The level of fitness of a cell is directly related to the intrinsic amount of energy available to it for acquiring external resources such as oxygen and nutrients, and depends on complex, dynamic cell-to-cell interactions (cooperation and/or competition). This process is complex and not fully understood; it is also subject to dynamic adaptations to everchanging microenvironments. During these cellular interplays some cells will invariably secure more resources than others, i.e. will acquire greater

fitness. This contributes to the development of new clones and/or subclones which will shape intratumor heterogeneity (ITH). Under such external pressures, a subset of cells will succeed in developing metastatic capabilities, detectable at molecular level, which will enable them to escape the tumor, while others will not and will thus perish. This collective cell death translates visibly into tumor necrosis, a classic histological sign of tumor aggressiveness.

The punctuated model of evolution is characterized by 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 constituent of the tumor burden. *BAP1*-mutated clear-cell renal-cell carcinomas (CCRCC) are paradigmatic examples of these punctuated-type neoplasms. As noted by Turajlic et al.[3], this subset of CCRCC pursues a highly aggressive clinical course, with multiple early metastases and a dismal prognosis in all cases. A primary/metastases matched multi-region study of 100 CCRCC has shown that metastatic competence is achieved basically by chromosome complexity, and that 9p and 14q losses are the characteristic drivers of metastases[4]. Along with high levels of chromosome complexity, punctuated tumors typically display low levels of ITH.

Although *VHL*- and *BAP1*-mutated cells do coexist in most of these cases, a recent study has revealed an ecologically-based geographical distribution of metastatic-competent clones[5]. As a result, metastatic-competent cells concentrate in the tumor interior, where hypoxia and nutrient shortages are at their greatest and the struggle for survival is fierce[5]. Here, the acquisition of metastatic capacities is a survival response.

Antiangiogenic drugs exert a similar effect, generating adverse (hypoxic) environments. However, collateral effects of this action induce drug resistances and promote the development of metastatic abilities. The therapeutic strategy of using the maximum tolerable dose in these patients needs to be rethought, as it is doomed to fail. Sooner or later tumor cells will select resistant-to-therapy clones to survive, thus transforming any previous neoplasm into a highly aggressive (punctuated-type) tumor[6].

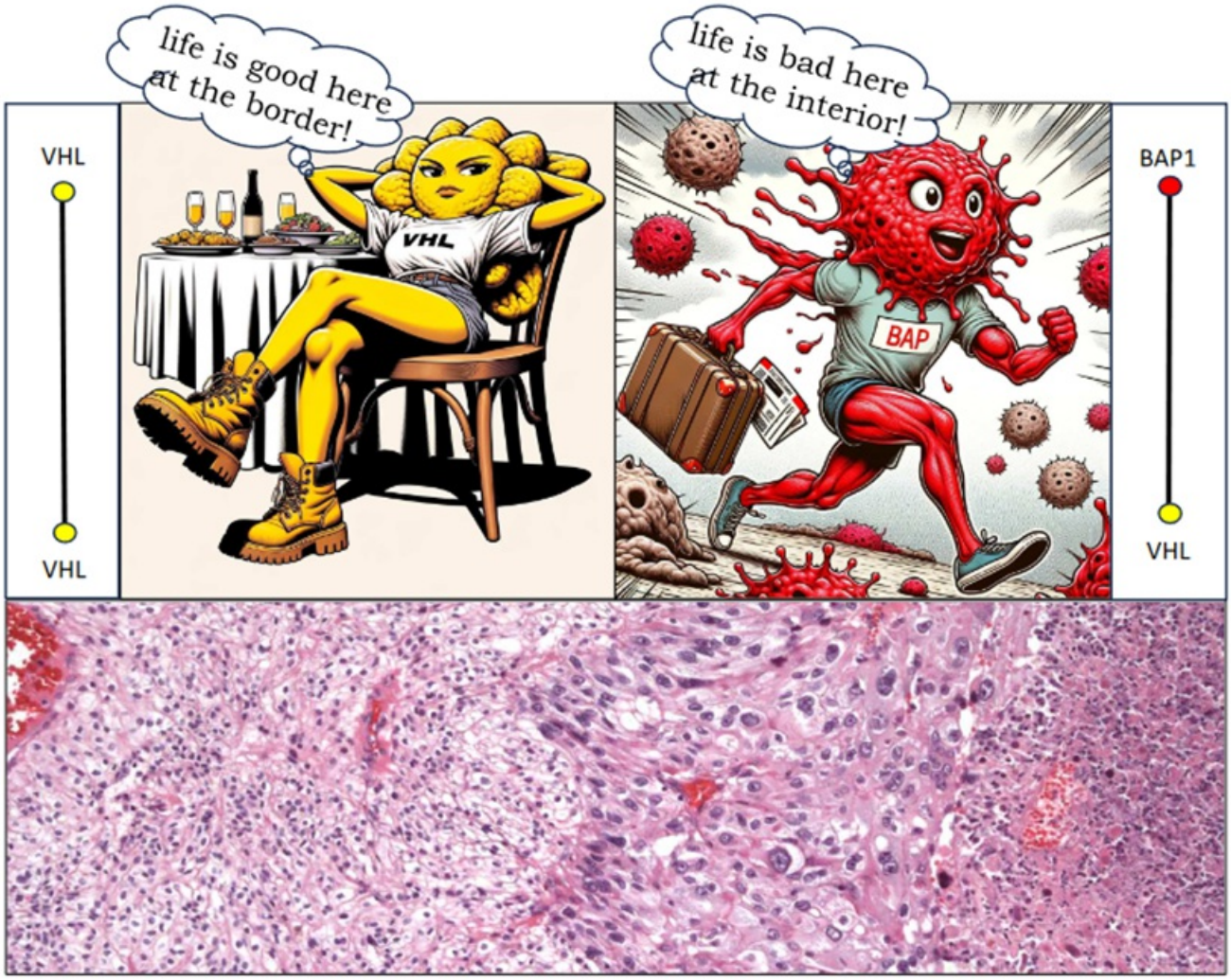

Figure 1. The top panels show a ChatGPT idealization of the behavior of two cells with *VHL* and *BAP1* gene mutations at the tumor border and in its interior with their respective linear and punctuated schematic evolutive patterns. The bottom panel shows the sharp interface of two clones within a clear-cell renal-cell carcinoma showing low (left, *VHL*-related, tumor periphery) and high (right, *BAP1*-related, tumor interior) histological grades.

This zonal arrangement favors the analysis of the *stay-or-leave* duality of tumor cells as per game theory models[7], where cells exposed to adverse microenvironmental pressures opt to leave the primary tumor whereas cells living in friendly contexts decide to stay and grow. From an ecological perspective, staying and growing is the default status of cells in a tumor. The acquisition of metastatic competencies is just an attempt to survive by escaping unfavorable situations. This dual behavior is idealized in Figure 1, in which a CCRCC shows a sharp frontier between two cell populations with evident morphological differences. This is an example of ITH at histological level which correlates with genomic signatures and anticipates the metastatic potential of a specific part of a tumor. Interestingly, this sharp frontier between low- and high-grade groups of cells identifies not only the geographical limit between the tumor border (<1cm to the tumor capsule) and the tumor interior (>1cm), as previously proposed[5], but also the edge that separates two different evolutionary patterns, i.e., linear and punctuated. Environmental conditions are favorable at the tumor border, where a competent blood supply assures optimal levels of oxygen and nutrients. In this favorable context tumor cells stay and grow and the tumor expands

and invades locally. Conversely, neo-angiogenesis in the tumor interior is progressively incompetent and the increasing levels of hypoxia lead to collective tumor cell death, which is identified as necrosis under the microscope. In fact, tumor necrosis is seen by pathologists as a reliable feature of tumor aggressiveness. In this unfavorable background, from an ecological perspective, tumor cells try to escape by developing metastatic competencies.

Tumor cells may adopt different behaviors depending on their environmental conditions[8], which opens up new possibilities for analyzing tumors under this dual *stay-or-leave* attitude. This is an extremely promising field and may become the next frontier in oncology if other approaches such as mathematics are incorporated to further our understanding of cell-to-cell social interactions. There are examples of how intercellular cooperation (including tumor-to-non tumor and tumor-to-tumor exchanges) modifies cell behavior, e.g. in glioblastoma tumor cells[9] and other neoplasms. Indeed, a recent analysis has examined the possible interactions between *VHL*-deleted and *VHL*-non-deleted CCRCC cells[10]. The authors find that the metastatic capability of both cell lines while growing independently is minimal; however, when they are combined their metastatic capability is rampant.

In summary, this short paper highlights the advisability of a translational approach to improve our knowledge of tumor biology. Bringing together different perspectives, including the histological, genomic, ecological, and mathematical, can help to clarify many of the still-hidden intricacies that govern tumor evolution and its behavior.

References

1. ^*Reynolds, B.A. et al. Ecol. Evol. 10, 8538-8553 (2020).*
2. ^*Davis, A. et al. Biochim. Biophys. Acta Rev. Cancer 1867, 151-161 (2017).*
3. ^*Turajlic, S. et al. Cell 173, 595-610 (2018).*
4. ^*Turajlic, S. et al. Cell 173, 581-594 (2018).*
5. a, b, c *Zhao, Y. et al. Nat. Ecol. Evol. 5, 1033-1045 (2021).*
6. ^*Viossat, Y. et al. Nat. Ecol. Evol. 5, 826-835 (2021).*
7. ^*Dwivedi, S. et al. Sci. Rep. 13, 16758 (2023).*
8. ^*Maruyama, T. et al. Curr. Opin. Cell Biol. 48, 106-112 (2017).*
9. ^*Oliveira, A.I., et al. Cell Commun. Signal. 15, 37 (2017).*
10. ^*Hu, J. et al. Signal Transduct. Target. Ther. 8, 155 (2023).*