This is the theory – Response to Tez on the origins of paediatric cancers (https://doi.org/10.1002/bies.202000324)

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Sir,

We read the recent correspondence by Mesut Tez[1] arguing that our proposal that tissue-disruption-induced cellular stochasticity (TiDiS) is at the origin of both aging and cancer[2] should be considered as a hypothesis and not as a theory. We argued that disruption of the tissue equilibrium, and the subsequent increase in cellular stochasticity, might be the initiator event in both processes. We agree that the TiDiS concept is a bold attempt to reconsider the respective role of the tissue equilibrium, epigenetic drift and genetic alterations, and as such can be considered as a hypothesis because it opens radically new research perspectives that have not been formally experimentally tested yet. However, we think that the TiDiS concept is already more than a hypothesis at this stage and offers a new coherent framework that allows the reinterpretation and integration of many experimental findings in both fields. Moreover, we formulated our proposal in line with works arguing that the reduction of gene expression variability and the acquisition of epigenetic and phenotypic stability through direct or long-range cellular interactions during cell differentiation can serve as a solid ground for building a new theoretical framework in both developmental and cancer biology. In particular, we previously offered new perspectives on oncogenesis,[3] taking multiple myeloma as a paradigmatic example,[4] cancer stem cells[5] and stem cell biology,[6] all of which are based on the same foundation—that is, the central role of stochastic gene expression. This collection of works, well supported by experimental facts and written in the same perspective, can hopefully accord the TiDiS concept the status of a theory. As such, it allows us to interpret and rethink observations that were previously interpreted differently in other theoretical frameworks, representing, in addition, the basis for formulating new hypotheses on the behaviour of biological systems.

Dr. Tez also questioned the relevance of the TiDiS concept in explaining paediatric cancers. This is an interesting comment, because indeed intuition would a priori suggest that the scenario we proposed should mostly concern cancers that occur in the second part of the life. First, we would like to recall that although dramatic and increasingly frequent, cancers in children remain relatively rare compared with cancers in adults. Then, our response to Dr. Tez' comment will be two-fold. It is generally admitted that the aetiology of paediatric cancers, even if far from being totally elucidated, is different from that of adult cancers. We cannot exclude the possibility that the TiDiS concept could be another illustration of the differential processes involved in the initiation of cancers in adults and children. That being said, it is still interesting to examine deeper the extent to which the TiDiS concept could, at least partly, be relevant in explaining paediatric cancers as well. Notably, tissue disruption could also be involved in the early steps of these cancers, not linked to the aging, but because the tissue equilibrium is more precarious in childhood (growing and remodelling tissues and organs). They would therefore be more sensitive to disruption and more at risk, especially if genetic abnormalities pre-exist. Tissue disruption in children would necessarily have a different origin than inflammaging, for example, and exogenous (environmental) factors could be more explicitly involved. As rightly noted by Dr. Tez, paediatric cancers almost always concern blood, brain and bones. An interesting route of enquiry would thus be to explore whether the microenvironmental conditions present in these specific compartments of the body are particularly compatible with the TiDiS concept, irrespectively of the individual's age. We have no definitive answer to this point, even if, interestingly, it has been proposed that these three compartments are among those that have undergone most change in the recent human evolutionary history, and as such would miss canalisation—that is, one might expect them to yield to more frequent cell derailments for insufficient natural defences against cancerous development (i.e., a mismatch between cancer risks and cancer defence).[7] If the density of the cell–cell interaction network is a major contributor among the cancer-suppressive mechanisms, as we previously suggested,[8] a lower connectivity in these compartments, especially during organ growth, would hypothetically explain their higher vulnerability to malignant development in childhood.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

1. Tez, M. (2021). What is the theory? *Bioessays*, *43*, 2000324.
2. Capp, J. P., & Thomas, F. (2021). Tissue-disruption-induced cellular stochasticity and epigenetic drift: Common origins of aging and cancer? *Bioessays*, *43*, 2000140.
3. Capp, J. P. (2017). Tissue disruption increases stochastic gene expression thus producing tumors: Cancer initiation without driver mutation. *International Journal of Cancer*, *140*, 2408–2413.
4. Capp, J. P., & Bataille, R. (2020). Multiple myeloma as a bone disease? The tissue disruption-induced cell stochasticity (TiDiS) theory. *Cancers (Basel)*, *12*, 2158.
5. Capp, J. P. (2019). Cancer stem cells: From historical roots to a new perspective. *Journal of Oncology*, 5189232.
6. Capp, J. P., & Laforge, B. (2020). A Darwinian and physical look at stem cell biology helps understanding the role of stochasticity in development. *Frontiers in Cell and Developmental Biology*, *8*, 659.
7. Leroi, A. M., Koufopanou, V., & Burt, A. (2003). Cancer selection. *Nature Reviews Cancer*, *3*, 226–231.
8. Giraudeau, M., Sepp, T., Ujvari, B., Renaud, F., Tasiemski, A., Roche, B., Capp, J. P., & Thomas, F. (2019). Differences in mutational processes and intra-tumour heterogeneity between organs: The local selective filter hypothesis. *Evolution, Medicine, and Public Health*, *2019*, 139–146.