Cell cooperation

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Avoiding cancer through collective behaviour

In many ways, cancer is the story of what went wrong. However, to understand it, identifying the mechanisms that maintain normal physiology is just as crucial as identifying what disrupts them. In the era of genomic data, most cancer research has focused on detecting gene mutations associated with cancer. This focus has yielded a list of oncogenes that, when mutated, can lead to cancer. That 'can', however, carries semantic weight: these mutations often merely predispose cells to tumorigenesis, reminding us that the underlying mechanisms are far more complex.

A particularly striking example is the case of the *BRAF* oncogene and melanocytic nevi. *BRAF* is the most commonly mutated gene in melanoma, yet the same mutation is routinely found in benign nevi or moles, which rarely progress to melanoma. Traditionally, this paradox has been explained by assuming that nevus cells enter an oncogene-induced senescent state that halts growth. Ruiz-Vega et al. revisit this widely accepted assumption in a mouse model of $Braf^{V600E}$-driven nevus formation, showing that it is unsupported by transcriptomic evidence and even contradicted by in vivo growth dynamics. In single-cell transcriptomic data of mouse nevi, hallmark signatures of senescence were notably absent compared with other skin cell types, including melanocytes outside nevi. In addition, the observed nevus size distributions were inconsistent with a senescence-driven explanation and with any purely cell-autonomous arrest mechanism. Together, these findings led the authors to propose an alternative explanation for growth arrest in nevi: a mechanism based on cell–cell cooperation.

Using mathematical modelling, the authors interrogated the implications of a purely cell-autonomous growth-arrest model (as indicated by the oncogene-induced senescence hypothesis) and demonstrated that a cooperative, feedback-based model more robustly explains the observed nevus size distributions, as well as the expected neighbour nevus sizes, even if the precise molecular mechanism remains to be identified. This study also highlights the value of examining the mechanistic basis of growth arrest from a systems-level perspective. On the one hand, a systems perspective leverages the information embedded in biological heterogeneity: many mechanisms could, in theory, halt nevus growth, yet only some can generate the observed size distributions. Conversely, recognizing that tissue maintenance may depend on cooperative interactions between cells introduces new conceptual frameworks and therapeutic opportunities for melanoma.

This work serves as a reminder that understanding cancer not only requires cataloguing mutations but also appreciating how collective cell behaviours shape tumour phenotypes. It also illustrates how mathematical modelling can move beyond data fitting to test which mechanistic explanations are compatible with observed patterns, thereby determining the limits of specific hypotheses. This resonates with our own research, in which we use mathematical models to interrogate mechanistic assumptions and explore the dynamical behaviours that they permit. Both our work and this study highlight how variability itself can become a source of mechanistic insight in complex biological systems such as cancer.

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Competing interests

The authors declare no competing interests.

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