RESEARCH HIGHLIGHT OPEN

The cost of cure: cancer therapies sculpt somatic evolution and signaling landscapes in normal tissues

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In a recent landmark study published in Nature, Pich et al. revealed that cancer therapies not only eradicate tumors but also impose strong evolutionary pressures on normal tissues, selectively reshaping core signaling pathways such as p53 and Nrf2.[1] This Research Highlight discusses how therapy-driven somatic evolution reframes targeted cancer treatment from a signal transduction perspective.

As advances in oncology continue to extend patient survival, the population of long-term cancer survivors is rapidly expanding. This clinical success, however, has revealed an underappreciated biological cost: systemic anticancer therapies exert lasting effects on ostensibly normal tissues. Although the DNA-damaging properties of cytotoxic agents and their mutational footprints are well documented,[1,2] how cancer treatments reshape the genomic and signaling architectures of histologically normal organs has been largely underexplored.

Pich et al. applied high-depth duplex sequencing to generate a high-resolution atlas of somatic evolution across 16 organ types from metastatic cancer patients.[1] This analysis reveals that cancer therapies function not merely as indiscriminate mutagens, but as potent evolutionary forces that selectively remodel signaling pathways, fundamentally altering the cellular composition of normal tissues.

By overcoming the sensitivity limits of conventional sequencing, duplex sequencing (>30,000× coverage) enabled reliable detection of ultra-rare somatic mutations in 168 cancer-free tissue samples from 22 individuals.[1] Using this approach, the authors quantified therapy-associated mutational burdens with unprecedented precision. Platinum-based chemotherapy acts as a systemic mutagen, yet its impact varies strikingly across tissues. Hematopoietic cells accumulated approximately 89 mutations per cell per treatment cycle—consistent with emerging evidence of therapy-driven clonal hematopoiesis[3]—whereas protected tissues such as the brain accumulated fewer than 27 mutations per cell per cycle.[1] This pronounced tissue specificity underscores how intrinsic factors, including proliferative activity, DNA repair capacity, and drug bioavailability, shape the mutational consequences of systemic therapy within a single host. Furthermore, while these cell-intrinsic factors are pivotal, remodeling of the normal tissue microenvironment provides an equally critical extrinsic selective pressure. Beyond direct DNA damage, systemic therapies induce a pro-inflammatory state and stromal alterations, processes that can be further elucidated through single-cell and spatial transcriptomics. These treatment-induced changes create a selective niche (or "fitness landscape") that indirectly facilitates the expansion of mutant clones, such as those harboring *TP53 or NRF2* mutations, which may confer a selective advantage in a damaged environment.

In particular, the authors observe convergent selection for disruption of the p53 signaling axis. Clonal expansions harboring driver mutations in *TP53* and *PPM1D* were pervasive in patients exposed to platinum-based chemotherapy.[1] Because *PPM1D* encodes Wip1, a negative regulator of p53, such mutations attenuate p53-mediated stress responses and confer a survival advantage under genotoxic pressure. Strikingly, similar selective expansion of *TP53*- and *PPM1D*-mutant clones was observed following immune-checkpoint blockade (anti-PD-1/anti-CTLA-4), despite the non-mutagenic nature of immunotherapy.[1] This finding implicates immune surveillance itself as a powerful selective pressure on the DNA damage response pathway. Under sustained immune stress, cells capable of dampening p53 signaling gain a competitive fitness advantage, enabling clonal expansion within otherwise normal tissues. A central conceptual advance of the study is the decoupling of mutational burden from clonal dominance. Rather than being dictated solely by the number of therapy-induced mutations, remodeling of normal tissues was driven by Darwinian selection operating through key signal transduction pathways.[1]

Ultimately, the functional consequences of therapy-driven clonal expansion warrant careful distinction between two potential outcomes. On one hand, the expansion of *TP53- or NRF2*-mutant clones may establish a field of cancerization, effectively increasing the target population for secondary oncogenic hits and raising the long-term risk of secondary malignancies. On the other hand, the dominance of these clones selected for stress tolerance rather than physiological optimization could contribute to accelerated somatic aging. This widespread clonal mosaicism may explain persistent tissue dysfunction and systemic toxicities that burden cancer survivors long after the cessation of treatment. Deciphering whether these clones represent harbingers of future malignancy or drivers of functional decline remains a critical frontier for improving the long-term health of the cancer survivor population.

Beyond the DNA damage response, the study also uncovered tissue-specific selection of antioxidant signaling. In liver samples, mutations in *NFE2L2*, encoding the master regulator Nrf2, were significantly enriched, particularly in patients with histories of chemotherapy exposure or chronic alcohol consumption.[1] These alterations likely promote constitutive antioxidant signaling, allowing normal hepatocytes to withstand persistent oxidative stress. This adaptive strategy mirrors mechanisms frequently

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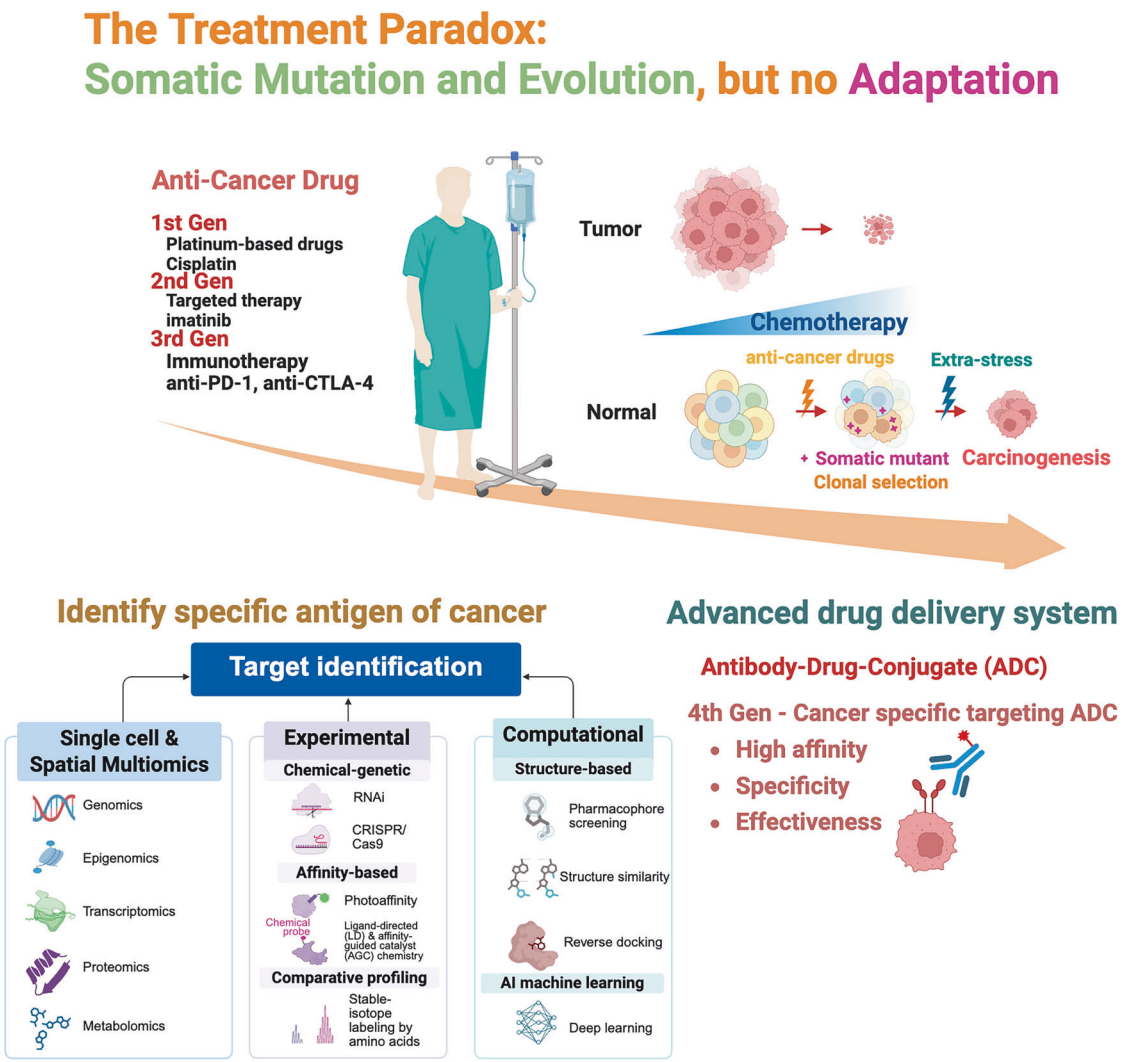

Fig. 1 Therapy-driven somatic evolution and signaling adaptation in normal tissues. Successive generations of systemic cancer therapies, including chemotherapy, targeted therapy, and immunotherapy, impose selective pressures on normal tissues. These pressures promote clonal expansion of cells harboring adaptive alterations in key signaling pathways, such as the p53 DNA damage response and NFE2L2 (Nrf2)-mediated antioxidant signaling. To minimize such off-target evolutionary consequences, modern drug development increasingly emphasizes cancer-specific target identification and optimized delivery strategies. Advances in single-cell and spatial multi-omics analyses, together with artificial intelligence-assisted target discovery, have accelerated the identification of precise therapeutic targets. In parallel, antibody-drug conjugates (ADCs) have emerged as a prominent delivery platform and are now considered fourth-generation anticancer therapeutics, enabling more selective tumor targeting while minimizing long-term effects on normal tissues. BioRender.com

exploited in hepatocellular carcinoma and chronic liver disease,[4] highlighting shared evolutionary trajectories between normal tissue adaptation and disease-associated signaling states.

Collectively, these findings compel a shift toward "evolution-aware" cancer therapy. Therapeutic strategies should be evaluated not only for their immediate antitumor efficacy, but also for their long-term capacity to reshape signaling networks in normal tissues. The substantial off-target mutational burden imposed by systemic chemotherapy underscores the potential value of targeted delivery platforms such as antibody-drug conjugates, which may limit collateral evolutionary pressure on healthy organs.[1] Moreover, integrating single-cell genomics and spatial transcriptomics will be essential to resolve how therapy-selected clones emerge within specific niches, including stem cell compartments and immune-privileged microenvironments.

Finally, translation of these insights into clinical practice may be enabled by longitudinal liquid biopsy approaches, allowing real-time monitoring of therapy-driven clonal dynamics and early detection of secondary malignancy risk. By illuminating how cancer therapies sculpt somatic evolution through selective rewiring of signal transduction pathways, Pich et al. provide a framework for rational cancer care that eradicates tumors while preserving the long-term integrity of normal tissues.

Figure 1 illustrates how successive generations of systemic cancer therapies impose selective pressures that drive clonal selection and adaptive rewiring of key signaling pathways, including p53 and Nrf2, in normal tissues.

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AUTHOR CONTRIBUTIONS

Y.-J.J. conceived the manuscript. Y.-J.J., I.-S.S., and S.-W.J. wrote the first version of the manuscript. I.-S.S. and S.-W.J. performed detailed revisions of the manuscript. Y.-J.J. created the figure. All the authors have read and approved the article.

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

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REFERENCES

1. Pich, O. et al. Somatic evolution following cancer treatment in normal tissue. *Nature* (2025).
2. Pich, O. et al. The mutational footprints of cancer therapies. *Nat. Genet.* **51**, 1732–1740 (2019).
3. Mitchell, E. et al. The long-term effects of chemotherapy on normal blood cells. *Nat. Genet.* **57**, 1684–1694 (2025).
4. Ng, S. W. K. et al. Convergent somatic mutations in metabolism genes in chronic liver disease. *Nature* **598**, 473–478 (2021).

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