Tumour driver mutations compromise between cancer growth and immune responses

Various theories have tried to explain the frequency and consistency of 'hotspot' mutations in many tumour-driving genes across different cancers. A model of the fitness benefit of these mutations shows that fundamental trade-offs occur between a tumour's growth and its visibility to the immune system, with potential therapeutic implications.

This is a summary of:
Hoyos, D. *et al.* Fundamental immune–oncogenicity trade-offs define driver mutation fitness. *Nature* https://doi.org/10.1038/s41586-022-04696-z (2022).

Cite this as:
Nature https://doi.org/10.1038/d41586-022-01138-8 (2022)

The problem

Although the evolution of tumours often seems chaotic, it is commonly driven by 'hotspot' mutations — those that occur more frequently in particular gene regions than would be expected by chance. These mutations tend to appear in a limited set of tumour-suppressor genes and oncogenes. A paradigmatic example is the tumour suppressor *TP53*, which is mutated in more than 50% of cancers, often in a narrow set of hotspot regions. There are many hypotheses for why hotspot mutations occur so consistently, including biased mutation rates, a greater ability to drive carcinogenesis and the possibility that the encoded mutant proteins (and thus mutant cells) can evade the immune system[1–4].

However, these hypotheses have typically been tested individually, restricting their scope and potentially hindering prevention and treatment. If a hotspot's preponderance is simply because it is not easily surveyed by the immune system, then the altered peptides it creates — known as neoantigens — might be poor targets for immune-based therapy. But if a hotspot's prevalence has another cause (such as a tumour-promoting function) and it can be recognized by the immune system, it would be an attractive target for such therapies. That's because many people's cancers would need those mutations, and so would present the neoantigens to the immune system. Understanding hotspot-generating mechanisms is therefore important to the theoretical and practical understanding of cancer.

The solution

We sought to develop a mathematical model that could explain the mutational distributions of common cancer-driver genes, focusing on *TP53*. Drawing on concepts from statistical physics and machine learning, we developed a 'free fitness' function (analogous to one for free energy)[5]. This encapsulates background mutational processes, alterations in function of the mutant p53 protein and the degree to which p53 neoantigens avoid immune surveillance. Using our unified framework, we quantified fundamental constraints on functional alterations and immune surveillance. We found that hotspot mutations in driver genes that alter normal protein function might not be able to simultaneously avoid immune surveillance; and if mutations can tolerate surveillance, they might be less likely to alter protein function.

This predicted evolutionary trade-off suggested that some *TP53* hotspots might make neoantigens that are more targetable than others — a theory that we tested. Our model predicted that some *TP53* hotspots in ovarian and bladder cancers had differential susceptibility to immune targeting. A similar finding emerged from a large-scale screening of *TP53* hotspot neoantigens in more than 100 healthy donors. Moreover, the model anticipated overall survival in multiple groups of patients (including individuals receiving immunotherapy), and helped to predict the age of cancer onset for people with Li–Fraumeni syndrome, who are predisposed to cancer owing to germline (inherited) *TP53* mutations.

We next asked whether *TP53* hotspots in cancers were already observed with the same high frequency in precancerous tissue. By analysing dozens of publications that identified mutations in lesions that were non-malignant — but possibly precancerous — we indeed found the same hotspots as in cancerous lesions. However, the ranking of their frequency was altered, implying that, at their first appearance, hotspot mutations might not yet avoid immune surveillance, and instead prioritize carcinogenic function. Surprisingly, our work suggests that immune surveillance is measurable during the transition to a cancerous state, rather than at the onset of hotspot formation.

The implications

Our work has several implications for understanding tumour evolution and designing interventions. We postulated that hotspot frequencies are due to deterministic features, which can be inferred to assess a hotspot's contribution to the fitness of cancer cells. In so doing, we derived a trade-off between a hotspot's cancer-driving function and the immunogenicity of its neoantigens, which resides in what we called a 'free fitness' landscape (Fig. 1). The implication is that some hotspots might be more visible to the immune system than others, making them better targets for precision immunotherapy (especially before a tumour forms, when there is less immune-driven selective pressure).

Our method was built within the framework of statistical physics, integrating multimodal data in an interpretable, mechanistic model. This approach could enable the use of real-world machine learning to quantify cancer-cell fitness and apply findings therapeutically.

Benjamin D. Greenbaum and **David Hoyos** are at the Memorial Sloan Kettering Cancer Center, New York, New York, USA.

EXPERT OPINION

"This an important effort to incorporate two elements of cancer development and therapeutic potential. It is one of the most ambitious attempts to date that I've seen to unify these two elements of tumorigenesis."

Paul Thomas is at the St Jude Children's Research Hospital, Memphis, Tennessee, USA.

FIGURE

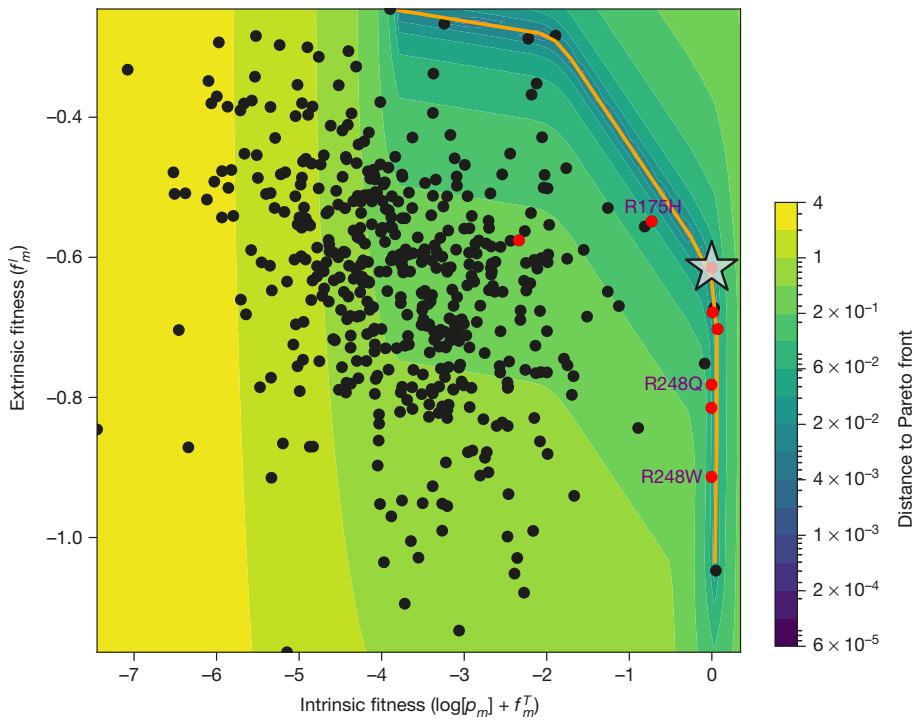

Figure 1 | Free-fitness landscape of *TP53* mutations. The *x* axis plots the intrinsic fitness, which is the sum of the log-transformed background mutational frequency (log[p_m]) and the positive functional fitness (f^T_m) of individual mutations (black dots). The *y* axis plots the mutations' negative immune fitness (f^I_m) (or extrinsic fitness). The Pareto front (orange line) delineates the space beyond which a mutation cannot improve on one feature (intrinsic fitness) without a trade-off in another (extrinsic fitness), as exemplified by the R175H and R248Q/W mutations. The grey star indicates optimal free fitness constrained by the front, and the heat map represents the distance to the front. *TP53* hotspot mutations are in red. Hoyos, D. *et al.*/*Nature* (CC BY 4.0).

BEHIND THE PAPER

Our work came from a desire to synthesize three major research threads in cancer evolution: how specific mutations drive oncogenesis; which cancer-cell mutations are due to intrinsic bias; and which features the immune system recognizes in a tumour. We sought a uniform mathematical approach, inspired by statistical physics and machine learning, to integrate these features into a model of the fitness benefit that cancer cells gain from mutations in *TP53* — the most mutated gene in cancer. Our eureka moment was realizing that, in such a model, these features are inextricably bound together, inducing an evolutionary trade-off that has testable predictions. Our interdisciplinary Program in Computational Immuno-Oncology at the Memorial Sloan Kettering Cancer Center allowed us to test and confirm several predictions of our model. Many contributors were involved in this work, and our collaboration was initiated through Stand Up To Cancer's Convergence programme.

B.D.G.

REFERENCES

1. Giacomelli, A. O. *et al. Nature Genet.* **50**, 1381–1387 (2018).
2. Baugh, E. H., Ke, H., Levine, A. J., Bonneau, R. A. & Chan, C. S. *Cell Death Differ.* **25**, 154–160 (2018).
3. Petitjean, A. *et al. Hum. Mut.* **28**, 622–629 (2007).
4. Marty, R. *et al. Cell* **171**, 1272–1283 (2017).
5. Łuksza, M. *et al. Nature* **551**, 517–520 (2017).

FROM THE EDITOR

I was excited by this paper because, through a theoretical approach, it tackles broad and interesting questions in cancer: the complicated relationships between the oncogenicity and immunogenicity of mutations. The elegant dissection of fitness advantages and costs illuminates the trade-offs that are at play during cellular transformation by cancer drivers, and contextualizes tumour evolution at the basic genetic level.

Victoria Aranda, Senior Editor and Team Manager, *Nature*