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Transforming biomarker development with exceptional responders

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Abstract

Curative therapy for cancer patients with advanced-stage disease remains elusive. While rare outlier responses to anti-cancer therapies exist, barriers limit our understanding of the molecular and genetic basis of such profound, life-altering responses. Here, we describe how phenotype-to-genotype studies are elucidating the molecular underpinnings of outlier responses and informing strategies to extend such unprecedented sensitivity to broader molecularly-defined patient populations.

Keywords

exceptional response; precision medicine; molecular oncology; genomics; sequencing

We are now emerging from the era of cancer gene discovery and into an age of genomically-driven oncology, enabled in part by the dramatic increase in our knowledge of the genomic basis of human malignancies [1]. The past decade has seen a reclassification of human cancers emerge based not on their histology, but on genetic alterations on which tumor growth and progression depend. Targeting such alterations with specific inhibitors has resulted in a profound clinical impact in multiple cancer types. In many patients, the extent and rate of responses are unprecedented, leading to the approval of various targeted drugs for use in the first-line setting, as with trastuzumab and combinations targeting HER2-dependent breast cancers, EGFR tyrosine-kinase therapy targeting EGFR-mutant lung cancers, and several others [1]. This has, in turn, spurred continued efforts to rationally design cancer therapies targeting the specific molecular aberrations on which individual tumors depend, the basis for precision oncology.

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Despite the growing number of these promising therapies, engendering complete and durable responses in advanced-stage patients remains challenging. Indeed, responses within even molecularly homogeneous populations of patients vary widely and drug resistance invariably arises. The community has, consequently, devoted enormous efforts toward characterizing the mechanisms of both intrinsic and acquired resistance to both single-agent and combination systemic, targeted, and immuno-therapies. The findings from such studies have stimulated the development of next-generation drugs and novel combination strategies.

While traditional clinical testing paradigms will continue to evaluate the efficacy of new therapies using statistically principled trials, these greatly undervalue the potential of individual cases of profound response to accelerate drug development or salvage existing therapies for new indications. Even a single complete and durable clinical response provides the preliminary evidence necessary for further exploration and development of that drug in patients sharing the genetic basis of that response. While not indicative of the overall response rate within an unselected population or tumor type, such cases represent irrefutable evidence of potentially profound activity that can accelerate the expansion and testing of a clinical hypotheses or salvage a hypothesis assumed to have failed. Moreover, the impact of such exceptional responders can be more effectively realized through in-depth analysis of their tumor biology rather than additional clinical testing in broader unselected populations. However, such outlier responses are routinely relegated to incidental findings, which underestimates their potential significance and impedes the exploration of their underlying biology. Until recently, the community lacked the tools to comprehensively explore the molecular basis of such responses. Consequently, little has been known about the basis of curative cancer therapy, but this is beginning to change.

Studies have begun to comprehensively analyze the molecular underpinnings of these extraordinary treatment phenotypes. These sequencing efforts have uncovered biomarkers that predict for enhanced sensitivity to specific targeted therapies, but also unexpected synthetic-lethal interactions and new biology. Multiple studies have identified how diverse yet rare somatic mutations in effectors of mTOR pathway activity (*TSC1*, *TSC2*, *MTOR*, *NF2*) can lead to exceptional responses to mTORC1 inhibitors [2–4]. The first of these studies explored a patient with metastatic bladder cancer that experienced a durable complete response to the mTORC1 inhibitor everolimus. Tumor genome sequencing revealed synergistic coincident *TSC1* and *NF2* loss-of-function mutations that rendered the tumor hyper-sensitive to mTORC1-directed therapy. Additional testing of clinical specimens validated *TSC1* as a biomarker of clinical benefit from such therapies [2]. Studies of other outlier responses to MAPK-directed therapy have linked *ARAF* mutations to sorafenib sensitivity in lung adenocarcinoma [5], *MAPK1* mutations to erlotinib response in head and neck cancer [6], *MAP2K1* mutations to selumetinib exceptional response in low-grade serous ovarian cancer [7], and others are still emerging.

While treatment with molecularly targeted therapies facilitate the mechanistic study of exceptional responses, these drugs are still given only to the minority of cancer patients. With the advent of immunotherapies, similar efforts to understand the basis of exceptional response to immune checkpoint blockade have begun to emerge, as in the case of genomic alterations leading to JAK/STAT activation in a patient with long-term response to PD-1-

directed therapy [8]. Chemotherapy, on the other hand, remains the mainstay of therapy for most patients. Therefore, similar studies have extended this paradigm to patients with outlier responses to combination therapies including systemic chemotherapy. In one such example, a hypomorphic mutation in the *RAD50* gene, which encodes a component of the Mre11 complex, was discovered in a metastatic ureter cancer that subsequent cross-species modeling confirmed abrogated ATM signaling, producing a synthetic lethality with cell cycle checkpoint inhibition to confer exceptional sensitivity to DNA damage-inducing agents [9]. This demonstrates how functional validation of the basis of outlier responses can reveal a new mechanistic understanding of key and highly conserved pathways like the DNA damage response.

Collectively, these studies have led to an emerging roadmap for how to study outlier therapeutic responses in a manner that produces validated biomarkers that can be used prospectively in patients (Fig. 1). However, fundamental steps in this process remain challenging. For instance, while deep mechanistic analysis of outlier patients can be powerful, it is generally not feasible due to limitations related to both tissue availability and experimental challenges inherent to working with primary human cancer cells. Researchers have, therefore, begun to explore exceptional responses in representative model systems, such as in the context of preclinical trials in mouse models. Indeed, the discovery and biochemical validation of an exceptional response to MEK inhibition in a *Kras*-driven mouse model of acute myeloid leukemia elucidated a long-standing mystery regarding the functional relationship between wildtype and mutant KRAS in modulating competitive fitness, pathway dependence, and drug sensitivity [10]. Overall, dissecting the biochemical basis of exceptional responses, while challenging, remains the key to generalizing rare therapeutic phenotypes into genotypes predictive of drug response in patients (Fig. 1).

Notwithstanding the power of this phenotype-to-genotype approach, the presence of similar mutations in other patients does not guarantee they also achieve an exceptional response, an observation which is likely due to other context-specific factors (Box 1). While the individual relevant aberrant genes are certainly necessary, they are unlikely sufficient to evoke such responses. Despite the recent approval of the first pan-cancer genomic biomarker of drug sensitivity [11], lineage remains an important determinant of drug response [12]. Moreover, we still poorly understand how the landscape of co-mutated genes or the clonal structure [9] of tumors dictate therapeutic response. Other factors that likely contribute to a patient's potential exceptional response to therapy include patient-specific aspects of immune system, microbiota, and germline genetics, and drug metabolism. This gap in our knowledge is demonstrated by reports of still unexplained exceptional responses [13, 14]. Yet, beyond understanding the context-specific mechanisms of extreme pathway dependence and inhibitor sensitivity, we must also understand what sustains the durability of such responses. How do these patients evade the drug resistance that plagues the vast majority of their similarly treated counterparts? In some patients, the basis of durability is linked to the same event that sensitizes the patient [15], while in others this may result from the genetic rewiring of a cellular program through a second alteration in the same pathway [2]. A greater understanding of the molecular origins of durable outlier responses is, therefore, a critical step in transforming single-patient anecdotes into broadly applicable biomarkers of drug sensitivity.

As a community, we must develop the clinical-scientific infrastructure to capture and study exceptional responses that include, among other things: patient consent, specimen acquisition, qualifying response criteria, reflex to comprehensive characterization, and a real-time data sharing framework. We must capture clinical outcomes data within the context of both rigorously designed prospective histology-agnostic clinical trials as well as real-world off-label drug use using established endpoints that, in aggregate, can be used to guide scientific discovery and regulatory indication extensions. In an example of an effort to systematize and democratize the phenotype-to-genotype study of exceptional responses to anti-cancer therapy, the National Cancer Institute recently established the Exceptional Responders Initiativeⁱ [16]. This effort will build on the early successes described above, which continue to uncover not only biomarkers of response now being validated in broader populations of molecularly characterized patients, but also new facets of drug sensitivity and molecular signaling.

The identification of the genomic mechanisms underlying exceptional responses is a necessary but ultimately insufficient step. This phenotype-to-genotype discovery must be married to efforts that confirm these therapeutic hypotheses in patients identified prospectively as harboring a rare lesion that has been associated previously with exceptional responses to therapy. Large-scale national and industry-led basket trials are enabling this genome-driven provisioning of therapy to individual patients including NCI-MATCHⁱⁱ, TAPURⁱⁱⁱ, Novartis Signature Trial^{iv}, Genentech MyPathway^v, and others. Critically, the genomic inclusion criteria of these studies have already been modified based on the data generated by exceptional responder analyses.

At its core, however, the serendipitous emergence and study of exceptional responders is a failure of the scientific and clinical community to understand precisely which patients should get which cancer therapies. Our goal must be to reduce the number of surprising exceptional responses to both new and old therapies. Rather, we want to elicit such responses intentionally, by, in part, moving prospective molecular characterization to earlier in the clinical care of cancer patients (Fig. 1). Overall, as we continue to define the compendium of molecular strategies by which tumors are rendered uniquely and durably sensitive to cancer therapy, biomarkers of clinical benefit will emerge to drive the testing of new rational treatment hypotheses in clinical trials.

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References

1. Hyman DM, et al. Implementing Genome-Driven Oncology. *Cell*. 2017; 168:584–599. [PubMed: 28187282]
2. Iyer G, et al. Genome sequencing identifies a basis for everolimus sensitivity. *Science*. 2012; 338:221. [PubMed: 22923433]
3. Wagle N, et al. Response and acquired resistance to everolimus in anaplastic thyroid cancer. *N Engl J Med*. 2014; 371:1426–1433. [PubMed: 25295501]

4. Wagle N, et al. Activating mTOR mutations in a patient with an extraordinary response on a phase I trial of everolimus and pazopanib. *Cancer Discov.* 2014; 4:546–553. [PubMed: 24625776]
5. Imielinski M, et al. Oncogenic and sorafenib-sensitive ARAF mutations in lung adenocarcinoma. *The Journal of clinical investigation.* 2014; 124:1582–1586. [PubMed: 24569458]
6. Van Allen EM, et al. Genomic Correlate of Exceptional Erlotinib Response in Head and Neck Squamous Cell Carcinoma. *JAMA oncology.* 2015; 1:238–244. [PubMed: 26181029]
7. Grisham RN, et al. Extreme Outlier Analysis Identifies Occult Mitogen-Activated Protein Kinase Pathway Mutations in Patients With Low-Grade Serous Ovarian Cancer. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology.* 2015; 33:4099–4105. [PubMed: 26324360]
8. Van Allen EM, et al. Long-term Benefit of PD-L1 Blockade in Lung Cancer Associated with JAK3 Activation. *Cancer Immunol Res.* 2015; 3:855–863. [PubMed: 26014096]
9. Al-Ahmadie H, et al. Synthetic lethality in ATM-deficient RAD50-mutant tumors underlies outlier response to cancer therapy. *Cancer Discov.* 2014; 4:1014–1021. [PubMed: 24934408]
10. Burgess MR, et al. KRAS Allelic Imbalance Enhances Fitness and Modulates MAP Kinase Dependence in Cancer. *Cell.* 2017; 168:817–829 e815. [PubMed: 28215705]
11. Le DT, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science.* 2017; 357:409–413. [PubMed: 28596308]
12. Hyman DM, et al. Vemurafenib in Multiple Nonmelanoma Cancers with BRAF V600 Mutations. *N Engl J Med.* 2015; 373:726–736. [PubMed: 26287849]
13. Vitale MG, et al. Erlotinib-induced complete response in a patient with epidermal growth factor receptor wild-type lung adenocarcinoma after chemotherapy failure: a case report. *J Med Case Rep.* 2014; 8:102. [PubMed: 24661457]
14. Lou E, et al. Complete and sustained response of adult medulloblastoma to first-line sonic hedgehog inhibition with vismodegib. *Cancer Biol Ther.* 2016:1–7.
15. Lheureux S, et al. Somatic BRCA1/2 Recovery as a Resistance Mechanism After Exceptional Response to Poly (ADP-ribose) Polymerase Inhibition. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology.* 2017; 35:1240–1249. [PubMed: 28221868]
16. Takebe N, et al. Biomarkers: exceptional responders-discovering predictive biomarkers. *Nat Rev Clin Oncol.* 2015; 12:132–134. [PubMed: 25687910]

Text Box 1**Context-specific facets that likely dictate exceptional responses**

Molecular and genetic features:

- Presence of sensitizing mutation
- The co-mutational landscape of the tumor
- Synthetic lethal interactions
- Germline genetics

Evolutionary aspects:

- Fraction of cancer cells harboring sensitizing mutation
- Clonal structure of the tumor
- Constraints on pathway rewiring in response to therapy

Cellular and organotypic:

- Cell type
- Immune surveillance and infiltration
- Drug distribution and metabolism
- Lineage-specific gene expression

Extrinsic to the tumor:

- Microbiome
- Interacting drugs

Resources

- i. NCI, Exceptional Responders Initiative, https://dctd.cancer.gov/majorinitiatives/NCI-sponsored_trials_in_precision_medicine.htm#h100
- ii. NCI-MATCH, <https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/nci-match>
- iii. TAPUR, <https://www.tapur.org/>
- iv. Novartis Signature Trial, <http://www.trials.novartis.com/en/clinical-trials/us-oncology/oncology/signature/about-patient/>
- v. Genentech MyPathway, <https://clinicaltrials.gov/ct2/show/NCT02091141>

Fig 1. Roadmap for extending exceptional responses to broader patient populations

Beyond studying exceptional responses in patients enrolled in biomarker-driven basket studies after initial molecular characterization, we must develop a mechanism to capture these clinical outcomes in patients treated off-label or with routine or investigational agents in an unselected population (1). Here, individual cases can be identified that experienced exceptional sensitivity to the therapy (2). The comprehensive molecular-genomic characterization of the tumor and matched normal specimens from such exceptional responders can reveal candidate genetic mechanisms of response (3) that can be studied experimentally *in vitro* and *in vivo* (4). Upon validation of such mutations, a pathway-aware approach can be taken to expand a multiplex biomarker of likely therapeutic sensitivity (5) that can be utilized to enroll molecularly characterized patients whose tumors share one or more lesions predicting for enhanced sensitivity to the therapy (6).