**IN THE SPOTLIGHT**

**Collapsing the Tumor Ecosystem: Preventing Adaptive Response to Treatment by Inhibiting Transcription**

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**Summary:** Adaptation and resistance to treatment are the results of a multitude of (epi)genetic events unmasked or directly triggered by therapies targeting the genetic driver(s) of a dominant cell population within a tumor mass. Rusan and colleagues report that drug-tolerant cells are sensitive to THZ1, a dual CDK7/12 inhibitor, which, by impairing the transcriptional machinery, can prevent cellular rewiring to survive therapeutic attack. Cancer Discov; 8(1); 17–9. ©2018 AACR.

See related article by Rusan et al., p. 59 (6).

Numerous examples in the cancer literature now demonstrate that, even after rapid regression induced by treatment with targeted agents, the emergence of resistant clones fuels regrowth of tumors over time. A representative example of this is the occurrence of resistance to vemurafenib, where a majority of relapse lesions occur at the same physical location as the original tumor, suggesting that a subset of cells survived treatment and drove disease recurrence (1). Multiple phenomena could underlie these events, including the possibility that a drug might not have reached all cells in the tumor, the preexistence of cells intrinsically insensitive to treatment, and/or the induction of adaptive responses in a subset of cells that enables them to survive treatment, potentially by maintaining cells in a quiescent state (2, 3). It is anticipated that these varied responses to drug, or functional heterogeneity, are enabled by the vast genetic heterogeneity of both primary tumors and their metastases, underscoring the need to devise combinatorial treatment approaches targeting diverse biochemical functions of distinct cell populations (4, 5).

In this issue of *Cancer Discovery*, Rusan and colleagues evaluated the effect of simultaneously treating tumors with a dual CDK7/12 inhibitor and a targeted therapy known to affect specific genetic cancer dependencies, for example, *BRAF* or *MEK1/2* (6). The authors hypothesized that this combinatorial strategy may exploit transcriptional reprogramming induced by drug treatment as a potential therapeutic vulnerability. Indeed, acquired resistance of clonal lineages depends upon rewiring of the molecular network to uncover mechanisms that protect cell populations from therapeutic challenge. However, eukaryotic cells have developed myriad strategies to regulate cellular functions, making the specific molecular outcomes following any given drug treatment difficult to predict, and negatively affecting our ability to develop effective combination drug strategies. The authors elegantly circumvent this by impairing the entire transcriptional machinery with THZ1, an inhibitor of CDK7/12 protein kinases, previously shown to broadly affect transcription by inhibiting the phosphorylation and activation of RNA polymerase II (7). It was known from previous work that cancer therapies induce and maintain coordinated transcriptional programs to induce drug-tolerant states, quiescence, stemness, survival, and other outcomes (2, 3, 8, 9). The analysis of transcriptional changes modulated by CDK7/12 inhibition when deployed in combination with targeted therapies led Rusan and colleagues to identify, beyond changes induced by each targeted agent, the downregulation of a consistent set of 34 genes (regulated by master transcriptional factors, e.g., *JUN*, *FOS*, *EGR1*) known to support and coordinate RNA polymerase II–driven transcription (7, 10). These findings provide evidence of a direct relationship between the induction of drug-tolerant states and the establishment of transcriptional programs that can be effectively counteracted by dual CDK7/12 inhibition as well as by CDK7 and CDK12 genetic suppression. THZ1 disrupted transcription by preventing the epigenetic remodeling required by surviving cells to counteract the effects of targeted agents, a mechanism similar to the previously observed case of enhancer and superenhancer occupancy controlled by BRD4 upon targeted kinase inhibition (11). In addition, the authors confirmed that adaptive mechanisms controlled by MAPK signaling are induced as a consequence of targeted therapy treatments (12, 13), suggesting a rationale for MAP/ERK signaling inhibitors in combination with THZ1, which suppresses ERK signaling and represses its downstream survival pathways. Indeed, in multiple preclinical models of specific oncogene-driven tumors, treatment with THZ1 in combination with one of several agents targeting MAP/ERK signaling (e.g., erlotinib, WZ4002, and crizotinib) resulted in delayed tumor growth, and no signs of additive toxicity were observed with the combinations. Of note, these therapeutic combinations were efficacious only in tumor contexts wherein the targeted therapy was matched with the genetic dependency of the tumor, supporting the requirement for on-target therapeutic activity to

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Figure 1. Relapsing tumors are the unpredictable outcome of competition among heterogeneous subpopulations coexisting in a tumor and redistributing upon treatment. Orthogonal pharmacologic strategies aimed at targeting surviving subclonal lineages or at collapsing the entire tumor architecture can prevent the emergence of resistant disease and the establishment of adaptation mechanisms. EMT, epithelial–mesenchymal transition.

elicit the THZ1-sensitive transcriptional reprogramming, as well as underscoring the utility of tumor genomic profiling for rational design of combination therapy approaches.

This story is provocative, as the authors propose that a partial inhibition of transcriptional activation might prevent cell reprogramming in response to treatment to yield more durable tumor responses. The excitement raised by this study is connected with the urgent need to expand the portfolio of pharmacologic agents that can address a functional cancer dependency beyond targeting a specific genetic mutation. This advance in our understanding of molecularly, and potentially clinically, relevant scenarios in which drugs impairing critical cellular functions can be successfully and safely applied has uncovered opportunities to interrogate analogous approaches to affect cancer care and survival (Fig. 1). However, it is prudent to reflect on a
few potential issues. First, if, as the authors argue, response to combined treatment with a CDK7/12 inhibitor requires tumor cells to be sensitive to a specific targeted agent, a successful clinical outcome will require that the vast majority of the tumor cell population be dependent upon that target. This may be the case in some cancers (e.g., BRAF-mutated melanoma) but not in others. Second, proper dosing and scheduling of a transcriptional inhibitor with the potential of significant toxicities beyond those typically managed by medical oncologists (bone marrow, skin, or gastrointestinal effects) will need to be carefully determined and accurately managed. Third, contrary to information published in the study by Rusan and colleagues, a similar, albeit not identical, CDK7/12 inhibitor has shown significant activity in preclinical models, and it is currently in a phase I clinical study as a single-agent therapy (14). While maintaining enthusiasm about this first-in-class mechanism reaching the clinic and potentially affecting patients’ lives, we eagerly await clinical read-outs that may support the hypotheses put forward by Rusan and colleagues, as this would open up truly novel and exciting possibilities. Adding a tool to our arsenal of therapeutics that could significantly delay, or even eliminate, disease recurrence using a “simple transcriptional repression trick” would significantly affect our ability to manage disease complexity.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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REFERENCES
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