Cell

Breaking Down Resistance

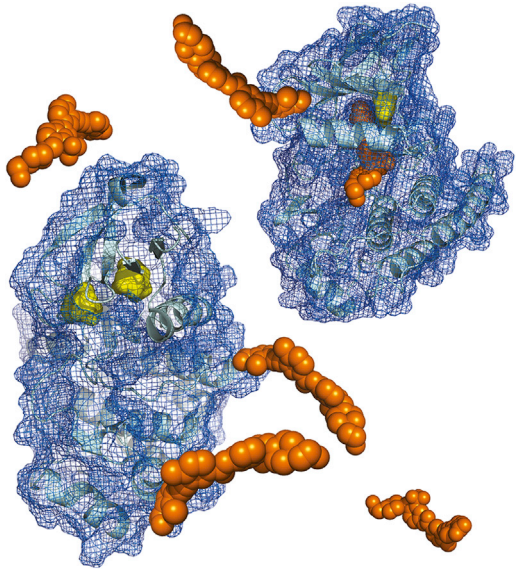
Years of efforts have been invested in developing targeted cancer therapies by identifying the unique features of cancer cells and designing specific molecules to eliminate them while sparing their healthy neighbors. Spurred on by the initial success of imatinib mesylate in treating Philadelphia chromosome-positive leukemia, the emergence of resistance to targeted therapies caught many off guard. Where is the resistance coming from? What makes the persisters special? And how might we stage a counteroffensive?

Unexpected signaling crosstalk underlies resistance to targeted therapy (Created by Caitlyn Webster; courtesy of Monique Dail and Kevin Shannon).

Leukemia has been a particular focal point for answering these questions. Multiple tyrosine kinase inhibitors (TKIs) have been developed to specifically target the leukemogenic BCR-ABL1 fusion protein, and patients receiving such treatments are known to develop not only single but also compound mutants in the *BCR-ABL1* gene that could confer resistance. A study from the laboratories of Michael Deininger and Thomas O'Hare (Zabriskie et al., 2014) takes a close look at these compound mutations residing in the kinase domain and establishes the sensitivity of different compound mutants to various clinically available TKIs. More importantly, they identify a group of compound mutants classified by the inclusion of one killer mutant, T315I, as the most resistant to all TKIs, and their structural modeling points could inform the design of a therapy targeting these lethal combinations.

In addition to selecting point mutants in the target domain, resistance can also be acquired in a more global and reversible manner. Indeed, the work published earlier this year by Bradley Bernstein and Michelle Kelliher (Knoechel et al., 2014) looks into the resistance to γ-secretase inhibitors (GSIs) that target oncogenic NOTCH1 activation in T cell acute lymphoblastic leukemia (T-ALL). What they have found is that chromatin in persister cells exhibits different epigenetic features that lead to distinct signaling programs and even changes in nuclear sizes. They take advantage of the reversible nature of epigenetic changes and show that by combining GSI with a chromatin modifier inhibitor, the persisters collapse.

A number of studies have reported that therapeutic resistance can arise from aberrant activation of additional pathways that circumvent the effect of targeting the primary oncogenic mechanism. An example of this is provided by Michael Green's group, who establish that inhibiting the mitogen-activated protein kinase kinase (MEK) can effectively eliminate stem cells in chronic myeloid leukemia triggered by the BCR-ABL1 fusion protein (Ma et al., 2014). While combinatory therapy that simultaneously targets two oncogenic pathways has been proposed for combating resistance in various contexts, recent work from Kevin Shannon's laboratory (Dail et al., 2014) suggest that this strategy should be implemented cautiously because it could inadvertently promote the selection of resistant cells. In particular, they show that although upregulation of NOTCH1 is well known as the molecular signature of T-ALL, the



The tyrosine kinase inhibitor ponatinib (orange) binds to the ABL1^{T315I} kinase domain (upper) but not ABL$^{E255V/T315I}$ (lower, point mutants in yellow) (Courtesy of Matthew Zabriskie and Nadeem Vellore).

leukemic cells resistant to the combo treatment of PI3K and MEK inhibitors exhibit reduced expression of NOTCH1 and develop cross-resistance to inhibitors targeting NOTCH1 signaling. This work presents a previously unappreciated scenario that instead of activating additional oncogenic pathways, cancer cells resistant to targeted therapy may actually dampen a major oncogenic signaling pathway, which evidently serves as an indirect approach for cancer cells to acquire resistance to the potential inhibition of a key oncogenic signature, in this case NOTCH1 activation. This unusual observation suggests that lack of NOTCH1 activation might be tumorigenic by releasing a brake on PI3K signaling.

When it comes to resistance to cancer therapy, there is little doubt that we are in for a protracted battle. Yet, we shouldn't forget how far we've come—from fantasizing that targeted therapy is the "magic bullet" to seeing it as an important avenue that is leading to a clearer view of the complexity and evolvability of cancer. That we are faced with resistance only means that we are getting closer to our goal.

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