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Perspective

A Convergence-Based Framework for Cancer Drug Resistance

David J. Konieczkowski,[1,*] Cory M. Johannessen,[2] and Levi A. Garraway[3]
[1]Harvard Radiation Oncology Program, Boston, MA 02114, USA
[2]Broad Institute, Cambridge, MA 02142, USA
[3]Eli Lilly and Company, Indianapolis, IN 46225, USA
*Correspondence: dkonieczkowski@partners.org
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Despite advances in cancer biology and therapeutics, drug resistance remains problematic. Resistance is often multifactorial, heterogeneous, and prone to undersampling. Nonetheless, many individual mechanisms of targeted therapy resistance may coalesce into a smaller number of convergences, including pathway reactivation (downstream re-engagement of original effectors), pathway bypass (recruitment of a parallel pathway converging on the same downstream output), and pathway indifference (development of a cellular state independent of the initial therapeutic target). Similar convergences may also underpin immunotherapy resistance. Such parsimonious, convergence-based frameworks may help explain resistance across tumor types and therapeutic categories and may also suggest strategies to overcome it.

Introduction

Most patients with advanced cancer die because their cancer exhibits or develops resistance to available therapies. This challenge remains pervasive despite many remarkable advances in cancer biology and treatment and has motivated renewed efforts to understand and combat cancer drug resistance. For example, addressing cancer drug resistance was one of the key recommendations from the Blue Ribbon Panel that advised the Beau Biden Cancer Moonshot initiative (Jacks et al., 2016).

Studies of cancer drug resistance yield several types of insights. First, defining mechanisms of resistance to a specific anti-cancer regimen may identify future therapeutic strategies against such resistance. Such knowledge might guide salvage treatment after resistance has already occurred or inform new up-front strategies that prevent its emergence. For example, identification of MEK reactivation as a mechanism of resistance to RAF inhibitor monotherapy in BRAF-mutant melanoma (Johannessen et al., 2010; Nazarian et al., 2010), or of $EGFR^{T790M}$ as a mechanism of resistance to first-generation EGFR inhibitors in EGFR-mutant lung cancer (Kobayashi et al., 2005; Pao et al., 2005), led to the development of new therapies with clinical efficacy against these resistance mechanisms (Mok et al., 2017; Robert et al., 2015).

Systematic characterization of drug resistance across tumor types and therapeutic categories may also enable new insights into cancer biology—regarding, for example, networks that differentiate the malignant state from normal, the cell-intrinsic and extrinsic factors regulating them, and how these pathways evolve to promote tumor survival during therapy. Investigating resistance to mitogen-activated protein kinase (MAPK) pathway inhibition revealed new aspects of feedback regulation within this pathway (Lito et al., 2014; Pratilas et al., 2009). Likewise, studies of EGFR inhibitor resistance in lung cancer highlighted the importance of intratumoral heterogeneity (Piotrowska et al., 2015).

Despite the potential benefits of such knowledge, systematic efforts to define the full spectrum of resistance mechanisms for any given therapeutic remain the exception rather than the rule in cancer research. In fact, the skeptic might even question whether studies of resistance in general offer the most efficient or incisive means to discover either novel therapeutic targets or disease-relevant biology. However, a synthesis of emerging genomic and functional portraits of cancer drug resistance begins to reveal overarching frameworks that both offer new insights into resistant states and suggest possible therapeutic approaches to overcome them.

Challenges in Cancer Drug Resistance

As noted in earlier reviews (Garraway and Jänne, 2012), research into cancer drug resistance has produced many discoveries with both basic and clinical significance. As knowledge of resistance mechanisms has expanded, one question has become how best to organize and understand them collectively. At times, individual drug resistance effectors have been almost reflexively aggregated into "pie chart" representations that imply a "one patient, one mechanism" distribution of resistance to a given agent. Such representations, however, are likely to be overly simplistic.

One major challenge is that resistance is multifactorial. Just as initial catalogs of high-frequency somatic alterations in the cancer genome subsequently expanded into a "long tail" of driver alterations (Garraway and Lander, 2013), so too has the diversity of resistance mechanisms begun to increase considerably (Van Allen et al., 2014). While some mechanisms function through well-understood effectors, many others do not. Moreover, although many resistance mechanisms are genomically encoded (e.g., somatic mutations or amplifications), non-genetic resistance mechanisms (e.g., protein phosphorylation or gene expression changes) have become increasingly recognized. Furthermore, the tumor microenvironment can also modify drug exposure and response (Straussman et al., 2012). Thus, both the number of resistance effectors and the ways in which they become dysregulated are likely quite large for any given therapeutic context.

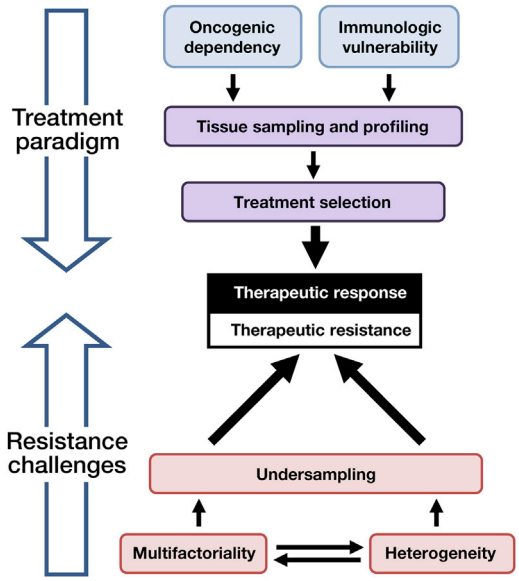

Figure 1. The Landscape of Cancer Therapeutics and Resistance
Recent research has more fully elucidated the landscape of cancer's oncogenic dependencies and immunologic vulnerabilities. Clinical interrogation of these features can guide treatment selection, leading to therapeutic response (top). However, drug resistance often limits cure or long-term control of advanced cancer. Resistance poses several challenges (bottom), in that it is multifactorial, heterogeneous, and therefore prone to undersampling. If resistance is to be overcome, new frameworks are needed to understand and address these challenges.

A second challenge is that resistance is heterogeneous. Heterogeneity between and within patients, or even within a single drug-resistant tumor focus (Sequist et al., 2011; Wagle et al., 2014), has been well described (reviewed in Meric-Bernstam and Mills, 2012). This heterogeneity can be spatial, both within a single tumor and among multiple metastases (Van Allen et al., 2014; Cai et al., 2015; Cooper et al., 2015; Gerlinger et al., 2012; Patel et al., 2014; Romano et al., 2013; Sanborn et al., 2015; Yates et al., 2015) as well as temporal (e.g., adaptation as a result of the selective pressure induced by therapy; Bhang et al., 2015; Juric et al., 2015; Kwak et al., 2015; Menzies et al., 2014; Shi et al., 2014; Waclaw et al., 2015). For example, varied response—or lack thereof—to a targeted therapeutic regimen across multiple metastatic lesions (Carlino et al., 2013; Menzies et al., 2014; Russo et al., 2016) implies underlying biological heterogeneity between those lesions. The simultaneous acquisition of resistance by multiple metastases underscores the fact that such resistant subpopulations may exist even prior to tumor dissemination (Sanborn et al., 2015; Wagle et al., 2011). Conversely, separate tumor foci can acquire similar resistance mechanisms independently through convergent evolution (Gundem et al., 2015; Juric et al., 2015).

A third challenge, arising out of the first two, is that resistance is prone to undersampling in translational investigation. One source of undersampling is technical: many studies have employed only one modality to query a small number of putative resistance mechanisms previously nominated by preclinical investigation. Other efforts have used large-scale genomic approaches, but such techniques also have limitations: a whole-exome sequencing study cannot identify transcriptional or post-translational resistance mechanisms, and vice versa. Moreover, clinical identification of resistance-associated alterations does not by itself demonstrate causality. Rather, experimental studies are necessary to evaluate their functional significance (Van Allen et al., 2014). The limited availability of paired pre-treatment (drug-sensitive) and post-treatment (drug-resistant) clinical samples has also constrained many of the above approaches. Finally, the aforementioned spatial and temporal heterogeneity may further compound undersampling.

Overall, therefore, cancer drug resistance is determined not by singular, mutually exclusive alterations, but rather by a multifactorial, heterogeneous landscape that is prone to undersampling (Figure 1). New approaches are needed to account for this complexity and facilitate future biological and therapeutic insights.

A Convergence-Based Framework for Cancer Drug Resistance

Given these challenges, the task of understanding and addressing cancer drug resistance might at first seem hopeless. A deeper view of this same complexity, however, makes it clear that resistance effectors are not randomly distributed. Rather, they appear to converge into recognizable patterns on the basis of their relationship to the drug target and its downstream pathways—an observation that in turn suggests the possibility of principled and broadly applicable strategies against resistance (Figure 2). This convergence-based framework, described in detail below, has two key properties. First, it reduces many individual resistance effectors into a much smaller set of resistance principles. Second, it may prove generalizable across many tumor types and therapeutic settings. In defining parsimonious classes of resistance mechanisms, this convergence-based approach may therefore assist in understanding and combatting the complex phenomenon of cancer drug resistance.

Convergences in Resistance to Targeted Therapy

Convergence 1: Pathway Reactivation

Targeted anti-cancer agents act against specific cellular dependencies, often proteins or pathways that have undergone oncogenic dysregulation. Correspondingly, many individual mechanisms of resistance to a given targeted therapy converge toward maintenance of the index oncogenic signaling output by re-engaging core pathway effectors downstream of the drug target (Figure 3). Arguably, pathway reactivation represents the most common resistance convergence described to date, as discussed in detail below.

Drug Target Alterations. Among the simplest ways to reactivate the pathway downstream of a drug-inhibited oncoprotein is to render the protein target itself insensitive to the drug. This effect is most commonly achieved through second-site mutations that arise *in cis* with the original oncogenic mutation. A now-classic example of this mechanism involves secondary mutations in the BCR-ABL fusion kinase that confer acquired imatinib resistance in chronic myeloid leukemia (CML) (Gorre et al., 2001). Since this discovery, secondary drug resistance mutations have been described in many kinase drug targets (reviewed in Daver et al., 2015; Lito et al., 2013; Zhang et al., 2009).

One of the best known kinase inhibitor resistance mutations affects the conserved "gatekeeper" residue, altering the

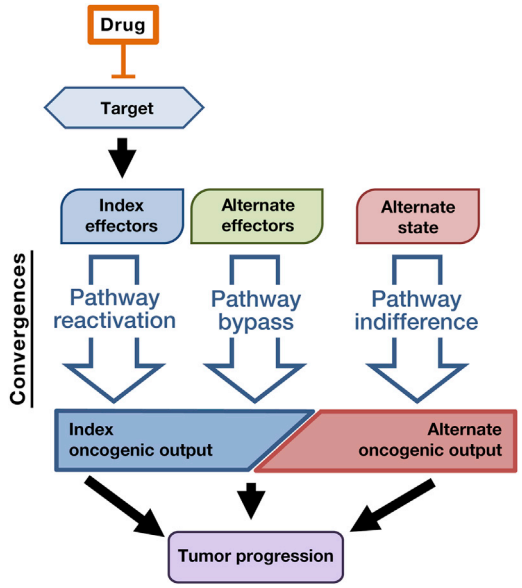

Figure 2. A Convergence-Based Framework for Cancer Drug Resistance

Mechanisms of resistance to targeted therapeutics converge into patterns on the basis of their relationship to the drug target and its downstream pathways. In a "pathway reactivation" convergence, resistance mechanisms re-engage the index effector pathway downstream of the drug target. "Pathway bypass" resistance uses alternate effectors to bypass the inhibited index effectors and re-engage the original downstream oncogenic output (e.g., transcriptional or translational state). "Pathway indifference," in contrast, is characterized by an alternative cell state that is indifferent to inhibition of the drug target as well as its index effectors and oncogenic output. In each case, resistance mechanisms support an index or alternate oncogenic output that drives continued tumor progression.

accessibility of a hydrophobic pocket critical for the binding of ATP-competitive kinase inhibitors. Gatekeeper mutations identified clinically in kinase oncoprotein drug targets include BCR-ABL^{T315I} (in CML; Gorre et al., 2001), EGFR^{T790M} (in non-small-cell lung cancer [NSCLC]; Kobayashi et al., 2005; Pao et al., 2005), ALK^{L1196M} (in NSCLC; Choi et al., 2010; Katayama et al., 2012), and KIT^{T670I} (in gastrointestinal stromal tumors; Heinrich et al., 2006). Third-generation tyrosine kinase inhibitors that retain efficacy against the EGFR^{T790M} mutation represent an important advance in the clinical management of this resistance mechanism in EGFR-mutant lung cancer (Mok et al., 2017), although they remain vulnerable to other resistance mutations in the drug target (Thress et al., 2015).

For allosteric (type IIB), non-ATP-competitive kinase inhibitors, resistance mutations outside of the gatekeeper residue can alter the intrinsic activity of the target kinase, as seen in resistance to MEK inhibitors (Emery et al., 2009), or interfere with drug binding, as observed with resistance to the BTK inhibitor ibrutinib (Woyach et al., 2014). In other cases, such as BRAF-mutant melanoma (Figure 3A), other genomic alterations of the target kinase such as amplification (Van Allen et al., 2014; Long et al., 2014; Shi et al., 2012, 2014) and alternative splicing (Poulikakos et al., 2011) contribute to resistance.

The importance of drug target alterations as resistance effectors is not limited to kinase inhibitors. In prostate cancer, for example, where signaling through the androgen receptor (AR) is central to oncogenesis (Figure 3B), the efficacy of AR-directed therapeutics can be thwarted by AR mutation (Taplin et al., 1995), amplification (Visakorpi et al., 1995), or overexpression (Chen et al., 2004). These genomic events restore AR activity by converting first-generation AR antagonists into partial agonists or by rendering AR sensitive to alternative steroid hormone ligands. Second-generation anti-androgen therapies (e.g., abiraterone and enzalutamide) are also susceptible to target-based resistance mechanisms. For example, abiraterone resistance can be driven by AR amplification or the AR^{T878A} mutation, which renders AR responsive to progesterone instead (Chen et al., 2015; Romanel et al., 2015). Similarly, the AR^{F876L} mutation converts enzalutamide to a partial AR agonist, conferring enzalutamide resistance (Balbas et al., 2013; Joseph et al., 2013; Korpal et al., 2013). The AR-V7 splice variant, which retains transcriptional activity but may abrogate enzalutamide binding, has also in some reports been associated with drug resistance (Antonarakis et al., 2014; Miyamoto et al., 2015). Analogously, in estrogen receptor (ER)-positive breast cancer, mutations in *ESR1* encoding ERα result in constitutive, estrogen-independent ERα activation and are associated with resistance to anti-estrogen therapy (Robinson et al., 2013; Toy et al., 2013).

Upstream Effectors. Downstream pathway activation as a resistance mechanism can also be achieved by effectors that act upstream of the drug target. In BRAF-mutant melanoma, for example, resistance can be conferred by mutations that activate NRAS (Van Allen et al., 2014; Nazarian et al., 2010; Romano et al., 2013) or by loss of the NF1 tumor suppressor, which negatively regulates Ras proteins (Maertens et al., 2013; Shalem et al., 2014; Whittaker et al., 2013). Further upstream, receptor tyrosine kinases (RTKs) including MET (Straussman et al., 2012; Wilson et al., 2012) and EGFR (Girotti et al., 2013) can override single-agent RAF inhibition by activating both Ras and C-RAF, restoring downstream MEK/ERK signaling. RTKs may also contribute to resistance to RAF or phosphatidylinositol 3-kinase (PI3K) inhibition through relief of feedback inhibitory mechanisms engaged by oncogenic mutations (Chandarlapaty, 2012; Corcoran et al., 2012; Le et al., 2016; Prahallad et al., 2012). Autocrine or paracrine activation of RTKs (Montero-Conde et al., 2013) represents another upstream resistance mechanism, one that can in some cases originate from the tumor microenvironment (Straussman et al., 2012; Wilson et al., 2012).

Parallel Effectors. Downstream pathway reactivation and drug resistance can also be achieved by effector proteins operating in parallel to the target (onco)protein. For example, resistance to anti-EGFR monoclonal antibodies in colorectal cancer (Bertotti et al., 2015; Siravegna et al., 2015) and to EGFR tyrosine kinase inhibitors in EGFR-mutant NSCLC can be driven by engagement of alternative RTKs including MET (Bardelli et al., 2013; Engelman et al., 2007), ERBB2 (Takezawa et al., 2012; Yonesaka et al., 2011), and IGF1R (Guix et al., 2008). Likewise, EGFR (Katayama et al., 2012; Sasaki et al., 2011), ERBB3 (Wilson et al., 2015), and KIT (Katayama et al., 2012) can rescue inhibition of ALK in ALK-rearranged NSCLC (reviewed in Niederst and Engelman, 2013). In BRAF-mutant melanoma (Figure 3A), single-agent RAF inhibition can be rescued by alternative MAP3Ks, including COT/MAP3K8 (Johannessen et al., 2010, 2013), which reactivates MEK and ERK signaling.

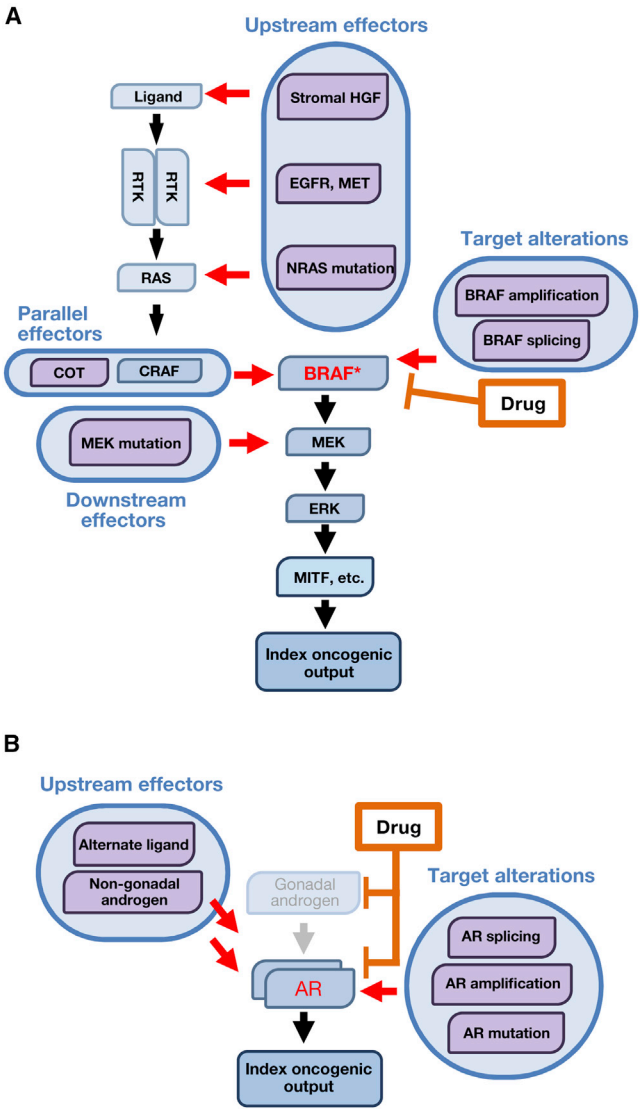

Figure 3. Pathway Reactivation as a Resistance Convergence

Pathway reactivation confers drug resistance by re-engaging index effectors downstream of the drug target, thereby maintaining the original oncogenic signaling output.

(A) In BRAF-mutant melanoma, MAPK pathway inhibitors target BRAF and its index effectors in the MAPK pathway. Pathway reactivation mechanisms include target alterations (e.g., amplification or alternate splicing), which render BRAF insensitive to drug inhibition, as well as recruitment of upstream, parallel, and downstream effectors, which reactivate index effectors in a BRAF-independent fashion. These mechanisms reactivate the index MAPK pathway effectors downstream of BRAF, conferring resistance to BRAF inhibition.

(B) In prostate cancer, oncogenic signaling through the androgen receptor (AR) is targeted by androgen-deprivation therapy and anti-androgen therapy. Resistance to AR-directed therapy can be mediated by pathway reactivation mechanisms including target alterations, which render AR itself resistant to drug inhibition, and recruitment of upstream effectors (non-gonadal androgens or alternate AR ligands), which reactivate drug-inhibited signaling through AR. In either case, the index oncogenic signaling downstream of AR is reactivated, conferring drug resistance.

Downstream Effectors. Reactivation of downstream effectors, independent of upstream signaling, can also confer pathway re-engagement. In BRAF-mutant melanoma (Figure 3A), for example, activating MEK mutations drive resistance to RAF and MEK inhibition (Van Allen et al., 2014; Carlino et al., 2015; Emery et al., 2009; Oddo et al., 2016; Wagle et al., 2011). Similarly, for EGFR-directed therapies in colorectal cancer, activating mutations in the downstream effectors KRAS (Amado et al., 2008; Diaz et al., 2012; Douillard et al., 2013; Van Emburgh et al., 2016; Misale et al., 2012), BRAF (Di Nicolantonio et al., 2008), and MEK (Bertotti et al., 2015; Russo et al., 2016; Siravegna et al., 2015) are associated with intrinsic and acquired resistance. In chronic lymphocytic leukemia, gain-of-function mutations in downstream PLCγ2 confer BTK-independent B cell receptor activity and resistance to the BTK inhibitor ibrutinib (Woyach et al., 2014).

Thus, many individual resistance mechanisms converge on reactivation of the index drug-inhibited oncogenic signaling pathway (Johannessen et al., 2010, 2013; Wilson et al., 2015). The same general principle appears to hold true in the clinical setting; for example, around 70% of BRAF-mutant melanomas clinically progressing on RAF/MEK inhibition have, via one mechanism or another, reactivated ERK phosphorylation (Van Allen et al., 2014; Kwong et al., 2015; Rizos et al., 2014; Shi et al., 2014; Wagle et al., 2014). The frequency of pathway reactivation as a mechanism of resistance may reflect biological parsimony, in that minimal re-wiring of the malignant cell is needed to escape pharmacologic inhibition.

Convergence 2: Pathway Bypass

While many mechanisms of resistance to targeted therapy converge on reactivation of the index intermediary signaling pathway, other convergences may also contribute. In the BRAF-mutant melanoma example above, a significant minority of drug-resistant cases do not seem to re-establish ERK phosphorylation (Van Allen et al., 2014; Kwong et al., 2015; Rizos et al., 2014; Shi et al., 2014; Wagle et al., 2014). At least some such instances may harbor resistance mechanisms that bypass index signaling pathways, finding alternative ways to re-engage the more downstream oncogenic output (transcriptional, translational, or otherwise) required by the malignant cell state (Hsieh et al., 2015; Pratilas et al., 2009). We denote this effect as a "pathway bypass" convergence (Figure 4). Of note, others have used the term "bypass" to describe resistance mechanisms that substitute for an individual protein drug target, thus reactivating the index intermediary signaling effectors (Niederst and Engelman, 2013). We, however, consider such mechanisms part of the "pathway reactivation" continuum, because they restore the original drug-inhibited signaling pathway. Here, we use the term "bypass" to describe mechanisms that circumvent the index signaling pathway as a whole, conferring resistance without reactivation of the original intermediary signaling effectors.

BRAF-mutant melanoma provides an instructive example of one possible pathway bypass convergence. Here, RAF/MEK inhibitor resistance can be driven by a MAPK-independent module that begins at the plasma membrane with G protein coupled receptor (GPCR) signaling. This GPCR activity triggers a cAMP/protein kinase A signal, which in turn engages the CREB transcriptional regulator to harness several transcription factors that confer RAF/MEK inhibitor resistance (Johannessen et al., 2013) (Figure 4A). In wild-type melanocytes, cAMP/CREB signaling downstream of the GPCR MC1R both provides an

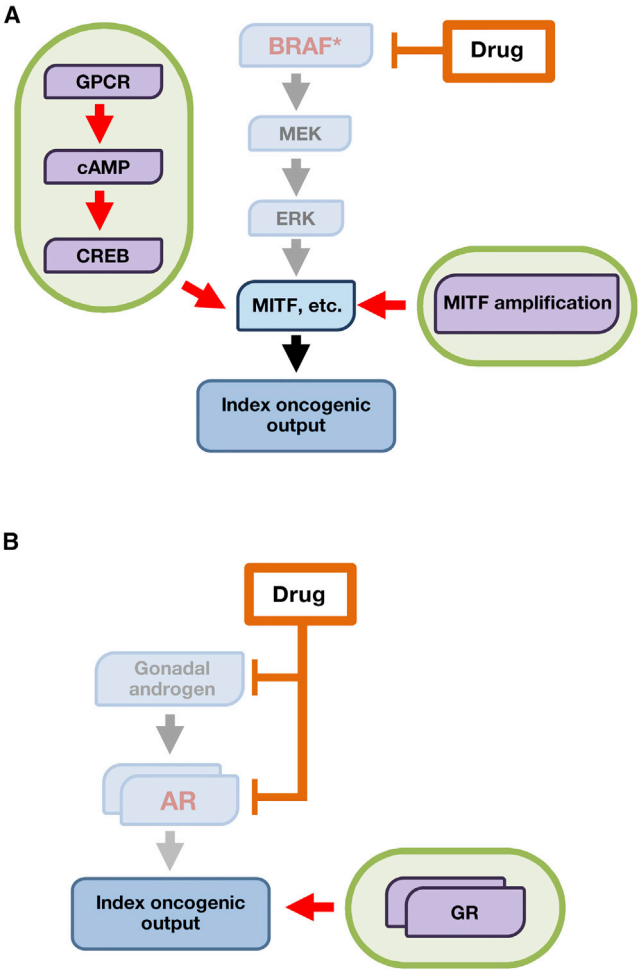

Figure 4. Pathway Bypass as a Resistance Convergence

Pathway bypass confers drug resistance by recruiting alternate effector pathways to sustain the index downstream oncogenic output (e.g., transcriptional or translational state).

(A) In BRAF-mutant melanoma, pathway bypass mechanisms reactivate the core MITF transcriptional output in a manner that is independent of upstream MAPK input. For example, a GPCR-cAMP-CREB signaling axis can substitute for MAPK signaling to sustain an MITF-driven transcriptional program. Likewise, MITF amplification can render MITF itself independent of MAPK signaling.

(B) In prostate cancer, signaling through the glucocorticoid receptor (GR) drives a transcriptional program similar to that of the index AR signaling pathway, rendering cells resistant to inhibition of the AR axis.

essential pro-survival signal and, via PKA, suppresses RAF-mediated MAPK activation (Dumaz and Marais, 2003). In the setting of oncogenic BRAF mutations, cAMP/CREB signaling becomes dispensable and its inhibitory effect on MAPK signaling is lost (Dumaz et al., 2006; Garraway et al., 2005). Following RAF/MEK inhibition, loss of MAPK signaling can then be rescued by restoration of GPCR/cAMP/CREB signaling (Johannessen et al., 2013). Crucially, both MAPK and cAMP/CREB converge on a core set of transcriptional outputs, including ETV1 (Jané-Valbuena et al., 2010; Wang et al., 2017) and the melanoma oncogene and master lineage regulator MITF (Bertolotto et al., 1998; Huber et al., 2003; Johannessen et al., 2013; Khaled et al., 2010; Price et al., 1998). Thus, the GPCR/cAMP/CREB module effects resistance by sustaining a key transcriptional output of the oncogenic MAPK pathway, but in a manner that bypasses the index RAF/MEK/ERK module.

An analogous situation occurs in prostate cancer, in which blockade of AR by enzalutamide can be bypassed by signaling through the glucocorticoid receptor (GR) (Arora et al., 2013) (Figure 4B). GR and AR, similar to CREB and MAPK in melanoma, appear to converge on a similar gene expression program that sustains tumor survival. Thus, following therapeutic inhibition of AR signaling, activation of GR may rescue the original oncogenic transcriptional output in an AR-independent fashion. Reactivation of an "AR-on" transcriptional phenotype probably also contributes to abiraterone resistance (Miyamoto et al., 2012), although the distinctive contributions of AR bypass versus AR-dependent mechanisms in this setting are less clearly resolved at present.

Pathway bypass mechanisms may also contribute to resistance in several other settings. In resistance to ALK inhibition in NSCLC, a putative bypass module operates independently of both MAPK and PI3K signaling by engaging members of the P2Y purinergic receptor GPCR family to transduce a signal through protein kinase C (Wilson et al., 2015). Pathway bypass resistance to PI3K inhibition in ER^+ breast cancer can engage PIM kinases or other effectors and may converge not on a specific transcriptional program but rather on a TOR-dependent translational output (Le et al., 2016). Likewise, PARP inhibition is synthetic lethal with BRCA1/2 deficiency in human tumors, and PARP-inhibitor resistance can arise by pathway bypass mechanisms, including loss of 53BP1 (Jaspers et al., 2013) or REV7 (Xu et al., 2015), which restore function of the index drug-inhibited homologous recombination pathway (without restoration of PARP activity itself).

Together, these examples suggest that pathway bypass mechanisms can reactivate fundamental oncogenic transcriptional or translational outputs through engagement of alternative intermediary effectors. As with pathway-dependent convergences (above), we speculate that for any given therapeutic regimen, multiple pathway-independent resistance mechanisms may converge onto a much smaller number of bypass modules which in turn re-engage the core transcriptional or translational programs that underpin the oncogenic dependency being targeted.

Convergence 3: Pathway Indifference

Both pathway reactivation and pathway bypass resistance convergences re-engage downstream oncogenic transcriptional or translational outputs disrupted by drug therapy. In contrast, a growing body of evidence supports the existence of an additional, fundamentally distinct type of convergence centered on alternative malignant cell states that are independent of the index oncogenic dependency. This "pathway indifference" may arise despite the continued presence of a driver alteration that conferred a therapeutic vulnerability in the treatment-naive setting. Here, the term "pathway indifference" is not intended as a catch-all classification for unknown mechanisms of resistance. Rather, it is proposed to describe a specific phenotype: an alternative cell state (transcriptional or otherwise) that is independent of the index oncogenic pathway and that confers drug resistance despite continued inhibition of the index drug target and its downstream outputs.

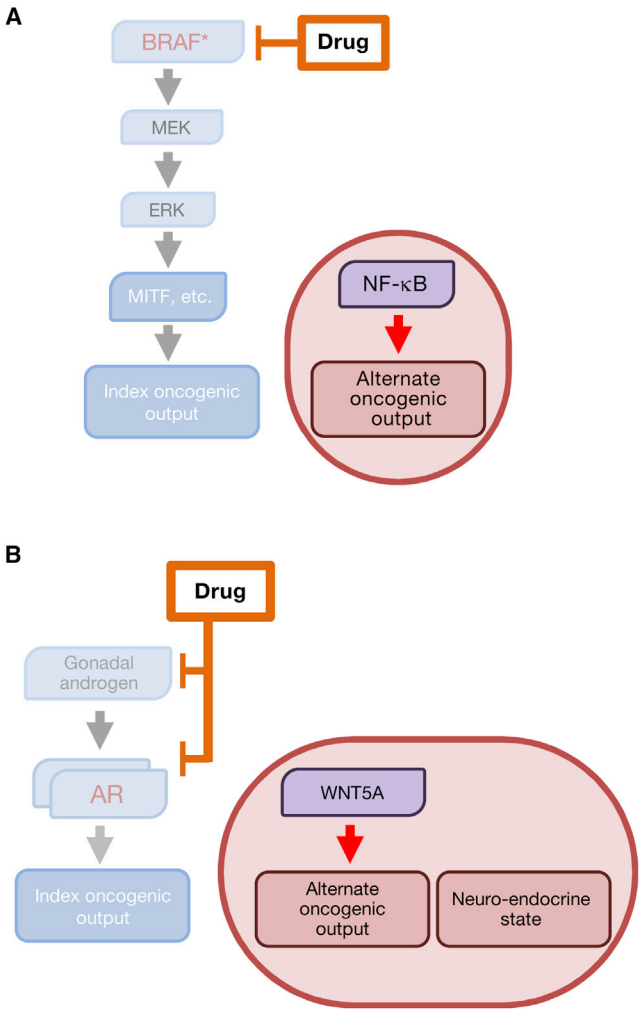

Figure 5. Pathway Indifference as a Resistance Convergence
Pathway indifference confers drug resistance via an alternate cellular state that is independent of the index drug-inhibited pathway and its original oncogenic effectors.
(A) In BRAF-mutant melanoma, the index drug-sensitive transcriptional state is characterized by MAPK-dependent activity of the MITF transcription factor. Resistance to MAPK pathway inhibition can be achieved by transition to an NF-κB-driven, low-MITF transcriptional state that does not require MAPK input for its maintenance.
(B) In prostate cancer, alternative AR-independent cellular states are characterized by Wnt5A-driven and neuroendocrine-like transcriptional programs and are indifferent to inhibition of the AR signaling axis.

One well-known example of pathway-indifferent resistance occurs when EGFR-mutant NSCLC is treated with EGFR inhibitors. Biopsies obtained at the time of drug resistance reveal that some of these cancers show markers of a mesenchymal-like (Sequist et al., 2011; Yauch et al., 2005) or small-cell lung cancer-like (SCLC-like) state (Piotrowska et al., 2015; Sequist et al., 2011; Yu et al., 2013). Importantly, the activating EGFR mutation that conferred initial sensitivity to EGFR inhibition is preserved in the relapsing SCLC-like tumor, implying a common origin of both populations. Thus, the pathway indifference phenomenon appears to represent either outgrowth of an SCLC-like subpopulation originally present within the EGFR-mutant NSCLC tumor population or an adaptive cell state switch that arises within NSCLC cells that survive drug exposure (Hata et al., 2016, reviewed in Oser et al., 2015). Of note, these possibilities (clonal outgrowth versus *de novo* acquisition) apply in principle to the emergence of any resistance mechanism.

A related phenomenon has been observed in melanoma (Figure 5A). Around 20% of BRAF-mutant melanomas exhibit intrinsic resistance to RAF/MEK inhibition (Chapman et al., 2011; Robert et al., 2015; Konieczkowski et al., 2014; Larkin et al., 2014). Sensitivity to RAF/MEK inhibition correlates strongly with a transcriptional profile governed by the aforementioned MITF transcription factor, which requires MAPK input for its activity. In contrast, melanomas that are intrinsically resistant to RAF/MEK inhibition display lower expression of MITF and its target genes, but instead elaborate a transcriptional profile characterized by NF-κB activation and expression of the AXL RTK (Konieczkowski et al., 2014; Müller et al., 2014; Tap et al., 2010; Zipser et al., 2011). Although either AXL expression or NF-κB activation can confer MAPK resistance, neither appears to be required to maintain the pathway-indifferent resistant state (Anastas et al., 2014; Konieczkowski et al., 2014; Wood et al., 2012). In other words, these factors may be sufficient but not necessary for intrinsic resistance to RAF/MEK inhibition in melanoma. Thus, particularly in the intrinsic resistance setting, an alternative transcriptional state can confer pathway-indifferent resistance to RAF/MEK inhibition in BRAF-mutant melanoma.

An alternative cell state also appears relevant to pathway-indifferent drug resistance in prostate cancer (Figure 5B). During escape from androgen receptor blockade (i.e., development of castration resistance), many prostate cancers transition into a so-called "neuroendocrine-like" state that exhibits reduced AR expression (Beltran et al., 2011, 2012; 2016). This neuroendocrine state, which also lacks expression of AR-driven markers such as PSA and is resistant to further anti-androgen therapy, appears indifferent to signaling through the AR axis. Instead, this state appears to be governed by an alternative transcriptional program enacted, at least in part, by SOX2 (Bishop et al., 2017; Ku et al., 2017; Mu et al., 2017). Other studies raise the possibility of a distinct Wnt5A-driven state that arises during acquisition of androgen independence (Miyamoto et al., 2015). Hence, this phenomenon resembles the aforementioned cell state transitions in EGFR-mutant NSCLC and BRAF-mutant melanoma.

Finally, resistance to PARP inhibition may offer a distinct example of pathway indifference, in this case effected by loss of the underlying "BRCA-like" cell state that conferred synthetic lethal dependency on PARP1. Thus, secondary mutations in BRCA1/2 that restore BRCA1/2 function abolish the synthetic lethal relationship with PARP1 and confer indifference to PARP1 inhibition (Edwards et al., 2008; Norquist et al., 2011). The shift from such a genome-unstable to genome-stable state may differ in some respects from the aforementioned transcriptional state transitions. Nonetheless, and while the mechanistic details of these pathway-indifferent cell states are still emerging, it seems that a convergence involving such cell state transitions may contribute to drug resistance in multiple contexts.

Convergence-Based Resistance to Cancer Immunotherapy

The foregoing sections summarize the growing evidence in support of a convergence-based framework for resistance to

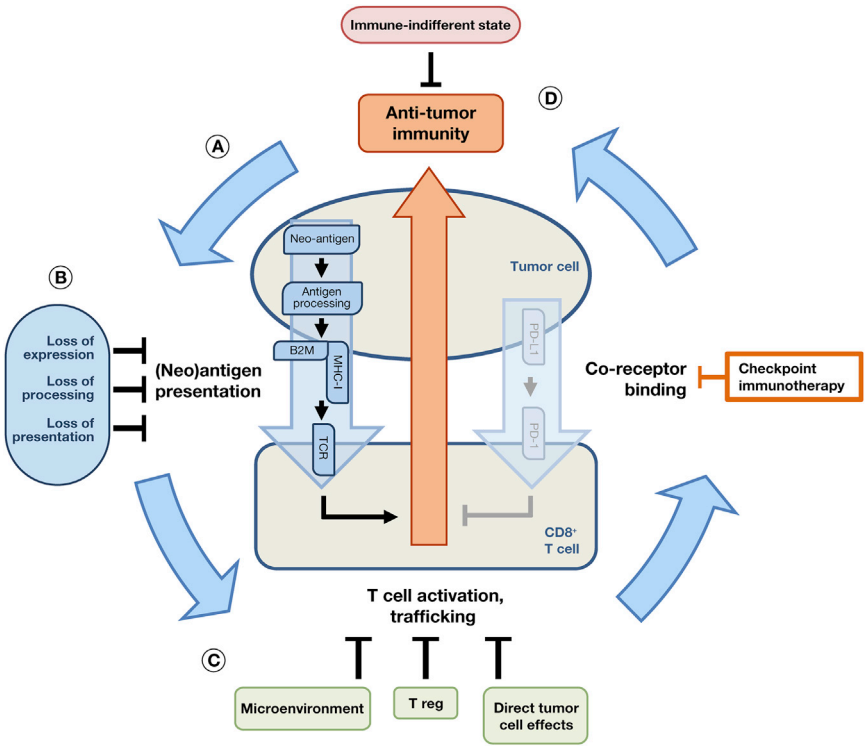

Figure 6. Convergences in Resistance to Immunotherapy

(A) Anti-tumor immunity requires a multi-step cycle to achieve immune cell clearance of tumor cells.

(B) Many immunotherapy resistance mechanisms converge on modulation of neoantigen expression, processing, or presentation, thus restoring the index state of escape from anti-tumor immunity.

(C) Alternatively, induction of T cell dysfunction can bypass anti-tumor immunity, either directly (e.g., through alternative checkpoint ligands) or indirectly (e.g., through T regulatory cells or the tumor microenvironment).

(D) Finally, certain oncogenes or malignant cell states may confer an "immune indifferent" resistance state.

targeted therapy. Given the profound and growing impact of immunotherapy across multiple cancer types, an obvious question is whether convergences may also be evident in resistance to immunotherapy. Of note, the dimensionality of the problem increases markedly in the setting of a multicellular anti-tumor immune response and an assortment of immunomodulatory microenvironmental factors. Moreover, characterization of mechanisms of resistance to immunotherapy remains in its infancy. Nonetheless, it is possible that the tumor/immune interface may also harbor relevant convergences.

As others have described, clearing of tumor cells by T lymphocytes depends not on a single pathway but rather on a multi-step "cancer immunity cycle." This process begins with (neo)antigen presentation to T cells, progresses to T cell priming, activation, and trafficking/expansion in tumor tissue, and concludes with cytotoxic T cell recognition of antigen/MHC complexes followed by killing of malignant cells (Figure 6A; reviewed in Chen and Mellman, 2013; Kim and Chen, 2016). The efficiency of this overall process is modified at each step by factors including the availability of immunogenic tumor antigens, immunomodulatory factors in the microenvironment, regulatory cells (such as myeloid suppressor cells and T regulatory cells [Tregs]), and engagement of T cell checkpoint cascades. Immunotherapy, in turn, targets specific steps in the above process that may be rate limiting for a particular tumor, allowing the cancer immunity cycle to progress and generating a therapeutic anti-tumor immune response. Resistance to immunotherapy, then, can arise from further aberrations that affect the same fundamental steps, thereby bringing the tumor immunity cycle to a halt. As seen with targeted therapeutics, resistance to immunotherapy will undoubtedly prove both heterogeneous and multifactorial and so may perturb multiple of these steps simultaneously in the same tumor. Moreover, resistance to immunotherapy can manifest as both an intrinsic and an acquired phenomenon.

In the face of this complexity, the characterization of the clinical landscape immunotherapy resistance mechanisms remains in its infancy. Nonetheless, certain themes have begun to emerge. For example, resistance mechanisms affecting antigen presentation have become evident in the setting of both intrinsic and acquired resistance to immune checkpoint blockade (Figure 6B). Somatic alterations predicted to reduce antigen presentation (e.g., in HLA and beta-2 microglobulin [B2M]; Shukla et al., 2015; Cancer Genome Atlas Research Network, 2014a) or processing (Giannakis et al., 2016) demonstrate enrichment in several cancer types, suggesting that intrinsic resistance to immune-mediated killing contributes to the evolution of primary tumors. Low mutation or neoantigen burden (Van Allen et al., 2015; Le et al., 2015; Rizvi et al., 2015; Snyder et al., 2014) have also been identified in the setting of intrinsic resistance to immunotherapy. Moreover, *B2M* mutations are associated with acquired resistance to anti-PD1 therapy (Zaretsky et al., 2016). Thus, a growing catalog of mechanisms implicates antigen presentation as a convergence for resistance to immune checkpoint blockade.

In addition, antigen-based mechanisms of resistance to chimeric antigen receptor (CAR) T cell-based therapies have been reported. In this setting, genetic deletion of specific epitopes recognized by CAR T cell clones facilitates tumor escape (Sotillo et al., 2015). While not modifying antigen presentation per se, these mechanisms may represent a convergence on antigen recognition (or lack thereof) in resistance to cellular immunotherapy. Indeed, convergence on antigen presentation and recognition might tentatively be considered analogous to pathway-based resistance. In targeted therapeutics, pathway-based resistance reactivates the index drug-inhibited signaling pathway, restoring essential downstream oncogenic outputs; the above immunotherapy resistance mechanisms, likewise, re-establish suppression of an index "pathway" of antigen presentation and recognition, restoring immune escape.

A second emerging commonality involves T cell dysfunction or "exhaustion" (Figure 6C; reviewed in Wherry and Kurachi, 2015). Here, one set of mechanisms may involve upregulation of alternate immune checkpoint ligands on malignant or other antigen-presenting cells. Alternatively, induction of T cell dysfunction (e.g., by indoleamine 2,3-dioxygenase, which diminishes the supply of tryptophan, an amino acid essential for T cell function; Holmgaard et al., 2013; Uyttenhove et al., 2003) or downregulation of T cell-activating factors (e.g., OX40/OX40 ligand; Guo et al., 2014) may achieve similar ends (reviewed in Mahoney et al., 2015), as may modulation by intratumoral Tregs (Overacre-Delgoffe et al., 2017). Likewise, disruption of interferon signaling via JAK mutation/deletion may render tumor cells non-responsive to immunotherapy (Garcia-Diaz et al., 2017; Manguso et al., 2017; Shin et al., 2017; Zaretsky et al., 2016). Akin to the pathway bypass convergence proposed for targeted therapeutics, these mechanisms restore the index oncogenic state (here, suppression of anti-tumor immunity) without directly re-engaging the index pathways (here, antigen presentation and immune checkpoint engagement) that originally determined it.

Other immunotherapy resistance mechanisms do not obviously alter either antigen presentation or T cell exhaustion. Some of these may represent states of indifference to anti-tumor immunity (Figure 6D). For example, certain oncoproteins may contribute to intrinsic resistance to immune checkpoint blockade. While immunotherapy offers significant clinical benefit in NSCLC as a whole, this effect appears attenuated in the setting of EGFR-activating mutations (Gainor et al., 2016). On the one hand, EGFR-mutant NSCLC often harbors a distinct mutational spectrum (Shukla et al., 2015; Cancer Genome Atlas Research Network, 2014b), suggesting that the oncogene driver itself may not be entirely responsible for immunotherapy resistance. On the other hand, mutant EGFR regulates both PD-L1 expression and the immune microenvironment in mouse models (Akbay et al., 2013), raising the possibility that aberrant RTK signaling may directly contribute to immunotherapy resistance in some fashion. Conversely, concomitant MAPK pathway inhibition may enhance responses to anti-PD1 therapy in other oncogene-driven cancers, such as BRAF-mutant melanoma and KRAS-mutant colorectal cancer (Cooper et al., 2014; Frederick et al., 2013; Hu-Lieskovan et al., 2015), although this effect may be attenuated by contributions of MAPK signaling to T cell function (Callahan et al., 2014). Alternatively, an EMT-like alternative cell state may be associated with intrinsic resistance to immunotherapy in melanoma (Titz et al., 2016). Finally, transition to cell states in which critical (neo-)antigen expression is lost may provide a distinct pathway-indifferent resistance mechanism. Thus, for example, in $CD19^{+}$ B-cell acute lymphoblastic leukemia, resistance to anti-CD19 CAR T cell therapy can be mediated by transition to a myeloid-like phenotype that lacks CD19 expression (Gardner et al., 2016; Jacoby et al., 2016); in contrast to specific loss of expression of a single neoantigen described earlier, this resistance mechanisms appear to involve a more fundamental transition to a cell state independent of CD19 and therefore indifferent to immunotherapy against it.

Although clinical characterization of immunotherapy resistance remains fragmentary (reviewed in Restifo et al., 2016), these preliminary observations suggest that resistance convergences—ones rooted in foundational tumor immunology mechanisms—may also pertain to this class of therapeutics. Such knowledge may eventually facilitate the identification of molecular subsets intrinsically less likely to respond to specific immunotherapeutic approaches and may also help clarify mechanisms of acquired resistance to immunotherapy. These insights may ultimately guide strategies to overcome resistance to immunotherapy.

Therapeutic Frameworks to Overcome Cancer Drug Resistance

Strategies to prevent the emergence of resistance or salvage the cancer patient after resistance has developed remain limited. Indeed, despite the aforementioned insights, the physician and patient are still very likely to run out of therapeutic options before the tumor runs out of resistance mechanisms (reviewed in Garraway and Jänne, 2012). Therefore, a critical question is how insights into tumor dependencies, immunologic vulnerabilities, and resistance convergences might help address this clinical challenge.

One intuitively appealing approach—what might be termed a "dependency-based" combinatorial framework—proposes to simultaneously target multiple dependencies that lack shared mechanisms of resistance. Theoretically, such combinations should make it improbable for a tumor to acquire resistance to an entire multi-drug cocktail simultaneously. Indeed, a compelling precedent exists for this approach in the treatment of infectious diseases, particularly the development of highly active anti-retroviral therapy for HIV. In both HIV and cancer, drug-resistant subclones arise via mutations or other stochastic changes and expand under the selective pressure imposed by therapy. Whereas this phenomenon thwarts effective disease control by monotherapies, it is countered by rational combinations that target parallel dependencies, thus enabling durable therapeutic control. One might even be tempted to argue that studies of drug resistance mechanisms—however biologically interesting—offer therapeutic value that is supplementary at best in comparison with this dependency-based combinatorial approach.

In fact, however, several difficulties constrain the application of this dependency-based framework to cancer patients. First, while most tumors do harbor multiple driver (epi)genomic alterations, many of these aberrancies remain poorly druggable—a fact that probably will not change quickly. Second, in HIV and other microbial settings, the biological dissimilarity between host and pathogen minimizes off-target toxicities. Thus, most antimicrobial drug combinations are safe as well as effective. In contrast, many "horizontal" combinations of targeted anticancer agents (i.e., those targeting multiple parallel dependencies) have proven unacceptably toxic (reviewed in Park et al., 2013; Yap et al., 2013). This phenomenon often reflects on-target toxicities since the targeted pathways are essential to the function of various normal tissues. Thus, it cannot be assumed that targeting multiple cancer dependencies in parallel will always be feasible. These challenges have given rise to recent efforts to combine targeted therapeutics with immunotherapy (Hu-Lieskovan et al., 2015; Ribas et al., 2013), as well as with other therapeutic classes such as chemotherapy and radiation therapy. Such studies will undoubtedly be followed with great interest, particularly in treatment-resistant settings.

In addition to the above dependency-based framework, an alternative "convergence-based" therapeutic approach might also be envisioned. This strategy would use the mechanistic convergences identified by the above resistance framework as "anchors" for combinatorial therapeutic intervention, simultaneously inhibiting both an index dependency and its major resistance convergences. In the context of such an approach, just as the convergence-based resistance framework suggests a parsimonious explanatory model for resistance, it may also offer predictive guidance for strategies to overcome resistance.

Pathway-based resistance mechanisms, for example, might be interdicted by "stacking" therapeutics against the target pathway. For instance, the same target can be inhibited with two drugs. This strategy has been exploited clinically in dual blockade of HER2 with both pertuzumab and trastuzumab (von Minckwitz et al., 2017; Swain et al., 2015) or lapatinib and trastuzumab (Blackwell et al., 2012) in HER2-amplified breast cancer; in BCR-ABL rearranged CML, an analogous strategy involving combined ATP-competitive and allosteric inhibitors of ABL has recently been proposed in the preclinical setting (Wylie et al., 2017). Of note, the individual drugs in such a dual-blockade approach must be non-competitive (e.g., have different target binding sites) in order to cooperate. Alternatively, multiple nodes in the same pathway might be targeted. For example, in prostate cancer, dual blockade of AR signaling with a "vertical" combination of ADT and abiraterone has demonstrated clinical superiority compared with ADT alone (Fizazi et al., 2017; James et al., 2017). Likewise, in BRAF-mutant melanoma, suppression of the MAPK pathway by combined RAF/MEK inhibition overcomes several mechanisms of resistance to, and is clinically superior to, single-agent RAF inhibition (Johannessen et al., 2013; Larkin et al., 2014; Robert et al., 2015). Conceivably, targeting a pathway-based convergence more distally (e.g., ERK inhibitors in BRAF-mutant cancers) might be still more effective. Unfortunately, such approaches remain constrained by the inevitable emergence of resistance to single-pathway blockade (Larkin et al., 2014; Robert et al., 2015). Nonetheless, the prevalence of pathway-based resistance raises the possibility that additional optimization of pathway inhibition might further improve clinical outcomes in many contexts.

Pathway bypass resistance mechanisms could be targeted either at the level of the bypass itself or at the convergent downstream oncogenic output. Targeting bypass pathways with horizontal combinations has been proposed based on preclinical studies. For example, inhibition of the GR bypass pathway restores sensitivity to AR inhibition (Shah et al., 2017). Such approaches may, however, face the same *in vivo* toxicity challenges discussed above if the bypass module also comprises a normal tissue dependency. On the other hand, combination immunotherapy directed against parallel checkpoint proteins (e.g., CTLA-4 and PD-1) has shown significant clinical benefit with manageable toxicity (Larkin et al., 2015; Postow et al., 2015; Wolchok et al., 2013, 2017).

Targeting the convergent oncogenic output (further downstream) could theoretically have efficacy against both the index pathway (both as primary therapy and in the setting of pathway-based resistance) and pathway bypass mechanisms of resistance. One challenge to this approach is that many such downstream convergences are transcriptional programs, which are not readily druggable directly. Many transcription factors, however, require chromatin factors as co-regulators, some of which are already targeted by therapeutics in the clinic. For example, it has been proposed that histone deacetylase inhibitors (which indirectly suppress MITF expression) could be combined with MAPK pathway inhibitors to overcome MITF-driven resistance in melanoma (Johannessen et al., 2013; Yokoyama et al., 2008).

Resistance mediated by pathway indifference, in turn, suggests either disrupting the drug-indifferent state (thus returning the cell to the index drug-sensitive state) or targeting novel vulnerabilities in the alternative state itself. There is preclinical evidence for the former strategy in EGFR-mutant NSCLC and in neuroendocrine prostate cancer, in which targeting effectors of the EMT-associated or neuroendocrine-like resistance states, respectively, restores sensitivity to inhibition of EGFR or AR (Kim et al., 2013; Ku et al., 2017; Marín-Aguilera et al., 2014; Mu et al., 2017; Zhang et al., 2012). Clinical evidence for the latter strategy likewise comes from EGFR-mutant NSCLC, in which relapse under EGFR inhibition has been associated with a transition from NSCLC to an SCLC-like cell state and with sensitivity to a drug regimen (carboplatin/etoposide) used in SCLC (Piotrowska et al., 2015; Sequist et al., 2011; reviewed in Oser et al., 2015). The extent to which these state transitions are mediated by epigenetic alterations remains uncertain, but, in T-cell acute lymphoblastic leukemia, preclinical evidence suggests that an epigenetic state resistant to NOTCH1 targeting via gamma secretase inhibition is in turn sensitive to epigenetic drugging via bromodomain inhibitors (Knoechel et al., 2014). Similarly, convergence-based approaches might show efficacy in preventing or attacking the alternative cell states associated with indifference to immunotherapy. For example, in cases where indifference to immunotherapy is mediated by specific oncogenic pathways, targeting those pathways may represent a promising strategy against resistance (Akbay et al., 2013; Cooper et al., 2014; Frederick et al., 2013; Hu-Lieskovan et al., 2015). In the future, broader clinical application of strategies against indifferent cell states will require clinically robust markers of such state changes as well as identification and targeting of their vulnerabilities.

Finally, certain strategies against resistance may be naive to the specific mechanism of resistance at work. For example, in the absence of drug resistance, mutations are frequently deleterious (Chmielecki et al., 2011; Das Thakur et al., 2013). Accordingly, following emergence of drug resistance, drug discontinuation can lead to drug-sensitive populations outcompeting the drug-resistant populations, re-emergence of drug sensitivity, and clinical response upon drug rechallenge (Browning et al., 2013; Chmielecki et al., 2011; Hata et al., 2013; Riely et al., 2007; Romano et al., 2013; Schweizer et al., 2015; Seghers et al., 2012; Sequist et al., 2011; Siravegna et al., 2015; Das Thakur et al., 2013, reviewed in Camidge et al., 2014). In the future, drug scheduling strategies based on these principles may prove helpful in forestalling the development of resistance or at least in modulating its clinical course.

Conclusion

Although the multifactorial and heterogeneous nature of cancer drug resistance remains a significant challenge, systematic

experimental and clinical studies across many cancer types have revealed a wealth of resistance mechanisms. This review has proposed a convergence-based framework—pathway reactivation, pathway bypass, and pathway indifference—to organize the multiplicity of individual resistance mechanisms to targeted therapeutics into a parsimonious set of generalizable principles. Importantly, this framework may not prove comprehensive, nor is it intended to be proscriptive. Rather, it seems likely that additional as-yet unsuspected convergences will emerge. Nonetheless, the most fundamental lesson from such consideration may not be the identity of specific resistance convergences themselves, but rather that even highly complex landscapes of resistance can be understood through the paradigm of convergence. Going forward, such frameworks may provide both explanatory power to aid biological understanding and predictive power to guide future therapeutic approaches. Ultimately, these insights may help to achieve durable disease control in patients with advanced cancer.

DECLARATION OF INTERESTS

D.J.K. and C.M.J. declare no competing interests. L.A.G. is a founder of and equity holder in Foundation Medicine and Tango Therapeutics.

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