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ACQUIRED RESISTANCE TO CLINICAL CANCER THERAPY: A TWIST IN PHYSIOLOGICAL SIGNALING

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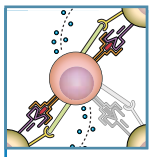

Wicki A, Mandalà M, Massi D, Taverna D, Tang H, Hemmings BA, Xue G. Acquired Resistance to Clinical Cancer Therapy: A Twist in Physiological Signaling. *Physiol Rev* 96: 805–829, 2016. Published May 3, 2016; doi:10.1152/physrev.00024.2015.—Although modern therapeutic strategies have brought significant progress to cancer care in the last 30 years, drug resistance to targeted monotherapies has emerged as a major challenge. Aberrant regulation of multiple physiological signaling pathways indispensable for developmental and metabolic homeostasis, such as hyperactivation of pro-survival signaling axes, loss of suppressive regulations, and impaired functionalities of the immune system, have been extensively investigated aiming to understand the diversity of molecular mechanisms that underlie cancer development and progression. In this review, we intend to discuss the molecular mechanisms of how conventional physiological signal transduction confers to acquired drug resistance in cancer patients. We will particularly focus on protooncogenic receptor kinase inhibition-elicited tumor cell adaptation through two major core downstream signaling cascades, the PI3K/Akt and MAPK pathways. These pathways are crucial for cell growth and differentiation and are frequently hyperactivated during tumorigenesis. In addition, we also emphasize the emerging roles of the deregulated host immune system that may actively promote cancer progression and attenuate immunosurveillance in cancer therapies. Understanding these mechanisms may help to develop more effective therapeutic strategies that are able to keep the tumor in check and even possibly turn cancer into a chronic disease.

I. RECEPTOR TYROSINE KINASES AND THEIR DOWNSTREAM SIGNALING AXES

Cancer is one of the major life-threatening diseases that continuously attract tremendous social attention. Latest epidemiological statistics highlight the global increase of cancer burden (290). In the United Kingdom, it is estimated that 50% of people will suffer from cancer disease at a certain stage in their lifetime (2). In 2014, out of 41 new drugs approved by the Food and Drug Administration (FDA), 22% (9 drugs) were designated for cancer therapy (186). Encouragingly, new anti-cancer drugs have shown great success in clinical cancer therapy with significantly improved survival rate over the past 30 years (266). However, a relevant shortcoming of targeted therapies is the quick emergence of acquired drug resistance. This is particularly frequent for small-molecule inhibitors that target receptor tyrosine kinase (RTK)-mediated oncogenic signaling pathways. Cancer cells resistant to these drugs usually exhibit a higher degree of genomic instability and show more aggressive phenotypes, such as accelerated metastasis to distant organs and tissues. Thus drug resistance becomes the major challenge in clinical cancer therapies. Development of novel therapeutic strategies towards overcoming drug resistance is a critical issue in clinical cancer therapy.

RTKs are a group of membrane proteins that are activated through tyrosine phosphorylation within their intracellular kinase domain. In the human genome, there are ~58 genes encoding RTK proteins (235). Although they differ in their patterns of expression and activation, such as the abundance on the cell membrane, the discrepant expression between cell and tissue types as well as at different develop-

mental stages, these RTK proteins are evolutionally conserved and are structurally similar on a molecular level, with an extracellular ligand-binding domain, a single transmembrane α-helix, and an intracellular kinase domain that mediates downstream signaling. RTKs are one of the most important molecular sensors that perceive extracellular signals and evoke cell responses through orchestrating intracellular signaling networks. Under physiological conditions, activation of RTKs regulates cell fate in many aspects, including proliferation, differentiation, migration, and metabolic homeostasis (108, 246).

The multiple functionalities of RTKs are achieved through two principal signaling axes: mitogen-activated protein kinase (MAPK) (35) and phosphoinositide 3-kinase (PI3K)/Akt (75, 296, 317). Mechanistic studies on molecular structure reveal that physiological activation of RTKs is initiated by binding of growth factors to the extracellular domain (ECD), which subsequently triggers RTK homo- or heterodimerization. Oligomerized RTKs undergo conformational changes that rapidly induce trans-autophosphorylation on key tyrosine residues within the COOH-terminal kinase domain. This domain not only stabilizes the active state of the RTK but also provides essential docking sites for other regulatory proteins that contain phosphotyrosine-binding motives such as SH2 (301). Once the signalosome is assembled, downstream signaling modules such as MAPK and PI3K/Akt are recruited and activated. These two pathways act as essential processors to direct cellular response at both transcriptional and translational levels in a context-dependent manner **(FIGURE 1)**. However, to maintain a metabolic homeostasis, developmental patterns require spatiotemporal controls of RTK activation. Indeed, activated RTKs not only integrate positive signaling loops but also modulate feedback to terminate their activities. Although other parallel mechanisms exist, MAPK and PI3K/Akt/mTOR cascades are capable of self-limiting excessive activation of RTKs through direct phosphoinhibition of the key adaptor proteins, which results in the interruption of the link between RTKs and their downstream targets (127, 162).

RTKs are frequently hyperactivated in malignant cells and play important roles in the maintenance of tumorigenic phenotypes in various cancers. Due to their substantial contributions to cell growth, RTKs are natural anticancer targets in the clinic. Aberrant constitutive activation of RTKs can be triggered by gene amplification (16, 278), genetic activating mutation (44, 289), gene rearrangement (258), and overexpression of the respective ligands in the tumor stroma **(FIGURE 2)**. Deregulated RTK activation exponentially amplifies downstream signals released from MAPK and PI3K/Akt which leads to uncontrolled cancer cell proliferation and tumor growth. Strategies to inhibit RTK (hyper-) activation have been developed, including blocking antibodies to neutralize the extracellular ligand-binding

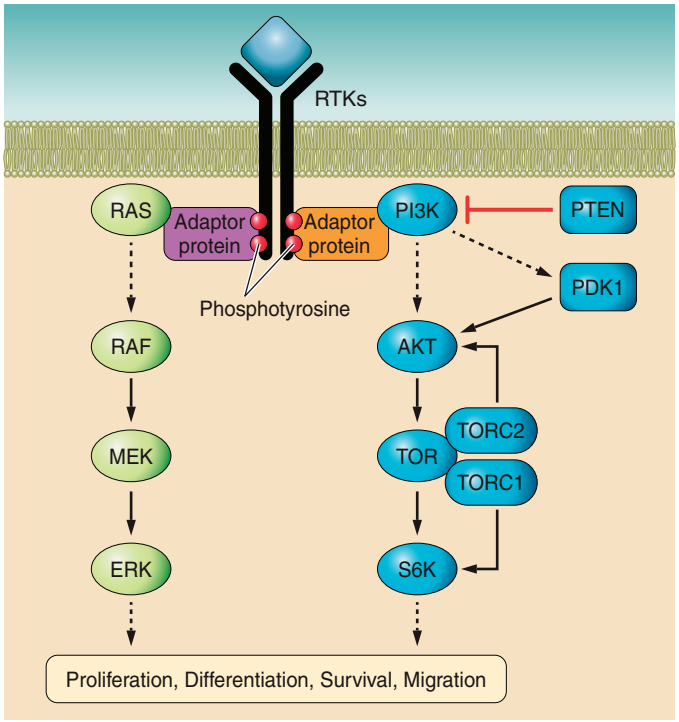

FIGURE 1. Signaling transduction of receptor tyrosine kinase (RTK). The two essential proliferative intracellular signaling pathways, PI3K/Akt/mTOR and RAS/MAPK, are activated downstream of RTKs. Under physiological conditions, these two pathways coordinate with each other to determine proper cell proliferation and organ size. AP, adaptor protein; red ball, phosphotyrosine.

moiety and small molecular compounds (RTK inhibitors, RTKi) to suppress the function of the intracellular kinase domain or prevent RTK dimerization. Since activation of RAS/MAPK and PI3K/Akt/mTOR is either the result of RTK dysfunctions or correlates with mutations further downstream (80, 120, 250), almost all key components along these two signaling axes, such as BRAF, MEK, PI3K, Akt, and mTOR, have been therapeutically targeted to allow for serial and parallel blockade of these two pathways.

ERBB family members, an important member of the RTKs, are frequently hyperactivated (gene amplification and active mutation) during oncogenic progression in many types of cancer, including head and neck squamous cell carcinoma (HNSCC), non-small-cell lung cancer (NSCLC), breast cancer, ovarian cancer, prostate cancer, glioblastoma multiforme (GBM), colorectal cancer, and bladder cancer (256, 283). We will use this family of RTKs as a representative model to discuss the mechanisms of acquired drug resistance in NSCLC and metastatic breast cancer patients undergoing targeted therapies because tumor progression is tightly correlated with therapy-induced drug resistance. In addition, we will also address recent exciting advances in understanding how resistance is developed in metastatic melanomas harboring mutant BRAF, another tumor model that is representative of both self-activating and bypassing mechanisms of therapy-induced resistance.

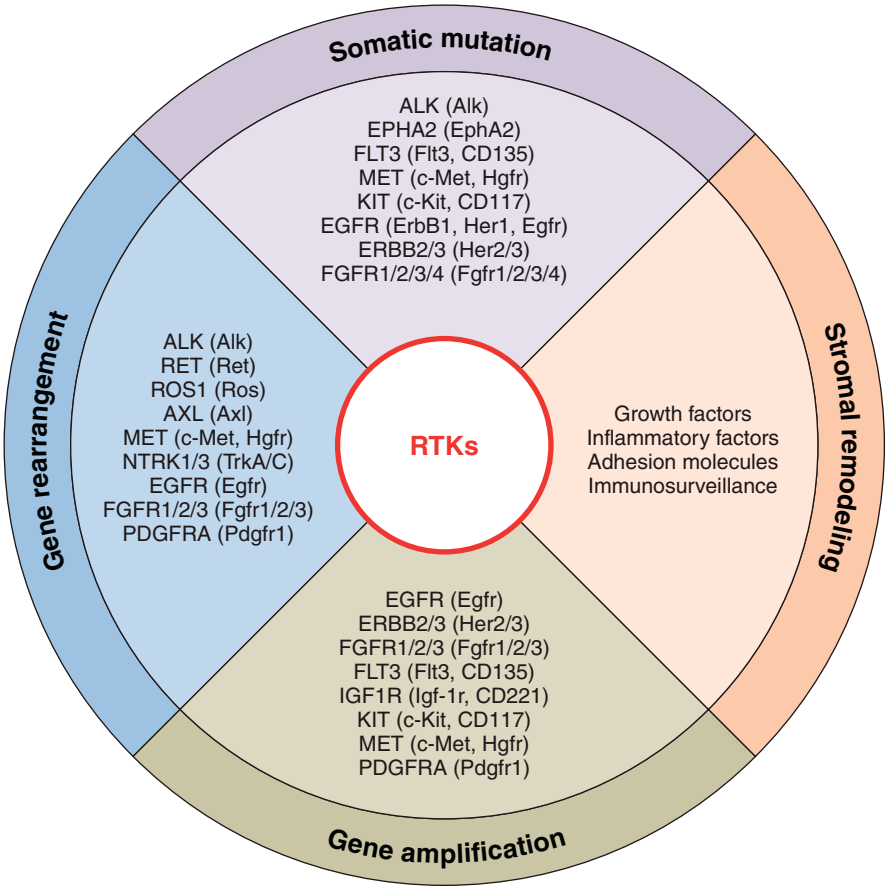

FIGURE 2. Aberrant activation of RTK signaling. Four major factors contribute to elevated activation of major RTK signaling that are frequently detected in human cancer: gene amplification, somatic mutation, gene rearrangement, and remodeling of cancer stroma. These are the predominant players that often lead to pathological activation of many RTK kinases that eventually promote uncontrolled cell proliferation. Persistent activation of RTKs amplifies downstream proliferative signaling, such as PI3K/Akt/mTOR and RAS/MAPK, and inhibits pro-apoptotic signaling like the Hippo pathway. Furthermore, RTK activation can also be caused by drug resistance through interference with signaling cross-talk. Such genetic remodeling encourages genomic instability to overcome cell cycle arrest, and therefore, the cells become cancerous with malignant proliferative and migratory potential.

A. Physiological Signaling of the ERBB Family

The human homolog of the erythroblastic leukemia viral oncoprotein v-erbB, known as the ERBB (also called EGFR or HER) family, is composed of four closely related members (EGFR and ERBB2-4) which localize on chromosomes 7, 17, 12, and 2, respectively (235). Despite the lack of an intracellular kinase domain on ERBB3, the family members share a high degree of similarities in their molecular structure, with a tandem cysteine-rich cascade in the ECD, one single transmembrane helix, and a classical intracellular kinase domain (303). A variety of extracellular ligands including epidermal growth factor (EGF), heparin-binding EGF (HB-EGF), transforming growth factor-α (TGF-α), epiregulin (EpRG), amphiregulin (AmRG), betacellulin (BTC), and neuregulin (NRG) are capable of binding to individual ERBB members and inducing unique homo- and/or hetero-dimerization (109). Dimerized ERBBs subsequently undergo conformational changes and trigger autophosphorylation on specific tyrosine residues within the intracellular kinase domain, which simultaneously switches on the ERBB signaling pathway. This activation pattern with a broad range of functional stimuli possibly reflects the versatility of ERBB signaling in different tissues and organs or at different developmental stages.

The signaling cascades downstream of the ERBB family include RAS/MAPK, PI3K/Akt, JAK/Src/Stat, PLC/DAG/PKC, and CDC42/Rac/Pak **(FIGURE 3)**. Depending on the patterns of dimerization, distinct pathways are activated and functionally regulate cellular transcriptional and translational programs that in turn direct cell cycle progression, proliferation, differentiation, angiogenesis, immunomodulation, polarity, migration, and inflammation in a cell- or tissue type-dependent manner (31). The physiological roles of the ERBB family have been broadly explored using genetic mouse models. Full-body knockout of Egfr leads to embryonic and perinatal lethality (175, 264, 265). Multiple organs and tissues including lung, heart, liver, brain, skin, and bone undergo immature development which accounts for the complex phenotypes seen upon genetic ablation of ERBB family members. For example, severely abnormal placental development and immaturity of the lung were observed in Egfr-knockout mice, leading to spontaneous embryonic or perinatal death. Impaired neural development with progressive neurodegeneration resulting from elevated apoptosis of neural cells in the brain was also observed in these mice (129, 145, 203). These genetic studies demonstrate that Egfr is indispensable during development. The observation of distinct patterns of lethality at different developmental stages of Egfr-knockout mice with different genetic backgrounds (265, 286) implies a partial compen-

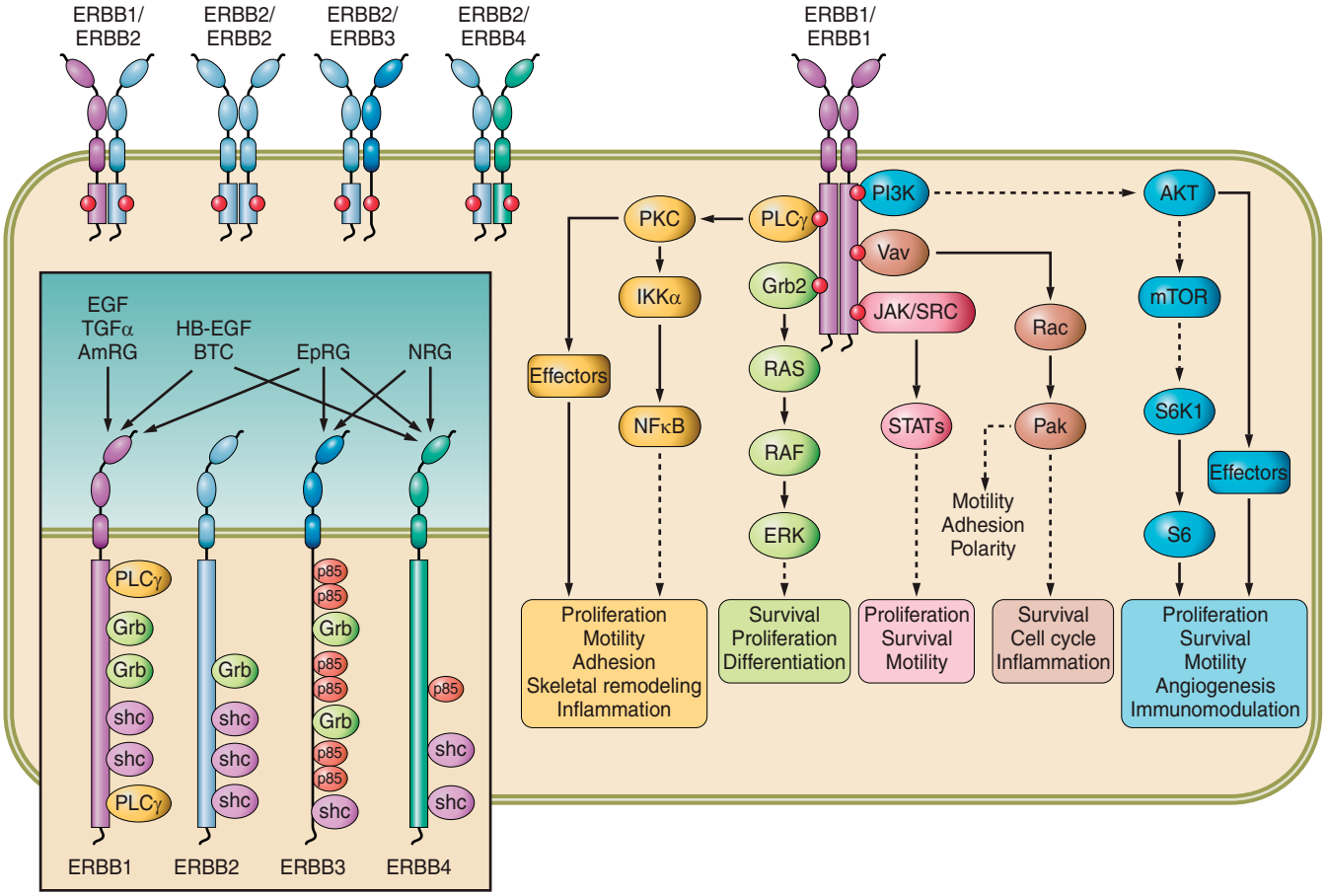

FIGURE 3. Physiological signaling pathway of ERBB family. ERBB signaling is initiated from induced dimerization between four ERBB family members. Five dimerization patterns are reported: ERBB1/ERBB1, ERBB1/ERBB2, ERBB2/ERBB2, ERBB2/ERBB3, and ERBB2/ERBB4. Among the four ERBB isoforms, ERBB3 does not have an intracellular kinase domain, but instead, it enhances ERBB signaling through partnering with ERBB2. In addition, ERBB3 preferentially activates PI3K/Akt as it can directly bind to the regulatory subunit p85 and activate PI3K. Thus ERBB3 activation is widely reported in many types of cancer. Downstream of ERBB are five major axes: PKC, MAPK, PI3K/Akt, and Rac and Jak signaling. In a context-dependent manner, activation of individual pathways contributes to many aspects of cell functionalities through genetic or epigenetic reprogramming.

sation by other ERBB family members in overcoming developmental defects attributed to loss of Egfr. This is indirectly supported by the fact that ablation of certain Egfr ligands, such as EGF and TGF-α, does not result in evident defects (155, 156). In contrast to Egfr, the loss of any other ERBB family member does not necessarily lead to embryonic lethality in mice, which indicates nonredundant roles of Erbb2, Erbb3, and Erbb4 during development. Erbb2 mainly impacts on mammalian neural (140, 146) and cardiac cell development (194, 215), which was confirmed in recent studies on the role of NRG in cardiomyocytes (48, 217) and directly links Erbb2 to cardiac regeneration (49). As expected, due to the direct interaction with Erbb3 and Erbb4, functional loss of NRG mimics Erbb3 or Erbb4 deficiency. Both Erbb3- or Erbb4-knockout mice show neuronal degenerative phenotypes and cardiac maldevelopment (71, 83, 88, 232, 287) similar to NRG-knockout mice (174). Nonetheless, it should be pointed out that functional interference with any single Erbb family member may trigger mixed phenotypic abnormalities with other isoforms, since the specificity of downstream signaling depends on dimerizing partners and a broad spectrum of ligands. Therefore, it is sometimes difficult to correctly define the biological roles of individual ERBB kinases (109).

B. Physiology Downstream of ERBB Signaling: RAF and PI3K/Akt

1. RAF signaling

The mammalian RAF (rapidly accelerated fibrosarcoma) family has three members, ARAF, BRAF, and CRAF (RAF-1), that are intracellular serine/threonine kinases. All three isoforms are ubiquitously expressed in developing embryos but have distinct expression patterns in adulthood. Araf and Craf are widely expressed in almost all tissues of adult mice, although Araf expression seems to be relatively higher

in the organs of the urogenital tract such as the kidney, bladder, testis, and ovary, as well as in lymphoid organs and lymphatic tissues such as thymus and spleen (277), whereas Braf expression is mostly restricted to the brain and testis (74, 312). Targeted deletion of Araf in mice leads to partially postnatal lethality, growth retardation, defective neurological and gastrointestinal development, and abnormality of limb development (225). In contrast to Araf, knockout of either Braf or Craf results in embryonic death (313, 314). These three mammalian RAF isozymes are evolutionarily conserved and share sequence identities of ~45% in the regulatory domain and ~80% in the kinase domain (333). The deficient phenotypes seen in KO mice and the differences in sequences of functionally defined protein domains indicate nonredundant regulatory roles during development. Although they have a common downstream signaling node, MAPK, their activating capacity is differentially regulated. For example, Braf and Craf differentially respond to NGF or cAMP stimulation (70, 112) and also show considerable differences of their activation driven by Ras (167). Moreover, Src can directly activate Araf and Craf but not Braf (163), and Braf is the major activator of MAPK pathway due to its higher binding capacity to MEK (a MAPKK) (207, 226, 311). This is not due to their expression level (33, 183) but their functional specificity in individual tissues (199). On the other hand, biological interactions between Raf family members are also indispensable for specific extracellular signaling triggers, for example, EGF (312) and downstream signal transmissions (173). Taken together, similar to the ERBB family, RAF family members have an extensive crosstalk, thus differentially regulating cell proliferation, differentiation, and survival through MAPK signaling across the entire development.

2. PI3K/Akt signaling

Similar to the activation pattern of RAF signaling, intracellular tyrosine phosphorylation on RTKs generates binding pockets for the SH2-containing subunit p85 and subsequently induces catalytic activity of the p110 subunit. These two subunits assemble the functional PI3K protein (PI3K class I) (8). Activated PI3K catalyzes phosphatidylinositol 4,5-bisphosphate (PIP_2) to phosphatidylinositol 3,4,5-trisphosphate (PIP_3), which promotes membrane targeting of pleckstrin homology (PH) domain-containing proteins such as Akt and phosphoinositide-dependent kinase 1 (PDK1) (98, 142). In response to RTK signaling, PI3K transduces physiological signals through intracellular kinases like Akt, protein kinase C (PKC) and phospholipase C (PLC). Among those, the PI3K/Akt axis plays a vital role in regulating cell growth, anti-apoptosis, and metabolic homeostasis. Subsequent Akt-directed phosphoregulation of a large number of specific substrates determines the cell fate depending on tissue type, developmental stage, and environmental stress. During embryonic development and postnatal organ/tissue formation and maturation, all three Akt isoforms play crucial roles in growth and metabolism **(TABLE 1)**. Akt1 is ubiquitously expressed in mammalian cells, and Akt2 is mainly detected in insulin-responsive tissues such as skeletal muscle and adipose tissue, whereas Akt3 is restricted to the brain and testis. Although Akt1 KO mice are viable, they have a smaller body size (~20 and ~25% reduction at birth and 14 mo after birth, respectively) than their littermates,

Table 1. *Tissue-specific distribution of Erbb, Raf, and Akt kinases in mice and the individual knockout phenotypes*

Genes	Tissue Distribution	Knockout Phenotypes
Egfr	Ubiquitous	Perinatal lethality; defects in the development of multiple tissues/organs including skin, lung, bone, heart
Erbb2	Intestine, stomach, epidermis, uterus, kidney, prostate	Embryonic lethality
Erbb3	Breast, epidermis, stomach, CNS, intestine, prostate, kidney, brain	Embryonic lethality
Erbb4	Brain, liver, heart, eyes, CNS	Embryonic lethality
Araf	Heart, brain, liver, kidney, lung	Partially postnatal lethality; defective development of multiple organs
Braf	Testis, brain	Embryonic lethality
Craf	Ubiquitous	Embryonic lethality
Akt1	Ubiquitous	Increased postnatal lethality; growth retardation; defect of development of placenta
Akt2	Muscle, fat, liver	Diabetic phenotype: hyperglycemia; hyperinsulinemia; insulin resistance; growth retardation; loss of adipose tissue
Akt3	Brain, testis	Neural degeneration; defect of brain development
Akt1/Akt2		Perinatal lethality; severe growth defect
Akt1/Akt3		Embryonic lethality (~E12.5)
Akt2/Akt3		Diabetic phenotype; defect of brain development

defects of testis development and abnormal spermatogenesis associated with elevated spontaneous apoptosis, and a shorter lifespan when challenged with genotoxic substances, probably due to a lack of pro-survival signals (41). In fact, mice without Akt1 show partial neonatal lethality (43), possibly due to a functional deficiency of the placenta (325). Unlike Akt1, Akt2 is mainly detected in muscle, fat, and liver, those tissues which are more sensitive to insulin or play a central role in glucose homeostasis. Akt2 null mice are also viable but exhibit diabetic phenotypes such as hyperglycemia, hyperinsulinemia, and insulin resistance (81), indicating that Akt2 is a key regulator of glucose metabolism (42). This is demonstrated in further studies showing that Akt2 phosphoregulates membrane targeting and activation of glucose transporter (GLUT4) in response to insulin signaling (100, 132). Similar to Akt1, Akt2 deficiency is also associated with moderate growth retardation that results from early metabolic disorders through reduced glycolysis and mitochondrial dysfunction (89). On the other hand, mice lacking Akt3 develop a smaller brain (20-25% reduction) (64, 292). Interestingly, these unique phenotypes governed by individual Akt isoforms are unlikely to be compensatory, suggesting nonredundant physiological functionalities of each Akt isoform across the entire lifespan. Although mice may survive the loss of a single Akt isoforms (63), double-knockout (dKO) of Akt1/Akt3 is embryonically lethal (324) with Akt1/Akt2-dKO mice dying shortly after birth due to severely mixed defective phenotypes of cell proliferation and differentiation (213). Similarly, Akt2/Akt3-dKO mice exhibit aberrant brain development and diabetic phenotypes (63), further demonstrating the specific roles of individual Akt proteins in different cell types and developmental stages.

II. TARGETED STRATEGIES IN CLINICAL CANCER THERAPIES

The latest report on the global cancer burden shows that the incidence of cancer continuously increased from 2002 to 2012 (209, 290). Remarkably, in last 15 years, lung cancer is the leading cause of cancer-related death for both males and females; in addition, breast cancer results in an equally high rate of death among females. Recent advances in the mechanistic understanding of tumor biology rationalize future therapeutic strategies by targeting the fundamental hallmarks of cancer (94).

In many types of cancer, including NSCLC and metastatic breast cancer, gene amplification and/or mutation-driven constitutive activation of the ERBB family facilitates uncontrolled cancer cell proliferation and invasion as well as the evasion of programmed cell death (130, 196). Therefore, ERBB family members have emerged as key therapeutic targets **(TABLE 2)**. Apart from the ERBB family, distinct deregulation of anaplastic lymphoma kinase (ALK) through oncogenic protein fusion with echinoderm microtubule-associated protein-like 4 (EML4) has been found to cause ~5% of NSCLC in clinic (271). Interestingly, using next generation sequencing (NGS), a recent study identified a novel oncogenic fusion of ALK with KIF5B-RET in NSCLC (147), indicating that ALK deregulation is more frequent in NSCLC than it was assumed before. These clinical observations are the rationale for suppressing tumor growth by blocking ERBB and ALK kinase activities. Thus targeting ERBB and ALK families with either small molecular inhibitors or blocking antibodies has become the first line of therapy for lung cancer and Her2-positive breast

Table 2. *FDA-approved major kinase (pathway) inhibitors*

	Generic Name	Brand Name	Target	Producer
Lung cancer	Gefitinib	Iressa	EGFR	AstraZeneca
	Erlotinib	Tarceva	EGFR	Roche
	Crizotinib	Xalkori	ALK	Pfizer
	Afatinib	Gilotrif/Giotrif	EGFR, ERBB2	Boehringer Ingelheim
	Ceritinib	Zykadia	ALK	Novartis
	Cetuximab	Erbitux	EGFR	Yeda & Sanofi-Aventis
	Panitumumab	Vectibix	EGFR	Amgen
	Bevacizumab	Avastin	VEGF-A	Roche
Breast cancer	Lapatinib	Tykerb	ERBB2, EGFR	GSK
	Trastuzumab	Herceptin	ERBB2	Roche
	Pertuzumab	Perjeta	ERBB2	Roche
Melanoma	Vemurafenib	Zelboraf	BRAF (V600E)	Roche
	Dabrafenib	Tafinlar	BRAF (V600E)	Novartis
	Trametinib	Mekinist	MEK1/2	GSK

Food and Drug Administration (FDA)-approved major kinase (pathway) inhibitors (including both small molecular compounds and therapeutic antibodies) in three types of cancer are shown. The inhibitors approved for therapeutic applications in other cancers, or still in clinical trials, are not included.

cancer patients. In fact, with the response rate above 50%, these targeted therapies significantly improve progression-free survival of NSCLC patients (204, 216) and breast cancer patients (11, 17, 24, 52, 86).

In contrast to other types of cancer, the incidence rate for melanoma has been steadily increasing for both men and women (266). When melanoma develops metastases, the five-year survival rate decreases dramatically from 98 to 15%. One of the hallmarks of metastatic melanoma is the constitutive activation of the MAPKKK kinase BRAF that harbors an oncogenic mutation (BRAF_V600E, V600K, or V600R) in ~50% of melanoma patients (20). Constitutively active BRAF promotes cancer cell proliferation through hyperactivated ERK signaling. Compared with the chemotherapeutic agent dacarbazine, treatment with one of the available small molecule inhibitors of BRAF (vemurafenib, Zelboraf, Roche and dabrafenib, Tafinlar, Novartis) significantly improves overall survival of melanoma patients (36, 272).

III. ADAPTIVE RESISTANCE TO TARGETED THERAPIES

Unfortunately, most of the targeted monotherapies against cancer eventually result in resistance. Cancer cells bypass proliferative inhibition through alternative activation of other survival pathways as functional compensation. Activation of these signaling pathways is mediated by various mechanisms on both a transcriptional and translational level, including induction of novel oncogenic mutations, inactivation of negative-feedback signaling loops, aberrant protein-protein interaction/oligomerization, oncogenic gene amplifications, suppressive gene deletions, conversion of apoptotic signaling to survival signaling, and deregulated immunosurveillance. Resistant cancer cells often exhibit an accelerated cell cycle, enhanced metabolism, and increased migration/invasion that ultimately leads to higher malignancy. Therefore, a better understanding of the underlying mechanisms of resistance will contribute to the development of novel therapeutic approaches that may help to turn cancer into a chronic disease.

A. Resistance to Targeted EGFR and ALK Signaling in NSCLC

Since EGFR was discovered and validated as a major druggable target in NSCLC, specific inhibition of EGFR signaling was shown to prolong both PFS and OS compared with conventional platinum-based chemotherapy and is now the accepted standard in the clinic. Although a subset of NSCLC patients treated with gefitinib or erlotinib benefit from a longer lifespan for a longer period of time (131, 157), including those patients with primary somatic mutation L858R on EGFR (178, 201, 205), two large cohort studies revealed rapid development of acquired resistance in the majority of the monotherapeutically treated patients like these (181, 239). Several independent studies reported that a secondary somatic mutation of EGFR, T790M, was emerging in relapsed NSCLC (126, 206). The decreased inhibitory efficacy of gefitinib against EGFR T790M was confirmed in genetically engineered cell lines expressing T790M mutants (206). Further studies indicated that T790M could also be detected in some patients before treatment, which was possibly responsible for their primary resistance to gefitinib (261) and erlotinib (238, 328). Indeed, with the help of next-generation-sequencing technology, it becomes clearer that T790M is a frequent primary mutation that is observed in a small number of malignant cell clones in NSCLC patients (281). Under selective pressure with an EGFR inhibitor, the T790M clone expands quickly and leads to resistance in ~50% of NSCLC patients. Although it is not fully understood mechanistically, studies from structural biology predict that the T790M mutation mediates steric hindrance in the ATP-binding pocket to limit the access of small molecular inhibitors (134) and increases ATP-binding affinity in the kinase domain of EGFR (332). Functionally, persistent activation of EGFR with the T790M mutation maintains hyperactivation of its downstream pro-survival signaling axes, including PI3K/Akt, JAK/Stat3, and MAPK.

In addition to the dominant gatekeeper mutation, amplification of other oncogenic RTKs in EGFRi-resistant NSCLC was also observed. C-Met, also known as hepatocyte growth factor receptor (HGFR), is a receptor tyrosine kinase that plays essential roles during embryonic development and wound healing and is overexpressed in EGFRi-resistant lung cancer (69). Mechanistically, overexpressed c-Met may heterodimerize with HER3 and subsequently mediates PI3K/Akt activation bypassing EGFR inhibition. Similarly, recent studies also identified gefitinib/erlotinib-mediated overexpression of AXL (337), amplification of HER2/HER3 (161), and activation of an FGFR autocrine signaling loop (284, 304). All of these mechanisms contribute to acquired resistance in NSCLC.

Although the specific tissue distribution pattern suggested a role of ALK in brain and neuronal development (110, 227), the lack of abnormal phenotypes in ALK knockout mice throughout their lifespan (305) makes it difficult to define the physiological role of this kinase. Despite these uncertainties in physiology, numerous reports confirmed its importance in driving tumorigenic progression in many types of cancer, most frequently as rearrangement/translocation-elicited oncogenic fusion proteins. In NSCLC patients, ALK is commonly fused with EML4, a microtubule-stabilizing protein guarding correct formation of cellular skeleton network (220). The resulting chimeric protein functions as an intracellular kinase promoting cancer cell proliferation, invasion, and anti-apoptosis through activating PI3K/Akt,

MAPK, and JAK/Stat signaling. Although inhibitors targeting ALK, such as crizotinib and ceritinib, showed immediate benefits in ALK-positive NSCLC patients (133), the short duration of response indicated an acquired resistance (122, 259). Sequencing analysis of crizotinib-/ceritinib-resistant tumors revealed multiple self-activating mutations on ALK (25, 59, 78) and bypassing activation of alternative oncogenic drivers such as KIT (122), IGF-IR (153), EGFR (320), and the GPCR family member P2Y (310). The resulting acquired resistance does not seem to be restricted to TKIs, since the use of blocking antibodies targeting EGFR, such as cetuximab and panitumumab, leads to similar outcomes (10, 309). Clearly, these resistant phenotypes are closely related to and possibly driven by the heterogeneity of NSCLC **(FIGURE 4)**.

B. Resistance to HER2-Targeting in Breast Cancer

The oncogenic role of HER2 has been extensively investigated in human breast cancer. Approximately 25% of invasive breast tumors overexpress HER2 (269, 270). Overexpression of HER2 is associated with a poor prognosis and survival rate (223, 224), and it is also observed as a response to chemotherapies (189, 202, 285). Trastuzumab (Herceptin, Roche) is a humanized monoclonal antibody that targets HER2 and has been approved for clinical breast cancer therapy by the FDA for 15 years. Trastuzumab treatment induces tumor regression through interference with HER2 signaling, in particular HER2 internalization/degradation (47), inactivation of proteolysis of ECD of HER2 (73, 182),

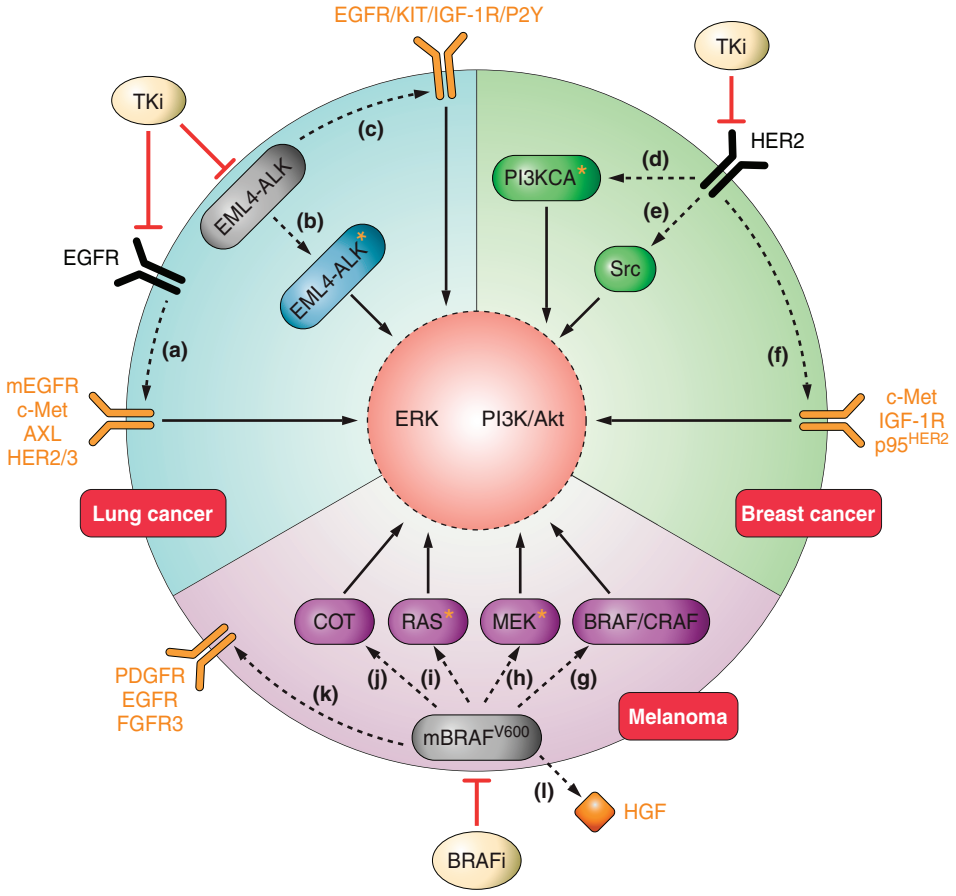

FIGURE 4. Representative mechanisms of drug resistance to clinical therapies in human lung cancer, breast cancer, and melanoma. Several molecular signatures are discovered that contribute to resistance. In lung cancer, *a*) inhibition of EGFR induces not only overexpression of alternative RTKs, such as c-Met, Axl, ERBB2/3, but also activating mutations of EGFR itself; *b*) targeted inhibition of oncogenic ALK fusion protein leads to ALK mutations and *c*) oncogenic activation of EGFR, Kit, IGF-1R, and P2Y kinases. In metastatic breast cancer, blocking HER2 activity frequently results in *d*) activating mutations on catalytic subunit of PI3K, *e*) activation of Src kinase family, and *f*) activation of RTK including c-Met, IGF-IR, and activating truncation form of HER2. In $BRAF^{V600E/K}$ melanomas, blocking kinase activity of mutant BRAF with Zelboraf or Tafinlar can *g*) induce active dimerization between CRAF and kinase-dead mutant BRAF that drives ERK activation, *h*) trigger activating mutation on MEK and *i*) RAS, or upregulate *j*) MAPK3K kinase COT and *k*) RTKs including PDGFR, EGFR, and FGFR. In the cancer environment, growth factor HGF overexpression is also reported to contribute to BRAFi resistance (*l*). All these genetic and/or epigenetic remodeling can empower cancer cells to activate the proliferative and survival pathways, MAPK and PI3K/Akt, to overcome kinase inhibitor-induced apoptosis.

and HER2-dependent angiogenesis (111). HER2-positive patients initially respond well to trastuzumab, but similar to other targeted therapies they often relapse within ~1 year of treatment, suggesting an acquired resistance promoting escape from HER2 blockade. Similarly, resistance to lapatinib, an FDA approved Her2 small molecule inhibitor, occurs rather fast (40, 302, 308). Several potential mechanisms of acquired resistance have been investigated.

In HER2-positive breast tumors including both primary and metastatic lesions that do not respond to trastuzumab, downstream activating mutations of the catalytic subunit of PI3K have been discovered (15). Mutant PI3K constitutively activates Akt-dependent cell proliferation and survival. Such hot spot mutations of PI3K are not only responsible for acquired resistance but also intrinsic primary resistance to trastuzumab. In fact, PI3K was identified as the most important mediator downstream of HER2 signaling in resistant breast tumors, in which PTEN, the negative regulator of PI3K, is simultaneously downregulated (191). Co-inhibition of PI3K overcomes trastuzumab resistance, placing PI3K as an essential co-target in future HER2 therapies (117, 326). This therapeutic strategy has been under evaluation in preclinical models and potentially provides clinical benefit (198). In addition to oncogenic mutations of PI3K, activating splicing of ECD of HER2 was also discovered in tumors resistant to trastuzumab. Masking of the antibody-binding site within the ECD leads to a silent response of HER2 to trastuzumab without impairing its intracellular signaling as shown by its capacity of maintaining hyperactivation of PI3K/Akt (6, 244), which in contrast is abolished by lapatinib (243). This indicates that the truncated HER2 with loss of trastuzumab recognition is potentially persistently active, which is partially confirmed in a recent report (30). Recent studies also revealed a nuclear fraction of the truncated form of HER2 that may also contribute to resistance (315). Another form of HER2 splicing is the truncation within its ECD, resulting from the deletion of exon 16. Tumors carrying this truncation showed increased growth, metastasis (4), and dimerization activity of HER2, resulting in antagonizing trastuzumab-induced complex disruption (177). Interestingly, this splicing variant was sensitive to trastuzumab in a mouse xenograft model. Therefore, it was suggested that this splicing variant may predict the likelihood of acquired trastuzumab resistance (32). Somatic HER2 mutations have been occasionally found in some tumors but are rarely associated with increased HER2 expression levels. It is unclear how or if these mutations contribute to cancer development and drug resistance.

With the support of more sensitive NGS technologies, a few activating mutations were identified in human breast cancers (9, 26, 66, 195, 255, 276). The roles of such emerging mutations are still being characterized, and the current data support the notion that some point mutations are possibly responsible for either primary or acquired resistance to HER2-targeted therapies (5, 21). In addition to the gain-of-function mutations of PI3KCA, increased activity of Src kinase in response to HER2-targeting has been shown to activate downstream PI3K/Akt bypassing HER2 in resistant breast cancer cells (212). Similar to PI3KCA, co-inhibition of Src kinase overcomes lapatinib-elicited resistance in vivo (230). Enhanced Src activation is also triggered by ECD masking with trastuzumab, and co-targeting both HER2 and Src has demonstrated synergistic effect in animal models (334). These observations provide a scientific rationale for Src kinase as a core component of targeted therapies in breast cancer (3, 268). Furthermore, induced overexpression of other oncogenes, mainly receptor tyrosine kinases, also contributes to resistant phenotypes compensating HER2 deactivation in resistant tumors. For example, IGF-IR overexpression can override trastuzumab-induced tumor regression through rescue of the cell-cycle program (154), which could be reversed upon blockade of IGF-IR (113). Consistent with this observation, enhanced oligomerization between HER2 and IGF-IR was observed in trastuzumab-resistant breast cancer cells (107, 149). Another key regulator of trastuzumab resistance is c-Met (257). c-Met is also reported to be overexpressed in a subset of invasive breast cancers and correlates with poor outcome (119, 321). Interestingly, c-Met was found to form active protein complexes with HER2 in NSCLC, implying a synergistic role in driving downstream PI3K/Akt and ERK signaling **(FIGURE 4)**.

Some members of the mucin protein family, such as mucin-1 and mucin-4, were also found upregulated and masked the trastuzumab-binding site on HER2 in resistant breast cancer cells (76, 192). It was also reported that dimerization of HER2 and HER3, rather than EGFR, plays an essential role in mediating downstream PI3K/Akt signaling (139). This dimerization pattern is not readily disrupted by trastuzumab (1), and increased HER3 expression upon TKI treatment may effectively enhance HER2/HER3 interaction (252), thus contributing to a reduced response to HER2 targeting. Following this rationale, disruption of dimerization with pertuzumab (Perieta, Roche), another FDA-approved humanized blocking antibody that specifically targets dimerization functionality of HER2, dramatically restored sensitivity to trastuzumab treatment (13, 27, 143). This synergistic efficacy was also confirmed in a clinical study (12).

C. Resistance to Mutant BRAF^{V600}-Targeting Therapy in Metastatic Melanoma

Approximately 50% of metastatic melanomas harbor an oncogenic mutation on BRAF which acts as a major driver to fuel out-of-control proliferation of tumor cells through MAPK signaling. Among the human melanomas with a

gain-of-function mutation on BRAF the substitution on V600 is: V600E (~70%), V600K (10~15%), and V600R (3~7%). V600E/K mutations biochemically mimic the phosphorylation-dependent active conformation of wild-type BRAF, thus resulting in constitutive activation as a monomer in a RAS-independent manner. Although ARAF and CRAF share high sequence similarity with BRAF in the kinase domain, mutations of ARAF or CRAF are very rare. BRAF mutations are not only restricted to melanoma, but also frequently detected in thyroid cancer (30~70%), ovarian cancer (~30%), and colon cancer (~10%) (51). Therefore, targeting mutant BRAF is a promising therapeutic strategy.

Two FDA and EMA approved small molecular BRAF inhibitors (BRAFi), vemurafenib/Zelboraf and dabrafenib/Tafinlar, specifically inhibit the BRAF kinase activity and lead to prolonged overall survival of melanoma patients (272). However, the majority of patients stop responding to BRAFi within 6–9 mo (36), indicating an acquired resistance to BRAFi. BRAFi-induced resistance can be mediated by several different mechanisms **(FIGURE 4)** including re-dimerization of the kinase-dead form of mutant BRAF with endogenous CRAF (96, 221), unfavorable disruption of the ERK-dependent negative feedback signaling loop (148), acquiring activating mutations of RAS and MEK (23, 67, 298, 300), upregulation of other pro-oncogenic kinases, such as COT (115), RTKs [platelet-derived growth factor receptor (PDGFR), EGFR, and fibroblast growth factor receptor (FGFR)] (193, 319) or RTK ligands like HGF (279). All of these mechanisms ultimately trigger the reactivation of MAPK and PI3K/Akt signaling that support melanoma cell survival. In fact, despite those spontaneously occurring mutations of RAS, MEK and possibly other undiscovered oncogenes, targeting mutant BRAF simply enhances physiological RAS/RAF/MAPK signaling in three ways. First, BRAFi induces self-activation of RAF signaling through an existing downstream feedback loop. This effect is essentially achieved through ERK-dependent transcriptomic programming of physiological inhibitors of RAF kinases (148, 222) or direct phospho-inhibition of physical binding between RAS and RAFs (60, 233). As a consequence, transient downregulation of ERK may also lead to proliferative activation of another pathway, mTOR/PI3K/Akt, through signaling cross-talk mediated by ERK (38, 214). Prolonged exposure of cancer cells to BRAFi eventually reactivates ERK. This indicates a fundamental role of ERK reactivation in BRAFi resistance. Indeed, ERK activation is a universal phenotype for both BRAF- and MEKi-induced resistance (95, 184). Simultaneous blocking of mutant BRAF and MEK improves anti-tumor activity of BRAFi (77, 152). On the basis of three positive phase 3 trials, the combination of BRAF (vemurafenib, dabrafenib) and MEK inhibitors (cobimetinib, trametinib) is a new standard for BRAF mutant melanoma. Second, BRAFi transactivates RAF signaling, mimicking functional assembly of a wild-type signalosome. Functional RAF signaling requires dimerization of RAF family members such as BRAF and CRAF to drive downstream MAPK activation. This is triggered by upstream RAS signaling in a CRAF-dependent manner. In melanoma cells with mutant BRAF, unlike the dimerization-dependent activation of wild-type RAF, $BRAF^{V600E/K}$ performs its kinase function as a monomer. BRAFi treatment only blocks its kinase activity but disguises the kinase-dead form as a "wild-type" BRAF that still has the capacity to dimerize with CRAF. As a consequence, the entire MAPK pathway is reactivated in this setting. Third, BRAFi can induce RTK signaling through a feedback loop. Feedback-induced overexpression includes PDGFR, HER3, and RAS, which potently promotes Akt phosphorylation through classical RTK/PI3K/Akt signaling (280). Investigating BRAFi resistance has unravelled a complex intracellular signaling cross-talk whose deregulation leads to unresponsiveness to targeted therapies.

D. Inhibition-Enhanced Activation: Feedback and Cross-talk Loops of PI3K/Akt/mTOR Axis at a Glance

The physiological roles of PI3K/Akt in gate-keeping cell proliferation and anti-apoptosis place this pathway as one of the most important defensive signaling cascades. This vital function is often malignantly hijacked due to an increased demand of metabolism in pathological contexts. In almost all cancer types, PI3K/Akt pathway is deregulated and essential for cancer cell proliferation. Tumor relapse from drug resistance also strongly relies on Akt-dominated anti-apoptosis. Thus targeting this signaling axis could potentially induce cancer cell death. Many different small-molecule inhibitors and biological substances specifically targeting each component along this pathway are currently in clinical studies. Although in vivo studies in cancer-modeled mice show a profound benefit in attenuating tumor growth and abrogating therapy-induced drug resistance through mono-targeting PI3K, Akt, and mTOR, or by dual-inhibition of PI3K/mTOR, inhibition of PI3K/Akt/mTOR also elicits resistance through feedback loops similar to other targeted therapies.

Several mechanisms are involved in inducing resistance. The first important mechanism is the interference of a pathway with its own physiological self-regulating feedback loop **(FIGURE 5)**. Nutrient-stimulated Akt activation through insulin and insulin growth factor-like receptors (IR and IGF-IR, respectively) is the major driver of downstream signaling in a physiological context. Along this signaling axis, the p85 regulatory subunit of PI3K is recruited to IR/IGF-IR through the insulin receptor substrate (IRS), an adaptor protein that anchors the assembly of the active PI3K kinase complex. Upon activation, Akt triggers the activation of ribosomal protein S6 kinase (S6K) and 4EBP-1 in a mTOR-dependent manner (135–137, 262).

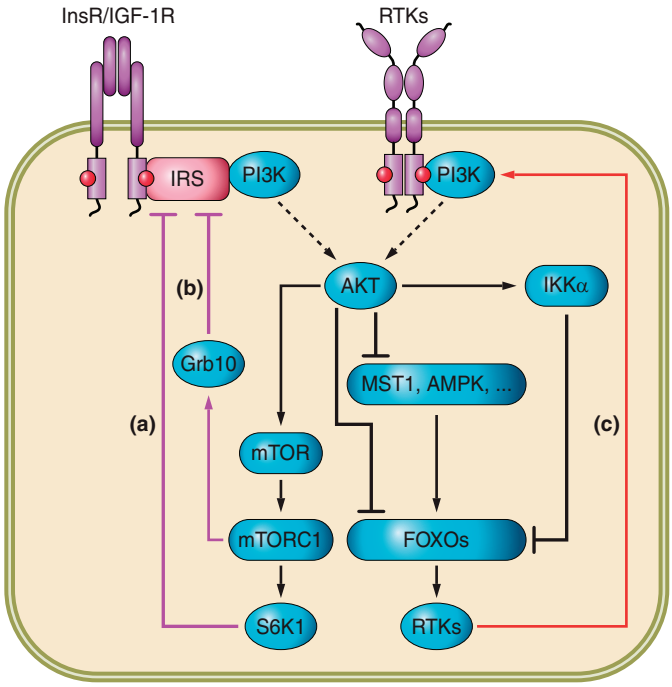

FIGURE 5. Physiological negative-feedback regulation and bypassing activating signaling loops of PI3K/Akt/mTOR pathway. PI3K/Akt/mTOR activation is initiated through PI3K by binding to RTKs. This process can be direct or mediated by a linker protein such as IRS. Under physiological conditions, insulin signaling is a strong driver of PI3K activation, which subsequently leads to ribosomal protein S6 kinase (S6K1) activation. To avoid unwanted PI3K activity, S6K1 is able to phospho-inhibit IRS that promotes the dissociation of PI3K from InsR or IGF-1R to reduce PI3K activity (*a*). Activated mTORC1 can also phosphorylate Grb10, an adaptor protein that interferes with IRS binding to InsR/IGF-1R, an alternative route to control PI3K activity (*b*). Several RTKs are transcriptionally regulated by FOXO proteins whose activities are negatively regulated by Akt through direct phosphorylation. Indirectly, Akt is able to activate IKK signaling that inhibits FOXO, or Akt inhibits MST1 and AMPK which activate FOXOs. Upon inhibition of PI3K/Akt, FOXO proteins rapidly translocate into nucleus and form active transcriptional complex that drives mRNA expression of RTKs (*c*).

Physiological homeostasis of metabolism is maintained through negative feedback signaling of S6K-driven phosphoinactivation of IRS, which avoids overtime activation of the PI3K/Akt/mTOR pathway (176). In addition, another parallel route was also discovered: mTORC1 phosphoactivates growth factor receptor-bound protein 10 (Grb10) (103), an adaptor protein that negatively regulates the activities of IR/IGF-IR and IRS (329). As a result, cooperation of these two major negative feedback loops provides a balanced Akt activity for proper cell proliferation. In parallel, activation of Akt sequesters transcription factor FOXO proteins in the cytoplasm through direct phosphorylation. FOXO proteins are considered negative regulators of cell proliferation through transcriptional inhibition of cell-cycle promoters like cyclin D (247) and through induction of several cell-cycle blockers, such as p21 (53) and p27 (57, 170). On the other hand, FOXO proteins are also involved in other cell functions such as driving RTK expression directly through transcriptional regulation. This is interesting because, for example, FOXO 1, 3, and 4 have been found to upregulate platelet-derived growth factor receptor (PDGFR) in neuroblastoma, a childhood malignancy (171). Additionally, other RTKs like insulin and insulin-like receptors (InsR and IGF-IR) (164), HER2 and HER3 (34, 82, 253) are emerging as transcriptional targets of FOXO family members that closely associate with the PI3K/Akt/mTOR activities in different cancer types. Moreover, several studies also pointed out the importance of the transcriptional interregulations between FOXO proteins (72). Due to the oncogenic demand for accelerated metabolism, RTKs including IR/IGF-IR signaling are often hyperactivated, thus continuously providing energy equivalents to fuel Akt activation (218). In addition to Akt, the IκB kinase (IKK), a downstream substrate of Akt, was also shown to phosphoinhibit FOXO activities (106), further preventing an unwanted activation of RTKs and cell apoptosis in stress conditions.

Interestingly, some proapoptotic kinases such as MST, the mammalian Hippo ortholog, and stress-activated AMP-activated protein kinase (AMPK), which are both inhibited by Akt, can directly phosphoactivate FOXO family members (62, 91, 141, 294, 331). This remarkable increase of PI3K/Akt activity in cancer cells quarantines their survival phenotype while antagonizing genomic instability-triggered apoptosis through (at least partly) FOXO transcription factors. In this regard, blockade of PI3K/Akt/mTOR pathway has been considered as one of the most promising strategies to suppress cancer cell proliferation. This concept has indeed been proven in a number of clinical studies with monospecific or dual-specific compounds targeting the PI3K/Akt/mTOR pathway. Everolimus, Temsirolimus (both mTOR inhibitors), and Idelalisib (a PI3Kδ inhibitor) have been approved for clinical use. However, based on the emerging image of the signaling landscape of autoregulation and compensatory reactivation (240), it is assumed that inhibition of PI3K/Akt/mTOR will eventually activate upstream RTK signalosomes. This multi-faced reactivation of RTK-mediated signaling reupregulates a variety of downstream oncogenes, which then leads to resistance to targeted inhibition therapies (125, 150, 188, 249).

IV. TUMOR HETEROGENEITY PROMOTES RESISTANCE

Tumor heterogeneity, namely, the intertumor and intratumor diversities, has been realized for a long time in clinic (99, 273) and is confirmed with improved sequencing technologies (14). Such diversities promoted through stemness of cancer cell and clonal evolution, and reflected by cell morphology, gene expression profile, metabolic, proliferative and migratory patterns have been observed in many types of cancer (254). Genetically, extrinsic factors such as exposure to radiation and cytotoxic reagents, as well as intrinsic genomic instability induce somatic driver muta-

tions (22, 58, 85) to allow accelerated cell proliferation and actively resist to environmental stress. Furthermore, such genetic heterogeneity is often accompanied by epigenetically induced deregulation of gene expression and pathway activation to elevate genetic plasticity that is in favor of cancer cell survival (282, 327).

Evolutionary reprogramming of tumor genome frequently correlates with decreased sensitivity in response to chemotherapy (56). The selective clonal expansion supports tumor cells to better adapt to stress conditions. In addition to the preexisting somatic driver mutations in certain tumor-initiating cells that actively accelerate their cell cycle, deactivation of single oncogenic signaling axis by targeted therapies ultimately triggers Darwinian selection to guide continuous cancer cell proliferation. This passive process leads to rapid growth of those cancer cells that are insensitive to the therapies. In fact, emerging studies have shown that the selectively expanded cancer cells are the source of tumor malignancy and account for tumor relapse in cancer patients (166, 236). The relapsed tumors often become more heterogeneic (197) and decline the response to cytotoxic reagents. A better studied model is the core node driving cell survival, the PI3K/PTEN/Akt pathway. In melanoma patients with disease progression posttreatment, the resistant tumors exhibited branched evolution marked by high frequency of oncogenic driver mutations along PI3K/PTEN/Akt and MAPK pathways (124, 260), indicating that the melanoma genomic heterogeneity is the key factor responsible for reduced efficacy of BRAFi treatment. Similarly, the PI3K mutation (H1047R) can activate a multipotent genetic program and cell plasticity at the early stage of breast tumor initiation and establish future intratumoural heterogeneity (128, 295). Independent clinical trial studies have also demonstrated that rapid clonal expansion of the cells harboring oncogenic mutations correlates with worse responsiveness (160, 197) and accelerated malignancy (245, 291). Taken together, tumor heterogeneity is an essential factor responsible for drug resistance through clonal evolution and expansion (185). As a consequence, current targeted chemotherapies fail to provide considerable survival benefit to the cancer patients due to the lack of systematic targeting of these genetically evolved, selectively expanded clones that escape from the targeted therapies. Therefore, functional targeting of individual oncogenic pathways is unlikely an effective therapeutic strategy; rather, it is more important to investigate the details of genetic divergence in each tumor, to design personalized, targeted combination therapies to avoid the selective enrichment of the insensitive clones. This has been demonstrated by recent efforts on strategic combination therapies that have shown promising potentials as effective therapies (144, 187). In addition, antibody-mediated specific cytotoxic targeting that directly and rapidly kills the cancer cells may effectively suppress clonal expansion and overcome drug resistance (65, 165). These ongoing studies strongly imply that heterogeneity may be used as a biomarker in clinic for determining personalized therapy (84), and targeting tumor heterogeneity resulted from deregulation of DNA-repair machinery (123, 237) and the gateway of gene activation (93, 263) in cancer cells emerges as a fundamental strategy to kill cancer cells.

V. IMPACT OF DEFECTIVE IMMUNOSURVEILLANCE IN RESISTANCE

It has been known for a long time that tumors are surrounded by diverse types of immune cells that impact tumor progression. Data from clinical studies have revealed that infiltration of certain types of immune cells, such as T helper 2 (Th2), regulatory T cells (Treg), T helper 17 (Th17), as well as macrophages and neutrophils can be associated with a poor prognosis (79, 92, 219, 228, 241), indicating a tumor-promoting role of a deregulated immune response. Tumor-infiltrating lymphocytes (TILs) are directed towards the tumor vicinity through individual chemokine signaling (318). Trafficking of TILs to this region often leads to a biological remodeling of the tumor microenvironment mediated by the local enrichment of secreted factors, which consequently signal to cancer cells to promote or suppress the anti-tumor functions of the TILs (45, 87). In addition to the cancer cell-TIL interaction, TIL-TIL interaction can also contribute to deregulated immune response such as infiltrating $CD4^+$ T-cell-mediated macrophage differentiation from M1 to M2 stage (55). At the same time, there is evidence indicating that the infiltration of tumors by $CD8^+$ effector cells can improve the prognosis of certain cancer entities. However, upon survival of intrinsic or extrinsic stress, including host immune defense, cancer cells actively disregard the host immunosurveillance and gain tolerance (61). Therefore, extensive studies have been focusing on the characterization of the unique roles of individual type of lymphocytes towards to their clinical value as biomarkers.

This neglect of the immune defense can be governed by T-cell anergy (190) and direct suppression of host immune cell functionality by cancer cells (54, 297). Selected cancer cells that survive environmental stress such as chemo- or radiotherapy are capable of undergoing genetic and/or epigenetic modifications to evade immune detection, an organized process called cancer immunoediting (248). As a consequence, this gain-of-capacity generally increases the malignancy of cancer cells. Under physiological conditions, the immune activity is attenuated through inhibitory signaling networks, among which the members of B7 protein family play a predominant role. B7 proteins, including B7-1, B7-2, B7-H1 (also called programmed cell death ligand 1, PD-L1), and B7-DC (also called programmed death ligand 2, PD-L2), are expressed on the surface of infiltrating lymphocytes with differential preference in distinct cell lineages (90). Negative feed-forward signals direct the inhibition of TCR-mediated proliferation to prevent tissue damage from

unfavorable immune responses through intercellular pairing with their targeted receptors, such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4, for B7-1 and B7-2) and programmed death 1 protein (PD-1) expressed on T cells, macrophages, dendritic cells (DCs), B cells, and NK cells (39). Under pathological conditions, disruption of this homeostatic regulatory machinery leads to T-cell apoptosis, thereby helping cancer cells to evade an immune attack (208). Advances from recent studies discovered significant basal level of PD-L1/2 on the surface of cancer cells (179, 211). The overexpression of PD-L1/2 empowers cancer cells to subvert the action of the immune system (116, 293). It has been observed to achieve this by blocking the signaling interaction PD-1/PD-L1/2 and B7-1/2/CTLA-4 between cancer cells and host immune cells potently inducing apoptosis of resistant cancer cells (293, 322). This indicates another resistance mechanism stemming from an unfavorable deactivation of the immune response and possibly triggered by targeted therapies **(FIGURE 6)**. Interestingly, PD-L1 expression is tightly associated with and possibly controlled by PI3K/Akt activation (318). This is consistent with the observation of downregulated PD-L1 expression by specific inhibition of Akt with pharmacological inhibitor MK-2206 in triple-negative breast cancer (179). Although the underlying molecular mechanisms are not yet fully understood, this signaling route seems to be a universal event as it was also reported in prostate cancer (46), mutant BRAF-harboring melanoma (7, 114), pancreatic cancer (336), and human glioma (210). Furthermore, overexpression of PD-L1 in tumors has been found to correlate with poor clinical prognosis, and its expression status could be useful to predict drug resistance (168, 169).

VI. CURRENT STRATEGIES TO OVERCOME RESISTANCE

Developmental homeostasis requires meticulous and tightly regulated switching of signaling activation. This is commonly achieved through functional interactions between different pathways. A representative module is the interplay between PI3K/Akt, MAPK and the Hippo pathways in which integral interactions of both help maintain proper cell proliferation and organ size. Despite the self-regulated feedback loops **(FIGURE 5)**, inter-inhibitory mechanisms between PI3K/Akt and MAPK signaling were also widely acknowledged (172, 275). Activated Akt can attenuate MAPK signaling by phospho-inhibition of Raf (180, 338), or indirectly through the mTORC1/S6K/IRS1/RAS/MAPK signaling feedback loop. Active ERK can also mediate the inhibition of IRS1 through phospho-activation of raptor-dependent mTORC1/S6K signaling (29) or inhibition of TSC1/2 (159). Such inverse inter-regulation has been confirmed in vivo (28). Moreover, with its suppressive function, Hippo signaling is involved in the regulation of PTEN, thus preventing over-activation of PI3K/Akt through p53

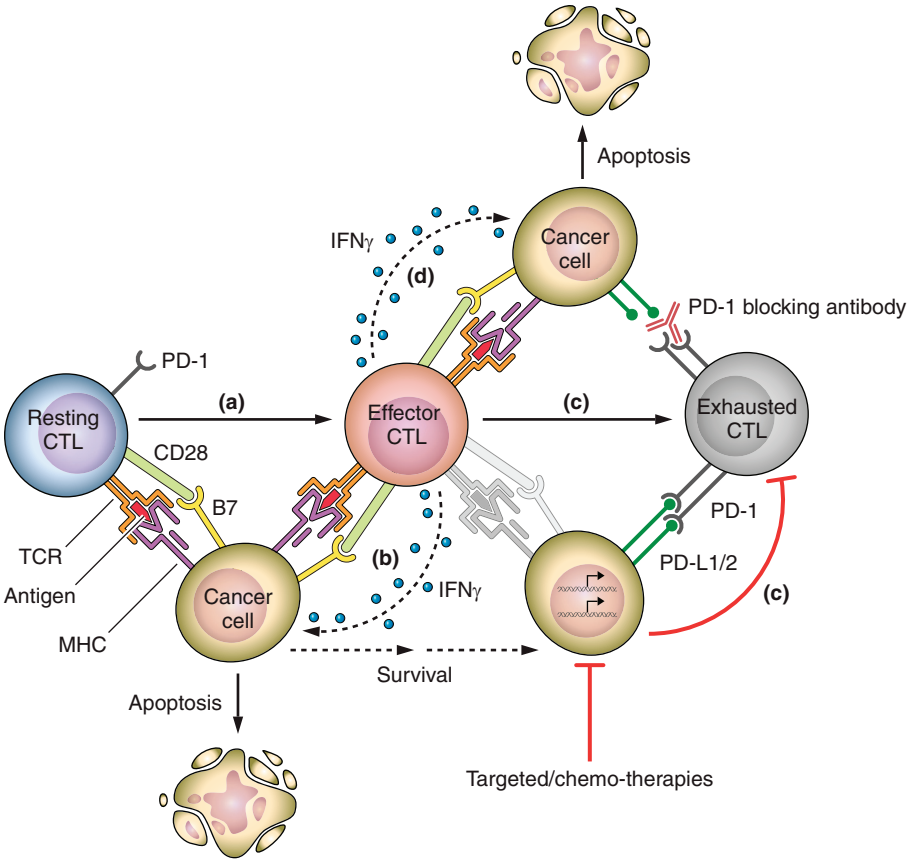

FIGURE 6. Mechanisms of cancer cell-mediated CTL activation and inhibition. Upon activation of CD8+ T cells mediated by binding to a cancer cell through TCR/Ag/MHC and CD28/B7 formation, resting CD8+ T cells are activated to become effector T cells (*a*) that release pro-apoptotic molecules like IFNγ that mediate apoptotic death of the vast majority of cancer cells (*b*). However, cancer cell survivors from T-cell attack may evolve to increase the expression level of B7 family members like PD-L1/2, which binds to PD-1 on the surface of CD8+ T cells. This interaction masks the formation of functional complex TCR/Ag/MHC and CD28/B7 and consequently induces T-cell exhaustion to protect cancer cells from immunosurveillance (*c*). Clinical targeted therapies often upregulate PD-L1/2 expression on the cancer cell surface. When this inhibitory interaction is disrupted with PD-1 blocking antibody, T-cell exhaustion is inhibited, and the killing effect is restored due to reaccumulation of functional cytotoxic T cells (*d*).

(274, 330, 335). Given the importance of shared signaling nodes downstream of a number of signaling cascades, it is not surprising that a compensatory activation will be triggered upon deactivation of any pathway. In fact, this is frequently reflected by the outcome of drug resistance in clinical monotherapies of cancer. Therefore, combination therapies including bispecific inhibition that simultaneously block compensatory activation of self or parallel signaling axes come to the center stage, and several clinical trials have shown clinical benefits to this over monotherapies. As mentioned above, two phase III studies of coinhibition of mutant BRAF and MEK with dabrafenib and trametinib in melanoma patients increased the overall survival compared with dabrafenib monotherapy (151, 234) (Combi-d trial: ClinicalTrials.gov Identifier NCT01584648; Combi-v trial: ClinicalTrials.gov Identifier NCT01597908). Combination between chemotherapy, trastuzumab, and pertuzumab has also become the standard of care in Her2-positive breast cancer patients (288), and another combined chemotherapy also exhibits significant advances in treating triple negative breast cancer patients (118). Other combinatorial strategies, such as cytotoxic reagents paired with several negative immunologic regulators, have been explored and seem to be promising (101, 138, 158, 229). Certainly, it will be interesting to investigate the therapeutic outcome when targeted kinase inhibition is combined with immunotherapy (105). A number of trials are currently running.

VII. DISCUSSION AND PERSPECTIVE

A. Targeting Oncogenic Mutations

Physiological signaling supports cell proliferation, differentiation, migration, and acute responses to overcome epigenetic and genetic stress. Functional interplay between pro-survival and pro-apoptotic signaling ensures homeostatic development. When the metabolic stability in a cell is interfered with and eventually disrupted, the cell fate becomes uncontrollable, often resulting in an accelerated cell cycle and a high degree of genomic instability that triggers further oncogenic mutations. Therefore, the development-oriented signaling cross-talk is a key factor to be considered for targeted inhibition. The first generation of small RTK inhibitors shares similar mechanistic actions and are generally reversible, such as FDA-approved gefitinib and erlotinib for NSCLC therapy. They competitively bind to the catalytic domain of EGFR to inhibit the phosphorylation of key tyrosine residues in a reversible manner. Although these types of inhibitors are effective, the majority of the patients stop responding to the therapy and inevitably acquire resistance in a rather short period of time. Such resistance can broadly be categorized into two types: "self-activating" and "nonself-activating." Self-activating resistance results from the reactivation of on-target or on-pathway elements, while nonself-activating resistance is mediated through alternative targets or pathways. On-target reactivation is often associated with acquired or clonally expanded mutations that desensitize the cancer cells to inhibitors, for instance, T790M mutations of EGFR in gefitinib-resistant NSCLC (206). Similarly, a substantial number of on-target mutations directly linked to resistance have been discovered, such as KIT (97) and ALK (242); on-pathway resistance can be mediated by either activating mutations or genomic amplifications on different components along the same pathway, which is represented by the MEK mutation upon $BRAF^{V600E}$ inhibition (67, 298) and PI3KCA gene amplification in resistance to trastuzumab (15). The second-generation inhibitors (200) aiming to overcome this drawback specialize in irreversible binding to the adjacent sites of the kinase pocket that form stable covalent bond. For example, the second-generation EGFR inhibitor afatinib potently circumvents $EGFR^{T790M}$-induced resistance to gefitinib (68). Nevertheless, it is also important to point out that such irreversible inhibition may target structurally similar members of the same family, including wild-type kinases. The persistent inactivation of physiological required enzymes with this class of irreversible inhibitors may cause relevant toxicity (121, 323). With the help of next-generation sequencing technology, the spatial and temporal resolution of specific clonal sequences of the tumor is dramatically improved and drives the discovery of genetic alterations that are druggable. Selective targeting of non-self oncogenic targets may substantially reduce toxicity, increase specificity, and avoid emergence of resistance.

B. Targeting Gene Amplifications

As described above, oncogenic amplification without activating mutation is another factor driving drug resistance in cancer **(FIGURES 2 AND 4)**. Amplified genes can be on both the "self-pathway" and on "non-self pathways." Mechanistically, gene amplification can "mistarget" the physiological feedback loops in the signaling network. To overcome this type of resistance, two major approaches are being explored in clinical studies. The first approach is a "combinatory blockade," namely, simultaneous targeting of two or three proteins as a cocktail therapy. Clinical data have already shown significant benefit through enhanced anti-tumor potency and delayed drug resistance. Cotargeting several cancer markers is not only applicable to the activation of non-self pathways but also to the activation of the downstream components on the same pathway (37, 104, 152). The other approach is to optimize the drug doses and schedules. It was shown that the dose of imatinib in clinical phase II and III studies can influence on-site occurrence of resistance (18, 19), so the dosing schedule could also potentially be a critical factor to attenuate vemurafenib-triggered resistance in melanoma therapy (50).

C. Targeting Cancer-Directed Immunosuppression

Recent advances in understanding the exhaustion of immune cells in the cancer environment significantly evoke the importance of immunotherapy. With the discovery of cancer cell-direct blockade of immunological checkpoints, in particular by CTLA-4 and PD-1 signaling, the therapeutic strategies have rapidly shifted to immunotherapy. As a consequence, we have seen a large number of trials with anti-CTLA-4 and anti-PD-1/PD-L1 antibodies, which reactivate the anti-tumor responses of the human immune system, resulting in durable and long-lasting responses in some cancer patients. However, similar to the on-targeted therapies, such checkpoints are intrinsically important for homeostatic immune reaction. Thus prolonged activation of a T-cell response potentiates toxicities in many different tissues/organs (306, 307); in some cases this can be severely detrimental to the patient (102). So, although immunotherapy targeting the checkpoints CTLA-4 and PD-1/PD-L1 has convincingly demonstrated a therapeutic benefit in a variety of malignant cancers, further studies on optimizing dose and schedule are required for clinic safety. Currently it is foreseen that, in combination with TKIs, interference with the checkpoint regulation in cancer may not only suppress the activities of the hyperactivated oncoproteins, but also induce anti-tumor memory of the immune system, achieving the synergistic effect from two directions. Although promising, relevant safety issues became evident in a few clinical trials that have been ongoing to evaluate a combination between immunotherapy and chemotherapy or targeted therapy (231). In fact, more observations have emerged that in certain circumstances the resistance to targeted therapies essentially associates with suppressed anti-tumor activity of T cells and results from impaired immune checkpoint controls (169). A number of immunological regulators are dysregulated despite adequate CTLA-4 and PD-1/PD-L1 function. Clearly, future discoveries of novel targetable checkpoint regulators hold the promise to strengthen the immunologic anti-tumor efficacy.

D. Targeting "Histologic Transformation"

It is also suggested that "histologic transformation" may cause acquired resistance. This category mainly includes epithelial-mesenchymal transition (EMT) (267, 299) and phenotypic changes (such as from NSCLC to SCLC) (251). EMT is also a key event during embryonic development at an early stage. Such a transition is crucial for cell migration and differentiation and exhibits high plasticity to facilitate cell fate and organ formation. EMT has been shown to support cancer cell anti-apoptosis and metastasis; therefore, it is also hypothesized to contribute to resistance. Nevertheless, due to its highly dynamic and plastic nature, it is still unclear whether and how EMT mechanistically promotes acquired resistance. In addition, while EMT is demonstrated in established cell lines and animal models, it is much more difficult to be identified in human tumors. Although some of these EMT-drivers do not seem to be important during postnatal development but are upregulated in metastatic cancers (for example, Twist; Ref. 316), it remains to be determined whether they are suitable targets for therapy.

Taken together, a better understanding of the mechanisms of cancer drug resistance is ultimately the driving force to develop novel therapeutic tools in the future.

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GRANTS

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DISCLOSURES

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