EMT Twists the Road to PI3K

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Summary: Epithelial-to-mesenchymal transition (EMT) is important for many developmental events and has been linked to tumor dissemination and therapeutic resistance. Salt and colleagues identify how EMT affects how proliferation signals flow to phosphoinositide 3-kinase in non–small cell lung cancer. Cancer Discov; 4(2); 149–51. ©2014 AACR.

See related article by Salt et al., p. 186 (3).

Originally identified as a key developmental process, epithelial-to-mesenchymal transition (EMT) has since been implicated in many aspects of cancer biology. EMT is a dynamic process with cells transitioning in either direction between the epithelial and mesenchymal differentiation states. Heterogeneity within a tumor is often observed with respect to the broad range of phenotypes along the EMT spectrum, as well as a range of differentiation states. As mesenchymal cells are more motile and invasive, the mesenchymal phenotype has been linked to increased invasion/metastasis in multiple types of cancer. In addition, EMT has been associated with the acquisition of cancer stem cell characteristics and, ultimately, poor patient prognosis (1). A growing body of evidence indicates that epithelial cells are more likely to initially respond to therapy, and an EMT is often observed in cancers that acquire resistance to treatment (2). Therefore, it is critical to uncover the mechanistic details underlying the induction of EMT and the resulting phenotypic changes. So far, the TGF-β signaling pathway has been identified as a primary driver, and a group of transcription factors, including Twist, Snail, Slug, and ZEB1, has been shown to be essential in invoking the broad range of phenotypes associated with the mesenchymal cell type (1). Less clear are the modifications to the signaling networks that regulate proliferation and survival occurring as a result of an EMT and that can lead to targeted therapeutic resistance. The differential ability of epithelial and mesenchymal cancer cells harboring the same driver oncogene to survive in the presence of a targeted therapy serves as evidence to suggest that rewiring of these pathways is occurring under selective pressure in cancer cells, but the overall scope and specific details of these changes are not yet well understood.

The study by Salt and colleagues (3) in this issue of Cancer Discovery used Twist- and Snail-inducible expression models of EMT to shed light on the changes in phosphoinositide 3-kinase (PI3K)-Akt pathway signaling that occur following an EMT in KRAS-mutant non–small cell lung cancers (NSCLC). Using this model, the authors showed that transition toward the mesenchymal state renders the cells more dependent on serum. This was explained by an neuregulin-1 (NRG1)-ErbB2 autocrine loop present in the epithelial state but lost in the mesenchymal state. Comparison of key proliferative signals indicated that the PI3K-Akt pathway, but not the extracellular signal–regulated kinase (ERK)1/2 [mitogen-activated protein kinase 1/2 (MAPK1/2)] pathway, was less active in the mesenchymal cells. Furthermore, the reduction in Akt activity was a result of the loss of its upstream activator, ErbB3, and restoration of ErbB3–Akt signaling could rescue the diminished proliferation of the mesenchymal cells in low serum. In the epithelial state, inhibition of any of the components of the NRG1-ErbB2-Akt pathway was sufficient to impair proliferation. Moreover, in tumor samples analyzed as part of The Cancer Genome Atlas (TCGA), mesenchymal lung cancers had decreased levels of ERBB3 and were enriched for higher expression and/or amplification of the PIK3CA gene.

The authors also explored potential mechanisms by which mesenchymal cells can reactivate Akt signaling to promote proliferation. Exogenous addition of several different growth factors or overexpression of PI3Kα was able to restore mesenchymal cell proliferation in low-serum conditions. Related to this, two recent studies have shown how specific growth factors can provide compensatory signaling and render cells resistant to targeted therapeutics (4, 5). During lineage differentiation, the transition toward the mesenchymal state alters the panel of growth factors that can control cellular proliferation and, consequently, provides a means of therapeutic resistance. Importantly, in the study by Salt and colleagues (3), mesenchymal cell proliferation driven by growth factor treatment can be reversed by the addition of a PI3K inhibitor. Taken together, these data are consistent with a rewiring of PI3K pathway signaling in mesenchymal cells such that it is no longer under the control of ErbB3 and yet still remains essential to the proliferation of these cells (Fig. 1). A number of previous studies have implicated PI3K reactivation in resistance to therapies, including during EMT. For example, in a subset of breast cancers, TGF-β promotes activation of PI3K by upregulating ErbB ligands rather than the receptors themselves to increase ErbB3 phosphorylation (6). Clearly, the specific mechanisms underlying EMT-induced therapeutic resistance would seem to be highly relevant to tumors with mesenchymal features.
reprogramming will be context-specific, which poses a major challenge when developing therapeutic strategies. In addition, recent reports revealing that Akt can phosphorylate Twist1 and lead to further activation of the pro-EMT pathways further underscore the complexity of the networks regulating proliferation and differentiation and the cross-talk that can occur between them (7).

Salt and colleagues’ (3) findings have several potential implications for the treatment of KRAS-mutant lung cancers (Fig. 1). Previous studies have shown that inhibition of both the PI3K and MAP–ERK kinase (MEK) pathways is required for maximal efficacy in this context (8). The toxicity of this combination in the clinic may potentially limit its implementation. Alternative strategies could target the upstream driver of PI3K signaling, which differs between normal tissues and may limit toxicity, increasing the therapeutic window. Recently, it has been demonstrated that different receptor tyrosine kinases (RTK) can promote PI3K signaling in KRAS-mutant cells in a context-specific manner (9). This variability suggests that the most effective inhibitor to combine with a MEK inhibitor may need to be identified on a patient-by-patient basis. Here, proteomics and other approaches might be necessary to identify key RTKs to inhibit along with MEK in each tumor. However, additional in vitro studies are required to determine whether the magnitude of RTK activity correlates directly to the control of PI3K–Akt in this setting.

As noted above, data from the TCGA reveal that PIK3CA expression is upregulated specifically in mesenchymal cells. This could mean that PI3Kα is the major functional PI3K isoform in this context and that PI3Kα-specific inhibitors could be effective at slowing mesenchymal cell growth. These isoform-selective drugs are entering the clinic and their increased specificity will likely lead to fewer side effects, thus raising the interesting possibility that a MEK–PI3Kα inhibitor combination will be less toxic, allowing for a higher dose regimen that could be efficacious in some KRAS-mutant cancers.

Rewiring of signaling is a recurrent theme in therapeutic resistance; to circumvent inhibition by tyrosine kinase inhibitors (TKI), cancer cells frequently use a second RTK to generate a bypass track to reroute key signaling pathways around the inhibited driver oncogene (10). In a subset of EGF receptor (EGFR)–mutant cancers, resistance to EGFR TKIs is conferred by amplification of the MET receptor gene, which then maintains activation of the PI3K pathway (11). In vitro studies on these cancers revealed that in both the pre- and post-resistance cells, PI3K signaling is regulated through ErbB3. In the case of mesenchymal transition, alterations to signaling pathways might provide an additional means of survival to cells no longer relying solely on the driver oncogene and could potentially serve as a target for therapeutic intervention. For instance, mesenchymal NSCLCs resistant to EGFR TKIs have been shown to downregulate EGFR and increase expression of platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR), and AXL (10).

The plasticity of cancer cells allows them to grow and survive despite frequent changes in their environment. The process of
EMT is an example of a dramatic shift in cell state that gives cancer cells the ability to migrate to and colonize a new environment as well as survive therapeutic insult. More generally, even less-dramatic changes in the differentiation state could shift how different extracellular cues regulate proliferation and survival. Indeed, relatively subtle, non-genetic changes might strongly influence the efficacy of targeted therapeutics. For example, highly differentiated NSCLCs are more susceptible to EGFR inhibitors consistent with a strong control of epithelial differentiation and maintenance by EGFR signals. Thus, selective pressure and fluidity along differentiation axes can yield cancer cells that have changed their portfolio of environmental cue dependencies, including growth factors, cytokines, and adhesion molecules. Interestingly, oncogenes such as RAS can cooperate with EMT-inducing signals, implying that some oncogenic drivers might favor EMT as a mechanism of therapeutic resistance (12). Rewiring of cell proliferation and survival pathways such as described by Salt and colleagues (3) provides a specific molecular explanation for these adaptive phenotypes. Future studies should provide additional insights into how different genomic contexts shaped by driving oncogenes can rewire upon differentiation and become susceptible to alternate therapeutic strategies. Ideally, these escape routes will be mapped out in enough detail that they can be suppressed at the onset of treatment, rather than upon the emergence of therapeutic resistance, and can be leveraged to counter intrinsic resistance and improve initial response. Although much remains to be understood about EMT and its impact on prognosis and therapeutics, studies such as the one in this issue (3) have begun to define specific mechanisms underlying the impact of EMT on therapeutic response and provide a road toward better anticancer therapies.

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

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REFERENCES
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