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NEWS AND VIEWS

Metabolic rewiring drives resistance to targeted cancer therapy

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Cancers are diseases of uncontrolled cell growth in which cells acquire mutations that allow for proliferation outside the context of normal tissue development. The genetic events that define tumorigenesis have been, to a large extent, cataloged (Stratton *et al*, 2009; Beroukhim *et al*, 2010). Therapies have been developed that interfere with these defined genetic aberrations (Slamon *et al*, 1989). These targeted agents however have largely achieved only modest clinical results, due to the acquired resistance that invariably and often rapidly follows. Resistance commonly occurs through the acquisition of compensatory mechanisms that bypass the function of the mutated gene (i.e., oncogene) that is targeted pharmacologically (Solit and Rosen, 2011).

In the work by Komurov *et al* (2012), the authors investigated the mechanisms that underlie resistance to the targeted agent, Lapatinib, in breast cancer. Lapatinib is an FDA-approved tyrosine kinase inhibitor that targets EGFR, the epidermal growth factor receptor, along with HER2, a tyrosine kinase frequently amplified and overexpressed in breast cancer. Receptor tyrosine kinases activate downstream signal transduction pathways that coordinate tumor cell growth (Shaw and Cantley, 2006). Breast cancer patients who are treated with Lapatinib often show a rapid and initially positive clinical response. The response however is transient due to the evolution of drug-resistant tumors and the median time to progression over the standard chemotherapy is merely 4.4 months (Geyer *et al*, 2006).

To investigate the molecular mechanisms leading to acquired resistance, the authors developed a model of Lapatinib resistance by engineering a breast cancer cell line resistant to the cytotoxic effects of Lapatinib (Figure 1; Moy *et al*, 2007). The authors cultured a drug-sensitive, HER2-overexpressing breast cancer cell line in the presence of increasing chronic sub-lethal doses of Lapatinib. Clones were isolated that had evolved a greater than 100-fold increased resistance to Lapatinib.

At first glance, one might expect that the resistance mechanism would involve an alternate route to the signal

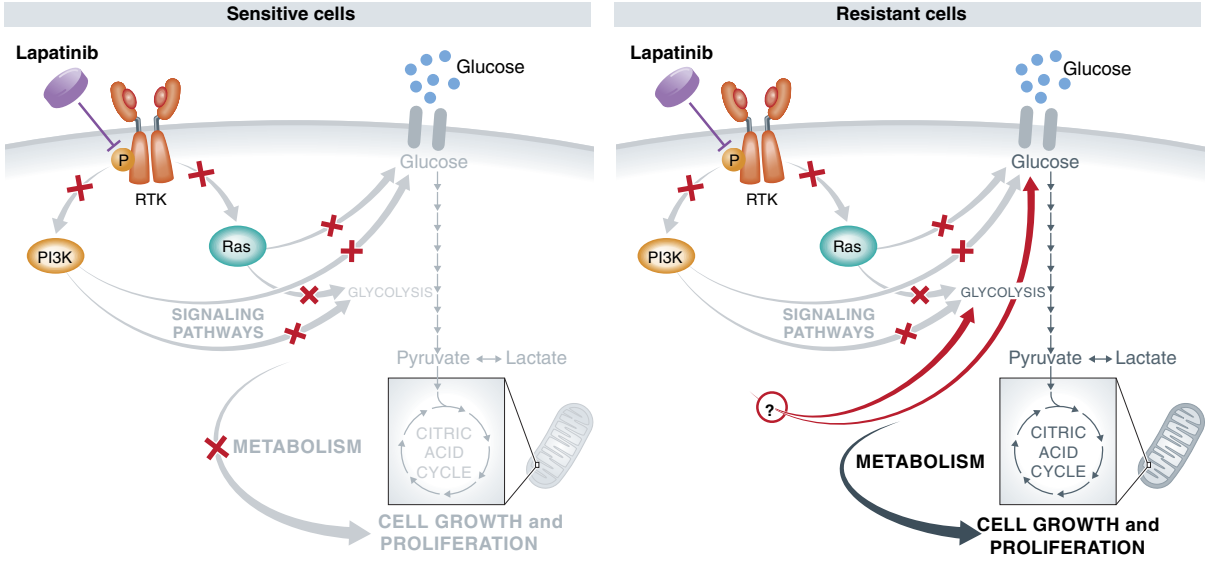

Figure 1 Metabolic adaptations drive acquired drug resistance in breast cancer cells. (Left) In drug-sensitive cells, cell growth and proliferation are dependent on receptor tyrosine kinase (RTK) signaling. RTK signaling induces Ras and PI3K pathway activity that in turn modulates (arrows) multiple aspects of cellular metabolism that are required for cell growth and proliferation. Upon treatment of Lapatinib, RTK signaling is disrupted and activity of its downstream effectors is abrogated. Consequently, Ras and PI3K signaling is inhibited and oncogene-dependent metabolic rewiring is prevented. As a result, cancer cell death is observed. (Right) In drug-resistant cells, the Ras and PI3K pathways remain inhibited by Lapatinib treatment. However, disruption of these signaling pathways is insufficient to alter cellular metabolism and stress responses. As a result, cells remain viable and continue to proliferate in the absence of RTK signaling and Ras and PI3K pathway activity.

transduction pathways that are downstream of the targeted receptor tyrosine kinase, as is often reported. This mechanism would involve the reactivation of the Ras, PI3K and mTOR pathways that are known to drive tumor growth (Shaw and Cantley, 2006). Counterintuitively, acute treatment of the resistant cells with Lapatinib was shown to abrogate the activity of these pathways to a similar extent to that observed in the parental, Lapatinib-sensitive cells. This result is striking because it suggests that the mechanism of resistance possibly occurs downstream of the immediate canonical growth factor-mediated signal transduction pathways involving Ras, PI3K and mTOR.

Identifying the mechanistic underpinnings of acquired drug resistance is challenging due to the enormous complexity and diversity of the processes affected downstream of growth factor signaling. Therefore, the authors employed a computational approach to integrate the transcriptional profiles of Lapatinib-sensitive and -resistant cells with a network of known molecular interactions. In brief, the method takes a distribution of gene expression as input (such as those upregulated in Lapatinib-resistant cells) and carries out a random walk through a known interaction network, using an algorithm that favors frequent visits of nodes that are both highly expressed and connected to highly expressed neighboring nodes (Komurov *et al*, 2010). In the course of this statistical sampling of the network, the frequency with which a node is visited is used to score the functional relevance of its interactions. Thus, the method integrates prior knowledge on molecular interactions with the global distribution of gene expression (in this case, the expression profiles of Lapatinib-resistant cells) to reconstruct a network of functional interactions.

From the analysis of this inferred Lapatinib-resistant network, clusters of biologically interpretable interactions emerged. Biological functions enriched within these clusters are related to multiple metabolic processes including the unfolded protein response, autophagy, glycolysis and gluconeogenesis. In addition, it was found that the resistant cells were more sensitive to glucose deprivation, had enhanced rates of glucose processing and were differentially susceptible to compounds that target metabolic stress responses. Furthermore, glucose deprivation of Lapatinib-sensitive cells selected for a resistant subset. Most importantly, applying the same network reconstruction algorithm to genes associated with poor prognosis within breast cancer patient cohorts identified networks with metabolic features common to those observed in the cell line model.

The relevant downstream molecular pathways that drive tumor growth from genetic mutation remain controversial. However, accumulating evidence points to a previously underappreciated role for the requirement of alterations in cellular metabolism in driving malignant progression (Levine and Puzio-Kuter, 2010; Li *et al*, 2012; Locasale *et al*, 2009; Yun *et al*, 2009). Komurov *et al* are able to show at least in one model system that cancer cell proliferation can persist even upon removal of canonical growth factor signaling pathway activity. Astonishingly, this continued proliferation nevertheless required a shift toward the very same metabolic state that is controlled by growth factor signaling.

The demonstration of resistance to oncogene-mediated targeted therapy through the adaptation of cellular metabolism suggests a fundamental, convergent role for oncogenes and signal transduction in promoting tumorigenesis—the rewiring of cellular metabolism. This rewiring may serve then as a basis for therapeutic intervention that could be less prone to acquired resistance. Perhaps further applications of a network-based approach could then help in identifying the therapeutic windows that discriminate healthy cells from those that have evolved metabolic resistance mechanisms.

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