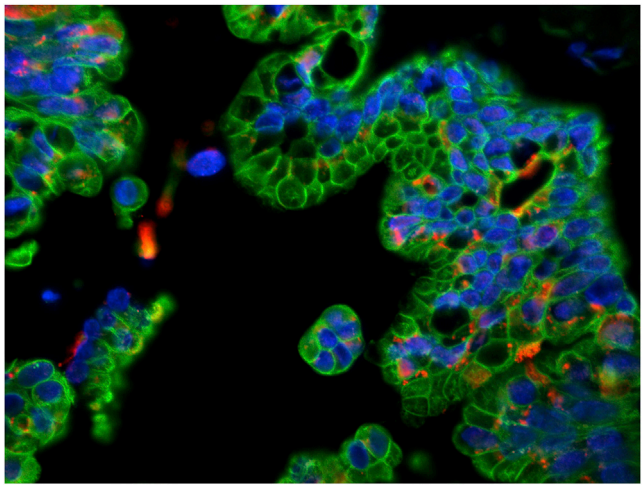
Cell

Targeting Resistance

Wrestling with cancer can be frustrating. Despite the progress in developing therapies that can effectively control tumor growth, the devil almost always strikes back with resistance. Even for the recent excitement in using immunotherapy to achieve unprecedented success in some cancer patients, resistance has been seen in clinical settings and is under active investigation (Restifo et al., 2016).

How do we tackle resistance to cancer therapy? One effective approach is to nail the culprit—pinpointing the cell population intrinsically insensitive to the treatment and targeting their vulnerability. Recent work from Tessa L. Holyoake and her team successfully applied this strategy on chronic myeloid leukemia (CML; Abraham et al., 2016). CML is characterized by the aberrant activation of ABL1 tyrosine kinase due to chromosome translocation, and tyrosine kinase inhibitors (TKIs) have been the standard treatment with clinical efficacy. However, patients with CML eventually relapse because the survival of leukemic stem cells (LSCs) does not rely on the elevated kinase activity and therefore cannot be eradicated by TKIs. Through integrated analyses, the team exposed the essential role of p53 and c-MYC on the CML network and an addictive dependency of LSCs on these two signaling hubs. They further showed that a combinatory treatment targeting p53 and c-MYC could effectively kill LSCs, raising the hope of using this approach for treating CML patients relapsing from TKIs (Abraham et al., 2016).

Leukemia is not the only type of cancer in which targeting intrinsic resistance from a specific population is starting to show promise. Indeed, by developing a mouse model with knockin reporters, Tannishtha Reya and colleagues were able to identify high expression of the stem cell determinant Musashi (Msi) as a marker for populations in pancreatic cancer with strong tumor-initiating capacity and conferring drug resistance. Inhibiting Msi significantly changed the trajectory of disease progression and almost doubled the survival time in mouse models. Moreover, simultaneously inhibiting two of its potential direct targets was effective in killing tumor cells resistant to gemcitabine, a FDA-approved chemotherapy drug for treating pancreatic cancer. To further establish Msi as a valuable target for drug development, the authors went on to develop antisense oligonucleotides specifically targeting MSI1, which successfully inhibited tumor growth in patient-derived xenograft (PDX) models (Fox et al., 2016).



Expression of the stem cell gene Musashi (red) in human pancreatic cancer (cancer cells: green). Image courtesy of Dawn Jaquish.

While drug resistance can be an intrinsic feature of a particular population within the tumor before the drug is even applied, it can also arise as an adaptive response to the treatment itself. Aiming to better understand this adaptation and to explore therapeutic opportunities, Scott Lowe and his team employed a systematic approach to screen for factors that could sensitize KRAS mutant lung cancer cells to trametinib, an FDA-approved drug targeting the downstream effector signaling of mutant KRAS. They found that activation of the FGFR pathway underlies the resistance of tumor cells to trametinib. Consistently, inhibiting FGFR1 with either shRNAs or ponatinib that has FGFR1 as one of its targets achieved synthetic lethality with trametinib in treating KRAS mutant lung cancer cells. Despite the profound efficacy in tumor suppression, this combinatory approach showed minimal, if any, toxicities in various in vivo models, including PDX, strongly supporting its therapeutic potential (Manchado et al., 2016).

Strategies narrowing down specific components in the signaling pathways conferring intrinsic or adaptive resistance represent a major direction of effort for targeting resistance to therapy. However, it's not the only way. As reported by Cerezo et al., rather than targeting a particular oncogenic driver in the context of melanoma resistant to BRAF inhibitors, using compounds to induce ER stress was proven effective in eliminating resistant cancer cells by promoting apoptosis and autophagy. Remarkably, this approach did not seem to affect normal melanocytes or fibroblasts, indicating a rather attractive therapeutic window for future development (Cerezo et al., 2016).

By definition, resistance is hard to eradicate. Nonetheless, in realizing what we have achieved along the way in this marathon of finding a cure for cancer, we have every reason to believe that we are heading in the right direction.

REFERENCES

Abraham, S.A., Hopcroft, L.E., Carrick, E., Drotar, M.E., Dunn, K., Williamson, A.J., Korfi, K., Baquero, P., Park, L.E., Scott, M.T., et al. (2016). Nature *534*, 341–346.

Cerezo, M., Lehraiki, A., Millet, A., Rouaud, F., Plaisant, M., Jaune, E., Botton, T., Ronco, C., Abbe, P., Amdouni, H., et al. (2016). Cancer Cell *29*, 805–819.

Fox, R.G., Lytle, N.K., Jaquish, D.V., Park, F.D., Ito, T., Bajaj, J., Koechlein, C.S., Zimdahl, B., Yano, M., Kopp, J.L., et al. (2016). Nature *534*, 407–411.

Manchado, E., Weissmueller, S., Morris, J.P., Chen, C.C., Wullenkord, R., Lujambio, A., de Stanchina, E., Poirier, J.T., Gainor, J.F., Corcoran, R.B., et al. (2016). Nature *534*, 647–651.

Restifo, N.P., Smyth, M.J., and Snyder, A. (2016). Nat. Rev. Cancer *16*, 121–126.

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