Eradicating tumor drug resistance at its YAP-biomechanical roots

Francesca Zanconato & Stefano Piccolo

Treatment with BRAF kinase inhibitors leads to rapid resistance and tumor regression in BRAF V600E mutant melanoma patients. However, the underlying mechanism of the developed tumor resistance is not fully clear. In this issue of The EMBO Journal, Kim and colleagues show that melanoma cells acquire resistance to BRAF inhibitors by changing cell shape, modifying their cytoskeleton and, in turn, activating the YAP/TAZ mechanotransduction pathway (Kim et al, 2016).

See also: MH Kim et al (March 2016)

Our way to understand tumor initiation and progression is centered around the notion that cancer is a genetic disease, whereby tumor cells become addicted to specific mutations in “driving” oncogenes that empower novel, often highly aberrant phenotypes. This notion has led to the expectation that blocking the activity of these mutant genes with targeted therapies should ultimately defeat tumors. This ideal scenario, however, clashes with the much grimmer reality of the clinical evidence, as such targeted therapies generally produce mere transient responses in most, if not all, mammalian cells (Dupont et al, 2011; Aragona et al, 2013). Importantly, expression of YAP/TAZ is associated with the combination of BRAF and MEK inhibitors (Kim et al, 2015). Indeed, YAP/TAZ are closely related transcriptional activators that serve as central mediators of multiple cellular mechanotransduction pathways (Dupont et al, 2011). In line, F-actin integrity and organization are leading regulators of YAP/TAZ nuclear localization in most, if not all, melanoma cells (Dupont et al, 2011; Aragona et al, 2013). Thus, expression of YAP/TAZ is associated to tumor progression in several human solid tumors, and their activation endows tumor cells with cancer stem cell properties that include chemoresistance (Cordenonsi et al, 2011). In the present paper, the authors find that prolonged exposure to PLX4032 in vitro leads to the emergence of insensitive cell clones that survive and proliferate in spite of continuous drug administration. The upris-
Based on the observation that suppression of actin remodeling can overcome survival to BRAF inhibitors, the authors performed a screening to identify kinases whose inhibition can synergize with BRAF inhibition to achieve a successful therapy. The screening revealed that TESK1, a kinase that inactivates Coflin (an actin-severing protein previously reported to inhibit YAP/TAZ activity [Aragona et al., 2013]), is relevant to keep YAP/TAZ in the nucleus of vemurafenib-resistant cells and that its depletion sensitizes cells to BRAF inhibitors. Interestingly, with the onset of drug resistance, melanoma cells gain a higher dependency on YAP/TAZ for their survival and proliferation, to the extent that YAP/TAZ inhibition (by siRNAs, or treatment with cytochalasin D or blebbistatin) is sufficient to block cell growth, even in the absence of the BRAF inhibitor. TESK1 itself is not activated by prolonged exposure to vemurafenib, but its function becomes essential as cells become independent of oncogenic BRAF, and dependent on YAP/TAZ.

The work of Kim et al. (2016) is consistent with prior reports on the role of YAP/TAZ in chemoresistance to RAF and MEK inhibitors, and to other chemotherapy agents (Cordenonsi et al., 2011; Lin et al., 2015a,b). For example, multiple tumor types, irrespectively of their genetic background, are vulnerable to combined inhibition of YAP and the MAPK pathway (Lin et al., 2015b). However, YAP/TAZ are never activated by mutations and only rarely amplified. Kim et al. (2016) have the merit to add a new layer to this picture, indicating that increased cellular mechano-responsiveness may be the culprit of YAP/TAZ-induced drug resistance.

It is thus tempting to combine different studies and propose the following model as mainframe of drug resistance (Fig 1): inactivation of MAPK signaling with BRAF/MEK inhibitors bears the side effect of increasing ECM deposition by the tumor stroma, in turn enhancing mechanotransduction and YAP/TAZ activation in cancer cells. YAP/TAZ are potent triggers of cellular fitness, likely as part of their CSC-endowing repertoire (Cordenonsi et al., 2011).

This scenario is at least consistent with a series of preliminary observations in the clinical context given that YAP levels anticorrelate with the clinical efficacy of BRAF and MEK inhibitors; also, YAP levels raise after a tumor develops drug resistance (Lin et al., 2015b). Furthermore, histological re-examination of residual disease specimens confirmed that BRAF inhibition modulates the fibrous ECM and induces an elongated melanoma cell morphology (Hirata et al., 2015).

We also note that a piece of evidence is however still missing to make all this a full circle, as there is not yet formal proof that the non-cell-autonomous “safe haven” provided by the fibroblast and their ECM nest is actually inducing the cytoskeleton-driven, cell autonomous activation of YAP/TAZ studied by Kim et al. (2016).

Melanoma immune therapy has made headlines because of its remarkable efficacy in a substantial fraction of patients (Flaherty et al., 2012). However, for those who do not respond, melanoma remains a devastating disease raising the need of better biomarkers and combinatorial therapies. It is tempting to speculate that attenuation of YAP/TAZ signaling—either by targeting matrix stiffness, melanoma cytoskeletal organization, or YAP/TAZ directly—may slow down proliferation and help the immune system to overcome the tumor.

Irrespective of these remaining gaps, the paper of Kim et al. (2016), and the other set of related evidence, greatly emphasize the role of YAP/TAZ and mechanotransduction as prime targets of cancer therapy.

References

© 2015 The Authors