Small-molecule inhibitors continue to be at the leading edge of cancer therapeutics. The discovery of Gleevec (STI-571), a tyrosine kinase inhibitor, was a milestone achievement in clinical oncology and this inhibitor has demonstrated remarkable efficacy in Philadelphia chromosome-positive (Ph) chronic myeloid leukemia. Since then, mechanism-based approaches have been used to specifically target various kinases and/or downstream oncogenic pathways that are critically involved in cell cycle progression and tumorigenesis. However, in addition to this approach, a more recent and novel use of small-molecule inhibitors has emerged as a promising endeavor in the field of cancer chemotherapy. Here, we briefly review the mechanistic basis of restoration of a tumor suppressor and its potential complications for cancer therapy.

The tumor suppressor function mediated by the retinoblastoma 1 protein (RB1) is principally attributed to its interaction with the E2F transcription factor 1 (E2F1). The RB1/E2F1 complex represses a number of E2F1-dependent transcriptional target genes that are required for the transition from G1 to S phase in the cell cycle. Because RB1 is inactivated by phosphorylation mediated by the G1 cyclin-dependent kinases 4 and 6 (CDK4 and CDK6), restoring RB1 function by inactivating CDK4/6 is theoretically an obvious approach. Although structural similarities among a number of CDK family members hampered the development of a CDK4/6-specific inhibitor for many years, some agents, including palbociclib (PD-0332991), have recently demonstrated promising results in Phase I/II clinical trials for human malignancies, including breast cancer.

Above and beyond RB1, another tumor suppressor that is critical for numerous growth inhibitory pathways is tumor protein p53 (TP53, best known as p53). The abundance of wild-type p53 protein is massively reduced as a result of ubiquitin-dependent and human homolog of double minute 2 (HDM2)-mediated degradation of p53. Therefore, dissociation of p53 from the p53/HDM2 complex is a reasonable strategy for rescuing p53 function. Based on the crystallographic structure of the p53/HDM2 peptide complex, small p53 peptides that mimic the region of p53 sufficient for HDM2 binding and small-molecule HDM2 antagonists have been shown to disrupt the p53/HDM2 interaction in vitro and in vivo. Some of these, including MI-219, Nutlin-3, and RG7112, have been found to be effective preclinically and have consequently moved into Phase I/II clinical trials. Although proteasome inhibitors such as bortezomib (PS-341) may not be as specific for stabilizing p53 as these HDM2 inhibitors, other growth-inhibitory gene products, including the cyclin-dependent kinase inhibitor 1B (CDKN1B or p27, Kip1) protein, can also be degraded in an ubiquitin-dependent manner. Therefore, it may be advantageous to re-establish a broad spectrum of growth-inhibitory functions by blocking the proteasome pathway.

Although the approach of re-establishing tumor suppressor function in tumors as a therapeutic option is mechanistically intriguing, there are potential dilemmas associated with the systemic restoration of tumor suppressor function. Tumor suppressor genes are frequently mutated or
deleted in cancer patients, and given that some of the mutant genes acquire oncogenic potential, this approach may simply reboot a mutant (i.e., oncogenic) tumor suppressor. Even if a tumor suppressor gene is intact, its function should not depend on other cancer-susceptible proteins. For example, the cyclin-dependent kinase inhibitor 2A (CDKN2A) gene is not frequently deleted in cancer cells, but is inactivated by DNA methylation. However, epigenetic reactivation of the CDKN2A gene may not be an effective approach if RB1 and/or p53 are deficient, because the tumor suppressor functions of the products of the 2 alternative reading frames of CDKN2A—p16INK4A and p14ARF proteins—largely depend on RB1 and p53, respectively. Therefore, for the tumor suppression approach to be fully effective, it will be important to identify a non-mutated (or non-deleted) tumor suppressor whose function does not rely on other tumor suppressors that might be already mutated or deleted.

Bridging integrator-1 (BIN1) was originally identified as a c-MYC oncoprotein-interacting tumor suppressor. The BIN1 gene itself is rarely mutated or deleted, but is frequently silenced in human cancer cells. Moreover, BIN1 acts as a tumor suppressor in vitro and in vivo in the absence of RB1 and p53. We recently demonstrated that BIN1, whose gene promoter is activated by E2F1, directly interacts with E2F1 and represses its transcription, implying that a negative-feedback loop regulates BIN1 gene expression. Interestingly, we found that E2F1 is poly(ADP-ribosyl)ated by poly(ADP-ribose) polymerase 1 (PARP1) and that PARP1 inhibition unlocks the E2F1–BIN1 negative-feedback loop to vigorously activate the BIN1 gene, which induces G2/M arrest in the cell cycle and/or apoptosis. Because of this so-called ‘synthetic lethality,’ PARP inhibitors have been actively used for clinical trials in breast cancer 1 and 2 (BRCA1/2)-deficient breast and ovarian cancers. However, it was unclear why PARP inhibitors alone also show therapeutic efficacy, even in cancer cells expressing wild-type BRCA1/2. Based on our recent data, the restoration of BIN1 by PARP inhibitors may offer a mechanistic rationale for expanding the clinical usage of PARP inhibitors over a wider range of tumor types, regardless of the status of RB1, TP53, and BRCA1/2 genes (Fig. 1).

Chemotherapy and radiotherapy are conventional treatments for eradicating tumors, but cancer often develops therapeutic resistance over time. Given that many tumor suppressors are proapoptotic in response to DNA-damaging agents, it would be clinically pertinent to increase the chemotherapeutic and radiosensitivities of cancer by combining standard treatments with agents that can restore the activity of silenced tumor suppressors, provided they are not mutated or deleted, in human malignancies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

1. Druker BJ, Tamura S, Buchdunger E, Ohno S, Segal GM, Fanning S, Zimmermann J, Lydon NB. Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells. Nat Med 1996; 2:561-566; PMID:8616716; http://dx.doi.org/10.1038/nm0596-561

2. Garber K. The cancer drug that almost wasn’t. Science 2014; 345:865-867; PMID:25146265; http://dx.doi.org/10.1126/science.345.6199.865

3. Khoo KH, Verma CS, Lane DP. Drugging the p53 pathway: understanding the route to clinical efficacy. Nat Rev Drug Discov 2014; 13:217-236; PMID:24577402; http://dx.doi.org/10.1038/nrd4288

4. Pagano M, Tarn SW, Theodoras AM, Beer-Romero P, Del Sal G, Chau V, Yew PR, Draetta GF, Rolfe M. Role of the ubiquitin-proteasome pathway in regulating abundance of the cyclin-dependent kinase inhibitor p27. Science 1995; 269:682-685; PMID:7624798; http://dx.doi.org/10.1126/science.7624798

5. Bates S, Phillips AC, Clark PA, Stott P, Peters G, Ludwig RL, Vousden KH. p14ARF links the tumour suppressors RB and p53. Nature 1998; 395:124-125; PMID:9744267; http://dx.doi.org/10.1038/25867

6. Sakamuro D, Elliott KJ, Wechsler-Reya R, Prendergast GC. BIN1 is a novel MYC-interacting protein with features of a tumour suppressor. Nat Genet 1996; 14:69-77; PMID:8782822; http://dx.doi.org/10.1038/ng0996-69

7. Prendergast GC, Muller AJ, Ramalingam A, Chang MY. BAR the door: cancer suppression by amphiphysin-like genes. Biochim Biophys Acta.2009; 1795:25-36; PMID:18930786

8. Kumari A, Iwasaki T, Pyndiah S, Cassimere EK, Palani CD, Sakamuro D. Regulation of E2F1-induced apoptosis by poly(ADP-ribosyl)ation. Cell Death Differ 2015 Feb; 22(2):311-22; PMID:25257171

9. Fong PC, Bose DS, Yap TA, Tutt A, Wu P, Mergui-Roelvink M, Mortimer P, Swaisland H, Lau A, O’Connor MJ, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. N Engl J Med. 2009; 361:123-134; PMID:19553641; http://dx.doi.org/10.1056/NEJMoa0900212

10. Pyndiah S, Tanida S, Ahmed KM, Cassimere EK, Choe C, Sakamuro D. c-MYC suppresses BIN1 to release poly(ADP-ribose) polymerase 1: a mechanism by which cancer cells acquire cisplatin resistance. Sci Signal 2011; 4:ra19; PMID:21447800; http://dx.doi.org/10.1126/scisignal.2001556