DePICTing p53 Activation: A New Nucleolar Link to Cancer

Lior Golomb[1] and Moshe Oren[1,*]
[1]Department of Molecular Cell Biology, The Weizmann Institute of Science, Rehovot 76100, Israel
*Correspondence: moshe.oren@weizmann.ac.il
DOI 10.1016/j.ccr.2011.08.017

p53 activation by ribosomal biogenesis stress is important for tumor suppression. In the August issue of *Nature Medicine*, Sasaki et al. identify PICT1 as a regulator of this process. PICT1 sequesters ribosomal protein RPL11 in the nucleolus, attenuating p53 induction. Excessive PICT1 may dampen the p53 response and promote cancer.

Ribosome biogenesis, the elaborate process of ribosome production, is tightly connected to cell growth and cell proliferation. Its deregulation has been implicated in a multitude of human pathologies (Narla and Ebert, 2010) and can also contribute to cancer. The cell's nucleolus acts as a hub for ribosome biogenesis. In recent years, the role of the nucleolus as a stress sensor has gradually been unfolding. In particular, many types of stress signals converge on the nucleolus to activate the tumor suppressor p53 (Boulon et al., 2010). Specifically, a group of ribosomal proteins (RPs), including RPL5, RPL11, RPL23 and RPS7, serve as stress signal transmitters; following stress, they are released from the nucleolus, bind Mdm2, and activate p53 (Zhang and Lu, 2009).

The Mdm2 E3 ubiquitin ligase is a pivotal negative regulator of p53 (Michael and Oren, 2003). In nonstressed cells, Mdm2 maintains constitutively low p53 levels. Upon stress, a variety of molecular mechanisms converge to abrogate the inhibitory effects of Mdm2, thereby enabling p53 accumulation and unleashing p53-mediated biological responses, including growth arrest, senescence, and apoptosis (Michael and Oren, 2003). As noted above, a variety of ribosomal proteins can bind directly to Mdm2 and quench its ability to promote p53 ubiquitylation and degradation, thus triggering a p53 response (Zhang and Lu, 2009). The physiological importance of this regulatory axis was recently demonstrated in mice expressing an Mdm2 mutant that cannot bind RPL5 and RPL11 (Macias et al., 2010). Cells cultured from such mice failed to mount a p53 response upon disruption of ribosomal biogenesis. Notably, the mice succumbed more rapidly to lymphoma. Better understanding of the molecular mechanisms governing the RPs-Mdm2-p53 axis might therefore provide clues toward improved cancer diagnostics and prognostics and possibly also novel therapeutic strategies.

Recent work by Sasaki et al. (2011) identifies PICT1 as a new pivotal regulator of this axis. To elucidate the biological functions of PICT1, Sasaki et al. attempted to produce Pict1 knockout mice, only to discover that Pict1 loss was lethal in early embryogenesis, owing to apoptotic cell death and growth inhibition. To circumvent this problem, they generated a "switchable" Pict1 embryonic stem cell model and found that the adverse effects observed following Pict1 ablation were due to excessive p53 activation. Similar p53-dependent effects were observed in thymuses of mice with conditional Pict1 inactivation as well as in cultured cancer cell lines.

To elucidate the molecular basis for p53 activation upon PICT1 depletion, Sasaki et al. (2011) undertook a proteomics approach and found that PICT1, which resides primarily in the nucleolus, can bind numerous ribosomal proteins, including RPL5 and RPL11. Interestingly, PICT1 depletion caused translocation of RPL11, but not of other RPs, from the nucleolus into the nucleoplasm, implying that PICT1 was specifically required for nucleolar anchoring of RPL11. Moreover, knockdown of RPL11, but not of other RPs, attenuated the accumulation of p53 upon PICT1 loss. Further analysis confirmed that in the absence of PICT1, the translocated RPL11 engaged Mdm2 within the nucleoplasm and inactivated it, leading to p53 stabilization and accumulation. The picture that emerges from these findings (Figure 1) is that PICT1 normally retains RPL11 in the nucleolus, thereby dampening the induction of p53 by ribosomal biogenesis stress and possibly additional types of stress that rely on inhibition of Mdm2 by free RPL11. This may set a threshold that prevents spurious p53 activation by physiological fluctuations in the rate of ribosomal biogenesis. Conceivably, excessive nucleolar PICT1 might hinder the cell's ability to mount an efficient p53 response, potentially promoting neoplastic processes. Of note, in cancer cells, ribosome biogenesis is often deregulated and aberrantly augmented, presumably placing cells under constant ribosomal stress. Elevated levels of PICT1 might enable such cells to cope with the chronic stress by retaining RPL11 more avidly in the nucleolus, thus quenching p53 activation (Figure 1). In line with this conjecture, in several human cancers high PICT1 levels were found to correlate with worse prognosis, particularly in tumors that retain wild-type p53, whereas reduced Pict1 expression delayed tumor progression in a mouse skin cancer model (Sasaki et al., 2011).

These findings position PICT1 as a potentially important new regulator of p53 function, whose deregulation can impact cancer development. They also raise many questions that remain to be answered. For instance, can excessively high levels of PICT1 actively drive tumorigenesis, similar to Mdm2 and its relative Mdmx/Mdm4? Is the PICT1 gene amplified or otherwise aberrantly hyperactivated in human tumors? And how is the restraining effect of PICT1 over RPL11 relieved under conditions of ribosomal

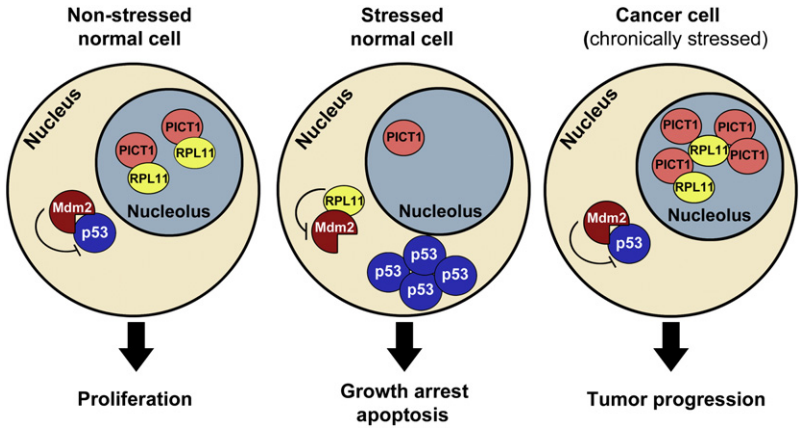

Figure 1. Regulation of p53 Activity and p53-Dependent Biological Outcomes by PICT1
PICT1 binds and retains RPL11 in the nucleolus, thereby enabling Mdm2 to inhibit p53 to ensure low basal p53 activity (left). When normal cells are confronted with ribosome biogenesis stress, PICT1 levels drop, releasing RPL11 into the nucleoplasm (middle). Other mechanisms, such as posttranslational modifications, might also facilitate RPL11 release. Within the nucleoplasm, free RPL11 binds and inactivates Mdm2, promoting p53 accumulation and activation (middle). In some cancer cells, elevated PICT1 levels may retain RPL11 more avidly in the nucleolus, thereby restricting p53 activation and enabling better coping with chronic stress associated with neoplastic transformation (right).

biogenesis stress in normal cells to enable effective p53 activation? Are stress-induced posttranslational modifications involved in such regulation? Furthermore, is the role of PICT1 unique, or is there a larger group of functionally similar nucleolar proteins that retain other ribosomal protein? With regard to the regulation of PICT1 by ribosomal biogenesis stress, Sasaki et al. (2011) do provide at least one important clue by showing that PICT1 protein levels decrease following treatment with drugs that induce such stress.

Finally, one interesting question raised by the findings of Sasaki et al. is what makes a gene qualify as a tumor suppressor. While PICT1 has previously been implicated as a tumor suppressor in glioma and ovarian cancer (Kim et al., 2008; Merritt et al., 2009), data from Sasaki et al. (2011) point in the opposite direction, invoking instead an oncogenic role for PICT1. The fact that PICT1 depletion unleashes a p53 response seemingly argues unequivocally in favor of the latter conjecture. But this is not necessarily so. In fact, p53 is a rather avid "guardian of tumor suppressors," activated when other tumor suppressors become defunct and presumably providing the cell with a safety net against cancer, as nicely exemplified for pRB and PTEN (Chen et al., 2005; Macleod et al., 1996). Moreover, similar to pRB ablation, PICT1 ablation induces expression of ARF (Sasaki et al., 2011), considered indicative of excessive mitogenic signaling. Yet, the delayed development of skin tumors in Pict1$^{+/-}$ mice and the better prognosis of patients with colorectal and esophageal tumors expressing low PICT1 levels (Sasaki et al., 2011) do imply that at least in those cancer types, PICT1 has oncogenic rather than tumor suppressor attributes. Figuring out what dictates whether deregulated PICT1 promotes or inhibits cancer is an open challenge for the future.

REFERENCES

Boulon, S., Westman, B.J., Hutten, S., Boisvert, F.M., and Lamond, A.I. (2010). Mol. Cell *40*, 216–227.

Chen, Z., Trotman, L.C., Shaffer, D., Lin, H.K., Dotan, Z.A., Niki, M., Koutcher, J.A., Scher, H.I., Ludwig, T., Gerald, W., et al. (2005). Nature *436*, 725–730.

Kim, Y.J., Cho, Y.E., Kim, Y.W., Kim, J.Y., Lee, S., and Park, J.H. (2008). J. Pathol. *216*, 218–224.

Macias, E., Jin, A., Deisenroth, C., Bhat, K., Mao, H., Lindström, M.S., and Zhang, Y. (2010). Cancer Cell *18*, 231–243.

Macleod, K.F., Hu, Y., and Jacks, T. (1996). EMBO J. *15*, 6178–6188.

Merritt, M.A., Parsons, P.G., Newton, T.R., Martyn, A.C., Webb, P.M., Green, A.C., Papadimos, D.J., and Boyle, G.M. (2009). BMC Cancer *9*, 378.

Michael, D., and Oren, M. (2003). Semin. Cancer Biol. *13*, 49–58.

Narla, A., and Ebert, B.L. (2010). Blood *115*, 3196–3205.

Sasaki, M., Kawahara, K., Nishio, M., Mimori, K., Kogo, R., Hamada, K., Itoh, B., Wang, J., Komatsu, Y., Yang, Y.R., et al. (2011). Nat. Med. *17*, 944–951.

Zhang, Y., and Lu, H. (2009). Cancer Cell *16*, 369–377.