Polo-like kinase 2: A new exploitable target to undermine mutant p53-dependent chemoresistance

Comment on: Valenti F, et al. Cell Cycle 2011; 10:4330–40

Marco Napoli,[1,2] Javier E. Girardini[3] and Giannino Del Sal[1,2,*]; [1]Laboratorio Nazionale CIB (LNCIB); Trieste, Italy; [2]Università degli Studi di Trieste; Trieste, Italy; [3]Instituto de Biologia Molecular y Celular de Rosario (IBR – CONICET); Rosario, Argentina; *Email: giannino.delsal@lncib.it;
http://dx.doi.org/10.4161/cc.11.3.19225

During the last decade, the role of p53 point mutants as determinants of tumor aggressiveness was conclusively demonstrated.[1] Based on a large body of evidence, a more complete picture of the consequences of p53 mutation in human cancer is emerging, where a single missense mutation transforms one of the most efficient tumor suppressor pathways into a powerful network promoting tumor progression. Indeed, these mutant p53 proteins are devoid of oncosuppressive abilities; on the contrary, they acquire novel oncogenic properties supporting several tumorigenic processes like cell proliferation, death resistance, genomic instability, angiogenesis and metastasis formation.[1]

Even if the mechanistic bases of mutant p53 oncogenic activities are still not completely understood, in most cases they rely on the ability of mutant p53 to alter the function of interacting partners and to globally perturb gene expression.[1] However, a major unresolved issue remains: how is mutant p53 activity regulated? Elegant in vivo data have clearly established that an oncogenic context is required to fully endow mutant p53 with its malignant functions, thereby suggesting that the alteration of signaling pathways is critical. In particular, activated Ras signaling was revealed to enhance mutant p53 associated genomic instability and tumor formation[2] and to promote mutant p53 phosphorylation required for the inhibition of the anti-metastatic factor p63.[3] Constitutive activation of EGFR/integrin signaling was also shown to collaborate with mutant p53 pro-metastatic function.[3] In line with these observations, Pin1-mediated isomerization following proline-directed phosphorylation was recently demonstrated to be essential in transducing cancer promoting signaling to unleash mutant p53-dependent aggressive tumor potential.[4]

In a previous issue, Valenti et al.[5] further elucidated how mutant p53 activity is engaged into the oncogenic circuitry by showing that mutant p53 functions are enhanced by Plk2 (polo-like kinase 2).

Plk2 belongs to a family of Ser/Thr kinases characterized for the presence of the polo domain responsible for recognition and binding to substrates. Plk family comprises four members (Plk1–4) implicated in the regulation of cell cycle and cell division. In particular, Plk2 is a wild-type p53 target gene induced in response to spindle damage to prevent mitotic catastrophe.[6] In the current study, Valenti and coworkers demonstrate that *Plk2* may also promote mutant p53 oncogenic activity by phosphorylating its C terminus. In particular, they identify Thr377 as one of the residues phosphorylated by Plk2 on mutant p53, a residue never described before as a phosphorylation site in neither wild-type nor mutant p53. Through these modifications, Plk2 enhances the transcriptional activity of the mutant p53/NF-Y complex, leading to aberrant expression of target genes increasing cell proliferation and drug resistance.

Intriguingly, the authors found that Plk2 itself is a mutant p53 target gene induced upon treatment with chemotherapeutic drugs, thereby establishing a positive feedback loop that amplifies mutant p53 functions and, in particular, chemoresistance. However, the mechanisms involved in *Plk2* induction by mutant p53 are different from those used by the wild-type counterpart: mutant p53 does not bind to p53 responsive elements on *Plk2* promoter; instead, it is tethered by NF-Y onto CCAAT-boxes and enhances p300 recruitment and histone acetylation.

These results emphasizes the complexity of the regulation of mutant p53, which, similarly to the wild-type protein but with fairly different outcomes, sits at the center of an intricate network linking upstream oncogenic signals to specific downstream events.

Nevertheless, the role of Plk2 in cancer biology deserves more investigation since experimental data suggest a complex scenario. Even if other reports support a Plk2 pro-oncogenic function,[7,8] *Plk2* promoter is silenced by hypermethylation in B-cell malignancies and ovarian cancer,[6,9] thereby suggesting that the role of Plk2 in tumorigenesis may be different according to the molecular context. This dual role may be explained, at least in part, considering that, acting as either wild type or mutant p53 target, Plk2 may contribute to tumor suppression or tumor promotion depending on p53 status.

From a clinical perspective, these findings could have relevant implications. It is well known that *TP53* mutation correlates with poor clinical outcome in several malignancies and that is also frequently associated with resistance to conventional therapies.[1] To tackle the aggressive behavior of these cancers, as the work by Valenti et al. suggests, Plk2 inhibition to selectively block mutant p53 function may provide an efficient therapeutic strategy.

References

1. Oren M, et al. Cold Spring Harb Perspect Biol 2010; 2:a001107; PMID:20182618; http://dx.doi.org/10.1101/cshperspect.a001107.
2. Hingorani SR, et al. Cancer Cell 2005; 7:469-83; PMID:15894267; http://dx.doi.org/10.1016/j.ccr.2005.04.023.
3. Muller PAJ, et al. J Cell Biol 2011; 192:209-18; PMID:21263025; http://dx.doi.org/10.1083/jcb.201009059.
4. Girardini JE, et al. Cancer Cell 2011; 20:79-91; PMID:21741598; http://dx.doi.org/10.1016/j.ccr.2011.06.004.
5. Valenti F, et al. Cell Cycle 2011; 10:4330-40; PMID:22134238; http://dx.doi.org/10.4161/cc.10.24.18682.
6. Strebhardt K. Nat Rev Drug Discov 2010; 9:643-60; PMID:20671765; http://dx.doi.org/10.1038/nrd3184.
7. Tan LB, et al. World J Urol 2010; 28:117-22; PMID:19506885; http://dx.doi.org/10.1007/s00345-009-0432-y.
8. Matsumoto T, et al. Proc Natl Acad Sci U S A 2009; 106:14542-6; PMID:19706541; http://dx.doi.org/10.1073/pnas.0904229106.
9. Syed N, et al. Cancer Res 2011; 71:3317-27; PMID:21402713; http://dx.doi.org/10.1158/0008-5472.CAN-10-2048.