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Cell Cycle News & Views

Mutant p53 succumbs to starvation

Comment on: Rodriguez OC, et al. Cell Cycle 2012; 11:4436–46; PMID:23151455; http://dx.doi.org/10.4161/cc.22778

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While the wild type form of p53 possesses strong tumor-suppressive activities, the p53 proteins that are commonly mutated in cancer often endow more malignant properties to the cancers they inhabit.[1,2] There are several lines of evidence supporting such oncogenic gain of function of mutant p53. Compared with p53-null mice, knock-in mice harboring mutant p53 proteins display different and more metastatic tumor spectra. Such mutant proteins are frequently present at far higher levels than the wild-type protein in tumors; in fact, the p53 protein present in the knock-in mice accumulates in tumors despite being inherently unstable in normal tissues,[3] suggesting that stabilization of mutant p53 protein is required for its oncogenic activity. Consistently, knockdown of mutant p53 protein in human cancer cell lines leads to reduced cell proliferation, invasion, motility, tumorigenicity and resistance to anticancer drugs.[1,2] Since epidemiological studies indicate that high levels of mutant p53 proteins correlate with tumor aggressiveness and poorer outcomes, it is important to understand how mutant p53 is stabilized in tumors and how it can be eliminated.

The Avantaggiati group in a recent issue of *Cell Cycle* have recently provided important new insight into this question.[4] They demonstrated that glucose restriction (GR) results in deacetylation and destabilization of endogenous mutant p53, but not of wild-type p53 protein. As protein degradation is mediated primarily by two pathways; the 26S proteasome and autophagy, the authors sought to identify which pathway is responsible for the degradation. They found that while the proteasome inhibitor MG132 treatment does not abolish GR-induced mutant p53 degradation, knockdown of autophagy genes such as Beclin-1, ATG5, ATG7 or pharmacological inhibition of autophagy prevents the degradation. Further, mutant p53 physically interacts with components of the autophagy machinery in a GR-dependent manner, suggesting that mutant p53 is a substrate for autophagic degradation. Interestingly, a C-terminal acetylation-mimicking mutant version of p53 (G245A-6KQ) is resistant to GR-dependent degradation. Taken together, these findings suggest that GR induces posttranslational modifications of lysines within mutant p53 proteins, which subsequently target them for autophagy-dependent degradation.

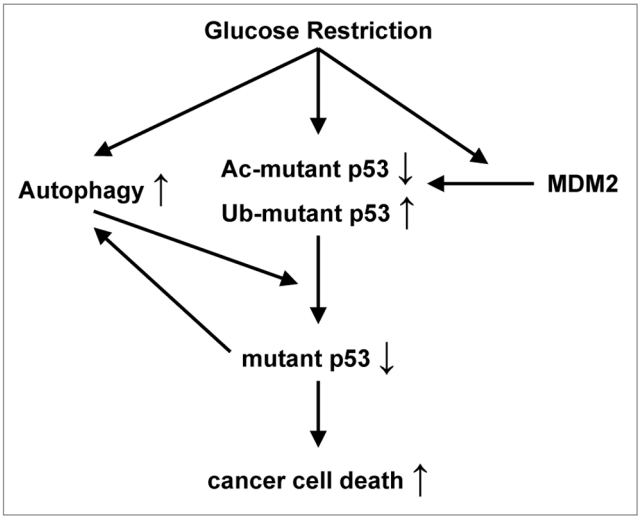

Figure 1. Glucose restriction induces post-translational modifications of mutant p53 (ubiquitination, Ub-mutant p53; acetylation, Ac-mutant p53), which, in turn, leads to its degradation by activated autophagy and ensuing autophagic cell death

The authors next examined the effects of GR-induced degradation of mutant p53 on autophagy and cancer cell death. As indicated by two markers of autophagy (LC3 conversion and p62 degradation), GR activates this process, and the subsequent mutant p53 protein degradation leads to a maximal induction of autophagy and cell death. Consistent with their previous observations, expression of G245A-6KQ mutant p53 confers at least partial resistance to GR-induced cell death. Next, the authors used two mutant p53 mouse models to investigate the effects of a low carbohydrate (LC) diet on p53 stability and tumorigenicity in vivo. In line with their ex vivo data, in knock-in mice harboring the tumor-derived p53 mutation (A135V) placed on an LC diet, p53 protein is destabilized in mammary glands, ovaries and adipose tissues, while p53 in wild-type mice is stabilized. In xenografted mice, mutant p53 expressing cancer cells show enhanced tumorigenicity compared with those that are either p53-null or bearing wild-type p53.[2] Strikingly, Rodriguez et al. found that an LC diet leads to a marked decrease in size of xenografted tumors with mutant p53, while this diet does not decrease tumors arising from the GR-resistant mutant p53G245A-6KQ expressing cells—it actually increases their growth.

The findings of Rodriguez et al.[4] raise several interesting questions. First, virtually every residue with the ~200 amino acid DNA-binding domain of p53 has been found to be mutated in different tumors, albeit with differing frequencies. Autophagy is activated when the proteasome fails to eliminate misfolded and aggregated proteins,[5]

and different mutant p53 proteins vary in their propensity for aggregation.[6] Is there a correlation between mutant p53 proteins' tendency to aggregate and their ability to be degraded after GR? Second, MDM2, the prime E3 ligase that ubiquitinates wild-type p53, cannot bind to p53 in Nutlin-3a-treated cells.[7] Since the authors found that while mutant p53 is ubiquitinated after GR, Nutlin-3a actually blocks GR-induced mutant p53 degradation, what is the role of MDM2 in the setting of their study? Last, but not least, AMP-activated protein kinase (AMPK) has been known to regulate autophagy[8] and may also be involved in GR-induced mutant p53 degradation. Is AMPK critical for the upstream signaling pathway to GR-induced mutant p53 degradation? Answers to these and other questions will provide the next chapters in this exciting story.

References

1. Brosh R, et al. Nat Rev Cancer 2009; 9:701-13; PMID:19693097
2. Freed-Pastor WA, et al. Genes Dev 2012; 26:1268-86; PMID:22713868; http://dx.doi.org/10.1101/gad.190678.112
3. Terzian T, et al. Genes Dev 2008; 22:1337-44; PMID:18483220; http://dx.doi.org/10.1101/gad.1662908
4. Rodriguez OC, et al. Cell Cycle 2012; 11:4436-46; PMID:23151455; http://dx.doi.org/10.4161/cc.22778
5. Kirkin V, et al. Mol Cell 2009; 34:259-69; PMID:19450525; http://dx.doi.org/10.1016/j.molcel.2009.04.026
6. Xu J, et al. Nat Chem Biol 2011; 7:285-95; PMID:21445056; http://dx.doi.org/10.1038/nchembio.546
7. Vassilev LT, et al. Science 2004; 303:844-8; PMID:14704432; http://dx.doi.org/10.1126/science.1092472
8. Mihaylova MM, et al.Nat Cell Biol 2011; 13:1016-23; PMID:21892142; http://dx.doi.org/10.1038/ncb2329

Can liberating p53 from E6 free patients from HPV-related head and neck tumors?

Comment on: Li C, et al. Cell Cycle 2013; 12:923-934; PMID:23421999; http://dx.doi.org/10.4161/cc.23882

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Over half a million patients are diagnosed with head and neck squamous cell carcinoma (HNSCC) each year in the world. Most of these patients present with locally advanced tumors, and less than 50% will live for 5 years after treatment.[1] Concurrent platinum-based chemoradiation protocols improve locoregional control and have become a standard therapeutic strategy. However, they are associated with acute, high-grade toxicity that includes neutropenia, mucositis, xerostomia and swallowing impairment.

Consumption of alcohol and tobacco smoke is the major risk factor for HNSCC. However, compelling evidence has accumulated over the last decade for infection of head and neck epithelium by high-risk human papillomaviruses (HPVs) as an emerging etiology for HNSCC (about 25% of all HNSCC cases). The prevalence of HPV-related HNSCC is increasing rapidly in North America and North European countries. Patients with HPV-positive tumors constitute a distinct clinical HNSCC subpopulation, who respond better to therapy and have improved relapse-free and overall survival.[2]

HPV-driven carcinogenesis is mainly a consequence of deregulation of the E6 and E7 viral oncoproteins.[3] E6 binds to the p53 tumor suppressor protein and the E6AP cellular E3-ubiquitin ligase (**Fig. 1A**), leading to p53 ubiquitination, proteasomal degradation and impaired function. The functional consequences include loss of p21-mediated control of the G_1/S and G_2/M checkpoints, reduced DNA-damage repair and cell cycle inhibition as well as decreased expression of the pro-apoptotic Bax and Puma factors and consequent diminished cell death. E7 binds to the Retinoblastoma protein (pRb) and induces its degradation (**Fig. 1B**). pRb inhibits cell cycle progression via inhibition of transcription factors of the E2F family. Loss of pRb activates E2F and promotes cell proliferation.

Most HPV-related HNSCC contain wild type *TP53*,[4] and their better response to genotoxic therapies could be due to activation of wild-type p53. Interestingly, inhibition of E6 in HPV-related HNSCC cell lines in culture leads to p53 stabilization and increases cell death.[5,6] However, there was no direct evidence that p53 is responsible for this effect. Proof is now provided by Li and Johnson.[7] They have confirmed that inhibition of E6 and E7 by siRNA in HPV-positive cell lines leads to p53 stabilization and triggers apoptotic cell death. In addition, they elegantly demonstrate the direct implication of p53 in this induced cell death by additional inhibition of p53. The authors further observe that Bortezomib, a proteasome-inhibitor (**Fig. 1A**), increases p53 and p21 levels and results in dose-dependent death of HPV-positive cells. This effect is partially impaired by anti-p53 siRNA treatment, showing that p53 is implicated to some extent downstream of Bortezomib. Interestingly, the use of sublethal doses of Bortezomib leads to cell cycle arrest of HPV-positive cell cultures at either G_1 or G_2/S to various extends, depending on the cell line. The authors provide convincing evidence that this effect is also dependent on both p53 and p21.

The impact of HPV on improving the survival of patients with HNSCC is now clearly established, and there is a debate about de-escalating and/or modulating standard therapies in order to both better manage HPV-related HNSCC and spare patients treatment-related toxicities. In this context, the work by Li and Johnson provides evidence for a direct role of p53 in the increased sensitivity of HPV-positive lesions to genotoxic agents. It also suggests that liberation of p53 from HPV E6 oncroprotein-mediated degradation, by inhibition of E6 or stabilization with the proteasome inhibitor bortezomib, could be interesting therapeutic options. Further work is required to assess the efficacy of bortezomib on irradiated HPV-positive and -negative cell cultures. A recent phase I clinical trial has demonstrated that the use of bortezomid with concurrent cisplatin-based chemoradiotherapy is well tolerated by HNSCC patients.[8] In the light of these new findings, it will be interesting to evaluate tumor response with respect to HPV-status

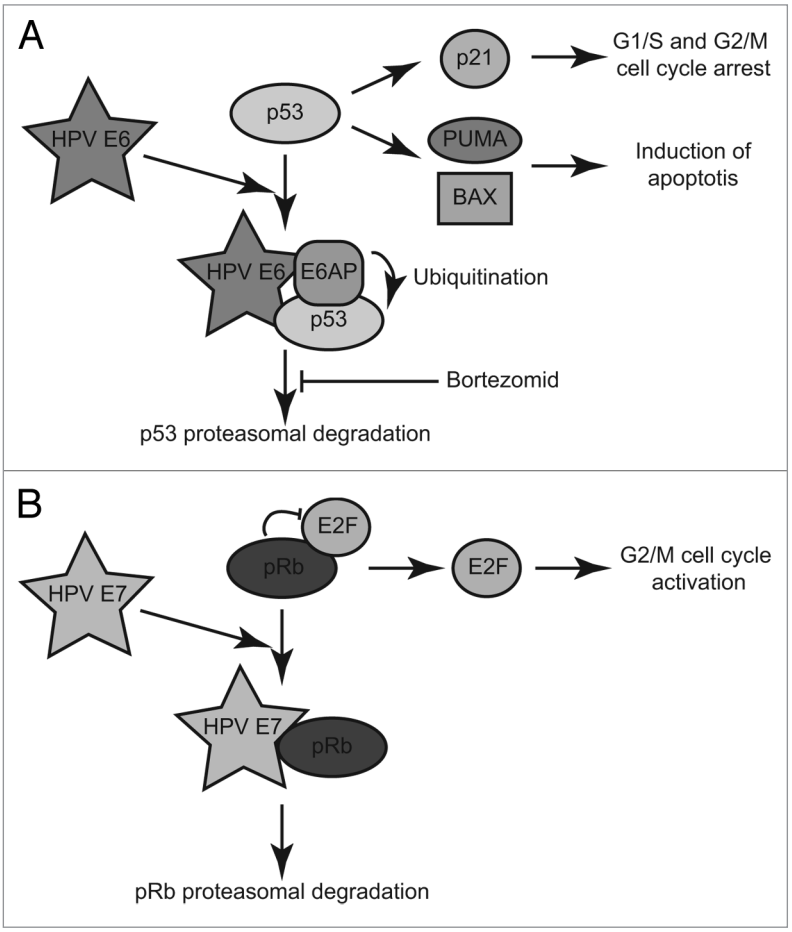

Figure 1. Model representing the role of the E6 and E7 viral oncoproteins in HPV-driven carcinogenesis. (**A**) The p53 tumor suppressor regulates cell cycle arrest at G_1 and G_2/M and apoptosis induction via the regulation of its target genes, such as p21, and Puma and Bax respectively. HPV E6-dependent proteasomal degradation of p53 is blocked by Bortezomib. (**B**) pRb controls the G_2/M cell cycle checkpoint via the inhibition of E2F. Binding of pRb to HPV E7 induces its proteasomal degradation, the activation of E2F and stimulation of cell proliferation.

References

1. Leemans CR, et al. Nat Rev Cancer 2011; 11:9-22; PMID:21160525; http://dx.doi.org/10.1038/nrc2982
2. Kostareli E, et al. Front Oncol 2012; 2:36; PMID:22655271; http://dx.doi.org/10.3389/fonc.2012.00036
3. Longworth MS, et al. Microbiol Mol Biol Rev 2004; 68:362-72; PMID:15187189; http://dx.doi.org/10.1128/MMBR.68.2.362-372.2004
4. Westra WH, et al.Clin Cancer Res 2008; 14:366-9; PMID:18223210; http://dx.doi.org/10.1158/1078-0432.CCR-07-1402
5. Sirianni N, et al. Oral Oncol 2005; 41:423-8; PMID:15792615; http://dx.doi.org/10.1016/j.oraloncology.2004.11.003
6. Rampias T, et al. J Natl Cancer Inst 2009; 101:412-23; PMID:19276448; http://dx.doi.org/10.1093/jnci/djp017
7. Li C, et al. Cell Cycle 2013; 12: In press; PMID:23421999
8. Kubicek GJ, et al. Int J Radiat Oncol Biol Phys 2012; 83:1192-7; PMID:22245208; http://dx.doi.org/10.1016/j.ijrobp.2011.09.023

Cenexin1 and Odf2: Splice variants with diverged cilium functions

Comment on: Chang J, et al.Cell Cycle 2013; 12:655–62; PMID:23343771; http://dx.doi.org/10.4161/cc.23585

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The primary cilium is an essential sensory "antenna" jutting from the cell surface of animal cells. Once thought to be a vestigial structure, the cilium has emerged in the last decade as a vital sensory organelle that impacts a broad spectrum of human diseases named ciliopathies.

The cilium contains a microtubule-based axoneme composed of nine doublet microtubules arranged in a radially symmetric pattern that grows from the distal end of the basal body. The basal body is a modified centriole, a structural component of the centrosome that contains a mother-daughter centriole pair. At ciliogenesis, the mother matures into a basal body for cilium assembly. The mother centriole is distinguished from the daughter by distal and subdistal appendages that are involved in basal body anchoring to the membrane prior to cilium assembly. Loss of Cenexin1, a component of the distal appendages, disrupts cilium assembly.[1] Therefore, dissecting the components of basal bodies and determining how they work will unravel the molecular mechanisms of ciliogenesis, providing a deeper understanding of ciliopathies.

Outer dense fiber protein 2 (*Odf2*), discovered in the sperm tail cytoskeleton,[2] is encoded by *odf2*, and is essential for several aspects of centrosome and cilium function. While *odf2* knockout in mouse F9 cells did not display obvious mitotic spindle assembly or cell division defect, RNAi knockdown in HeLa cells disrupted mitotic spindle organization in a Polo-like kinase 1 (Plk1)-dependent manner.[3] Moreover, knockout mice show a very early pre-implantation embryonic lethality.[4] The odf2 gene encodes at least ten proteins by alternative splicing. Among these, at least two classes emerge: those that have a ~190 amino acid C-terminal extension and those that do not have this domain. Isoform 9, which has the C-terminal extension, is referred to as Cenexin1, whereas isoform 6, without the extension, is *Odf2*.[5] This distinction is important, because the isoforms have different functions and patterns of subcellular localization. *Odf2* is produced predominantly in the testis, where it localizes within flagella (cilia) at structures called outer dense fibers. Cenexin1, on the other hand, is a broadly expressed mother centriole-specific protein[6] that localizes to the distal/subdistal appendages and is required for their assembly.[1] These differences

in localization suggest diverged functions for the splice variants at centrosomes and cilia.

In the March 15, 2013 issue of *Cell Cycle*, Kyung Lee's lab used mouse F9 *odf2*$^{-/-}$ knockout cells to show that Cenexin1, but not its variant *Odf2*, is necessary and sufficient for primary cilium assembly.[5] The *odf2*$^{-/-}$ cells, which express no endogenous *Odf2* or Cenexin1, are deficient in assembly of primary cilia and lack distal/subdistal appendages.[1] Chang and colleagues rescued cilium assembly in *odf2*$^{-/-}$ cells with Cenexin1 expression, but not with *Odf2*.[5] While rescue of cilium assembly in *odf2*$^{-/-}$ cells was shown previously,[1] the work from Lee's lab shows that this function is specific to the Cenexin1 isoform. Regarding *Odf2* function, work from another lab indicates that it is important for sperm morphogenesis, since about 50% of haploid sperm from *odf2* heterozygous mutant mice have an overt "kinked" shape and disruption of the outer dense fibers.[7]

Consistent with the role of Cenexin1 in ciliogenesis, Chang and colleagues show that it associates with Rab8a, a small G protein required for cilium assembly, in a GTP-dependent manner. This finding contrasts with a previous report that *Odf2*, rather than Cenexin1, bound to Rab8a.[8] The basis of this contradiction is unresolved. In addition, the authors showed that centriolar recruitment of Chibby, a distal centriole protein required for ciliogenesis, requires Cenexin1 but not *Odf2*.

Chang and colleagues go on to show that even low expression of full-length Cenexin1, or a Cenexin1 mutant (S796A) defective in Plk1 binding could fully remedy ciliogenesis deficit in *odf2*$^{-/-}$ cells. However, neither *Odf2* nor Cenexin1 deleted for its C-terminal extension rescued ciliogenesis. Consistent with these findings, immune electron microscopy revealed distal/subdistal appendage localization of Cenexin1 but not *Odf2*.

This study depicts a fascinating phenomenon, where, rather than having separate genes encode different proteins, splice variants from the same gene encode distinct functions and localization. In this case, Cenexin1 localizes to distal/subdistal appendages of basal bodies, whereas *Odf2* goes to the axoneme. Future findings will do doubt further illuminate the disparate functions of the proteins encoded by *odf2* in centrosome and cilium biology.

References

1. Ishikawa H, etal Nat Cell Biol 2005; 7:517-24; PMID:15852003; http://dx.doi.org/10.1038/ncb1251
2. Brohmann H,etal J Biol Chem 1997; 272:10327-32; PMID:9092585; http://dx.doi.org/10.1074/jbc.272.15.10327
3. Soung NK, et al. Dev Cell 2009; 16:539-50; PMID:19386263; http://dx.doi.org/10.1016/j.devcel.2009.02.004
4. Salmon NA,etal. Genesis 2006; 44:515-22; PMID:17078042; http://dx.doi.org/10.1002/dvg.20241
5. J Chang, et al. Cell Cycle 2013; 12: 655-62. PMID: 23343771; http://dx.doi.org/10.4161/cc.23585
6. Lange BM, etal J Cell Biol 1995; 130:919-27; PMID:7642707; http://dx.doi.org/10.1083/jcb.130.4.919
7. Tarnasky H, etal BMC Dev Biol 2010; 10:67; PMID:20550699; http://dx.doi.org/10.1186/1471-213X-10-67
8. Yoshimura S, etal J Cell Biol 2007; 178:363-9; PMID:17646400; http://dx.doi.org/10.1083/jcb.200703047

Akt destabilizes p57^{Kip2}: Akt at the converging crossroad?

Comment on: Zhao R, et al. Cell Cycle 2013; 12; 935-943; PMID:23421998; http://dx.doi.org/10.4161/cc.23883

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Cell cycle progression through the G_1 phase is tightly controlled by cyclin-dependent kinases (CDKs). Activity of CDKs is negatively regulated by two unrelated families of CDK inhibitors (CDKi), namely, INK and Cip/Kip. The Cip/Kip family of CDKi consists of three members, p21$^{Cip1/WAF1}$, p27^{Kip1} and p57^{Kip2}. In the context of human cancers, these three proteins are considered suppressors of tumorigenesis and tumor progression. Therefore, their levels of expression in both normal and cancerous cells are under complex transcriptional and post-translational regulations, including ubiquitination and proteasomal degradation.[1]

The upstream regulators leading to degradation of p21$^{Cip1/WAF1}$ and p27^{Kip1} proteins have been extensively studied. For both p21$^{Cip1/WAF1}$ and p27^{Kip1} proteins, Ser/Thr phosphorylation serves as a pivotal event that exports them out of nucleus and promotes their degradation in both cytoplasm and nucleus. Although multiple Ser/Thr kinases can phosphorylate p21$^{Cip1/WAF1}$ and p27^{Kip1}, Akt has attracted substantial attention because of its frequent activation in many types of cancer and its close association with several oncogenic receptor tyrosine kinases (RTKs), such as EGFR and HER2. In HER2-overexpressing breast cancer cells, Akt is often hyperactive and phosphorylates p21$^{Cip1/WAF1}$ at Thr145[2] and p27^{Kip1} at Thr157/Thr198,[3-5] resulting in their nuclear export and proteasomal degradation. Akt-mediated destabilization of p21$^{Cip1/WAF1}$ and p27^{Kip1} underlies the aggressive growth and progression of HER2-driven breast cancer.

Emerging evidence suggests that p57^{Kip2} plays an important role in embryonic development, hematopoietic stem cell quiescence and inhibition of cell cycle progression. Unlike p21$^{Cip1/WAF1}$ and p27^{Kip1}, the upstream pathways leading to p57^{Kip2} intracellular trafficking and stability are still not well understood. Nevertheless, it has been reported that TGF-β1 stimulates p57^{Kip2} phosphorylation at Thr310, leading to its ubiquitination and proteasomal degradation. Stress-activated protein kinase p38 phosphorylates p57^{Kip2} at Thr143 and enhances p57^{Kip2} association with and inhibition of CDK2.[6] Subunit 6 of the COP9 signalosome complex (CSN6) associates with p57^{Kip2} and Skp2, a component of the E3 ligase. This association, in turn, leads to Skp2-mediated p57^{Kip2} ubiquitination and subsequent degradation.[7] Interestingly, CSN6 can be phosphorylated by Akt at Ser60, which renders CSN6 more stabilized.

The elegant study by Zhao et al. showed for the first time that Akt interacts with and phosphorylates p57^{Kip2} at Ser282 and Thr310, resulting in p57^{Kip2} nuclear export, ubiquitination and proteasome-mediated degradation.[8] HER2-overexpressing breast cancer cells were found to express lower levels of p57^{Kip2} than those with normal HER2 expression. Constitutively active Akt induced p57^{Kip2} degradation, whereas a dominant-negative Akt mutant and PI3K inhibition led to p57^{Kip2} stabilization. The authors further showed that Akt-mediated phosphorylation and stabilization

of CSN6 contributed to $p57^{Kip2}$ degradation. Consistent with these observations, restoration of $p57^{Kip2}$ in HER2-amplified, $p57^{Kip2}$-deficient breast cancer cells led to reduced cell growth in vitro and the inability to form xenografts in nude mice, indicating that $p57^{Kip2}$ antagonizes HER2-mediated breast cancer cell growth and possibly HER2-related tumorigenesis. Analysis of patient breast carcinomas revealed for the first time that in patients with HER2-overexpressing tumors, low $p57^{Kip2}$ levels correlated with poor overall survival.

A significant implication for the novel Ak→$p57^{Kip2}$ signaling axis is that it may play an important role in embryonic development in addition to cancer. Unlike $p21^{Cip1/WAF1}$ and $p27^{Kip1}$, $p57^{Kip2}$-knockout mice uniquely displayed developmental defects and a phenotype that resembles the Beckwith-Wiedeman syndrome, a childhood overgrowth syndrome. The potential involvement of the Akt→$p57^{Kip2}$ link in embryonic development is worthy of investigations in future studies.

In light of the new findings reported by Zhao et al. combined with those published previously,[2-5] we now know that Akt phosphorylates all three members of the Cip/Kip family of CDKi (Fig. 1). This important discovery indeed revised the signaling landscape for the HER2→Akt signaling module, in that Akt plays a central role in lifting CDKi-mediated cell cycle arrest and therefore facilitates proliferation of HER2-amplified breast cancer. An immediate significant implication of these findings is that the newly discovered Akt→$p57^{Kip2}$ signaling axis may have a broad impact on different subtypes of breast cancers, such as triple-negative and basal-like breast cancer, given the fact that Akt can also be activated by other RTKs besides HER2, such as EGFR, IGF-1R, VEGFR, c-Met and PDGFR. Another potential implication is that the negative regulation of $p57^{Kip2}$ by Akt may also exist in other types of cancer, since Akt activation is a common phenomenon in a number of human cancers. Indeed, future investigations are needed to broadly explore the impact of the Akt→$p57^{Kip2}$ signaling axis on cancer and embryonic development.

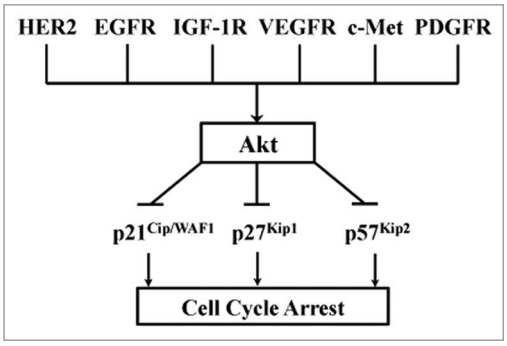

Figure 1. Akt at the converging crossroad connecting multiple receptor tyrosine kinases to all three members of the Cip/Kip family of CDKi. Akt is known to be activated by several upstream RTKs that are frequently activated in human cancers. These RTKs include HER2, EGFR, IGF-1R, VEGFR, c-Met, PDGFR and several others. It is also known that there are a number of proteins serving as the downstream effectors of Akt, such as, mTOR and two CDKi, $p21^{Cip1/WAF1}$ and $p27^{Kip1}$. Importantly, the study by Zhao et al. provided the first evidence that defines $p57^{Kip2}$ as the substrate of Akt, thus making Akt a central common Ser/Thr kinase that negatively regulates all three members of the Cip/Kip family of CDKi that contribute to cell cycle arrest. Consequently, these reported findings potentially place Akt at the converging point that connects multiple RTKs to all three members of the Cip/Kip family of CDKi, in order to unblock cell cycle arrest and support uncontrolled cell proliferation in cancer cells.

References

1. Lu Z, etal. Cell Cycle 2010; 9:2342-52; PMID:20519948. http://dx.doi.org/10.4161/cc.9.12.11988
2. Zhou BP, etal. Nat Cell Biol 2001; 3:245-52; PMID:11231573. http://dx.doi.org/10.1038/35060032
3. Liang J, etal Nat Med 2002; 8:1153-60; PMID:12244302. http://dx.doi.org/10.1038/nm761
4. Shin I, etal Nat Med 2002; 8:1145-52; PMID:12244301. http://dx.doi.org/10.1038/nm759
5. Viglietto G, etal Nat Med 2002; 8:1136-44; PMID:12244303. http://dx.doi.org/10.1038/nm762
6. Joaquin M, et al. EMBO J 2012; 31:2952-64; PMID:22569127. http://dx.doi.org/10.1038/emboj.2012.122
7. Chen B, etal Cell Cycle 2012; 11:4633-41; PMID:23187808. http://dx.doi.org/10.4161/cc.22887
8. Zhao R, etal Cell Cycle 2013; 12; PMID:23421998