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Cell Cycle News & Views

Live longer, drink (poly)phenols!

Comment on: Pietrocola F, et al. Cell Cycle 2012; 11:3851–60; PMID:23070521; http://dx.doi.org/10.4161/cc.22027

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A healthy diet rich in fruits and vegetables is an important part of a healthy lifestyle. Whereas epidemiological data sometimes fail to provide proof of this concept, molecular evidence is accumulating that clearly shows both preventive as well as therapeutic effects of compounds from natural origins. In the paper of Guido Kroemer's group about pro-autophagic polyphenols and their inhibitory effect on acetylation of cytoplasmic proteins, much emphasis is given to the relevance of this molecular mechanism in various diseases, including cardiovascular (French paradox) and neurodegenerative diseases as well as cancer.

In fact, more than 75% of all anticancer drugs used in the clinics are of natural origins or at least inspired from nature. Based on this observation, many international research groups aim at discovering molecular mechanisms triggered or inhibited by compounds from nature. These compounds are sometimes controversially considered an excellent source for future preventive interventions as well as natural anticancer drugs able to target the main hallmarks of cancer or their enabling characteristics.[1,2]

Accordingly, molecular hallmarks that are efficiently inhibited by various natural compounds from the daily diet could be documented over the last decade. In our recent review,[1] various compounds from the "garden" are matched with their target signaling pathways: diallylpolysulfides from garlic induce cell cycle arrest and lead to apoptotic cell death; epigallocatechin 3-gallate (EGCG), curcumin and capsaicin were reported to inhibit epidermal growth factor receptor (EGFR) cell signaling pathways; β-lapachone from the bark of *Tabebuia avellanedae* induces a reduction of the telomerase RNA level; flavonoids like luteolin or genistein inhibit mechanisms linked to metastasis formation; angiogenesis is inhibited by plumbagin; methyl jasmonate inhibits cancer cell metabolism by active induction of hexokinase release; cordycepin inhibits PARP-1-involved base excision repair and finally a wealth of compounds were shown to inhibit pro-inflammatory cell signaling mechanisms including NFκB and Jak/STAT. It becomes clear that even from our diet, nature provides arrays of molecules able to interfere with all crucial steps of carcinogenesis, covering initiation, promotion and progression of the disease.

Natural compounds that interfere with autophagic mechanisms are much less investigated and, accordingly, deserve particular attention, as they could lead to therapeutic applications in cancer types resistant toward apoptotic cell death. In the report by Pietrocola et al.,[3] authors show that pro-autophagic polyphenols reduce the acetylation level of cytoplasmic proteins, and that a cause-effect relationship between this deacetylation and autophagy induction by red wine components exists. Here, the authors investigated the effect of well-known mono- and polyphenols and demonstrate that these compounds have a differential potential to induce autophagy in human cells. Autophagy induction and inhibition of cytoplasmic protein acetylation could be convincingly established. Moreover, even though structurally tightly related, these compounds were able to generate differential effects and act on different cell signaling pathways. Of special interest beyond the fundamental aspect of their findings is the very efficient and easy methodology to detect and measure, by in situ fluorescence microscopic analysis, specifically cytoplasmic protein acetylation levels. This methodological approach has great relevance for analyzing specific subcellular protein acetylation levels.

The next challenge that remains after their observation: to identify the cytoplasmic protein(s) whose modulation of the acetylation level may be causative for the modulation of biological effects including autophagy. Can we soon expect a yet-to-be elucidated mechanism to be highlighted by the same authors?

Nature seems to produce compounds able to interfere with many, if not all, cellular mechanisms, including autophagy. This report opens an avenue for future research and yet adds an additional important cell signaling pathway that can be targeted for both chemoprevention and potentially also for therapeutic purposes.

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Predicting PARP inhibitor sensitivity and resistance

Comment on: Oplustilova L, et al. Cell Cycle 2012; 11:3837–50; PMID:22983061; http://dx.doi.org/10.4161/cc.22026

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The concept of precision therapy in cancer implies an ability to customize treatment according to the molecular makeup of the patient and the tumor. While many pharmaceutical agents are described as targeted therapies, their precise role in cancer treatment is unclear. Often the new drug's target is well-described, but the precise indication of when it should be used (i.e., a prospectively validated predictive marker) is often not defined. PARP inhibitors exemplify this paradigm well. The molecular target, poly ADP-ribose polymerase 1 (PARP1), and the interaction between drug and target are well-defined, and small-molecule inhibitors of PARP1 (PARP1i) have shown considerable promise for the treatment of BRCA1- and BRCA2-deficient breast, ovarian and prostate cancer.[1] Recent work suggests PARP1i may also have utility in the treatment of cancers with deficiencies in other DNA damage response proteins,[2] including ATM[3-5] and Mre11.[6] Nevertheless, experience in triple-negative breast cancer, a limited surrogate for DNA repair deficiency, has tempered enthusiasm for their use, emphasizing that the identification of molecular predictors of PARP1i sensitivity and resistance to guide their use remains a priority. Here, Bartek and colleagues attempt to address this issue directly, describing several key observations.[7]

First, they extend prior findings to show that depletion of either Nbs1 or Mre11, components of the MRN complex required for activation of ATM and initiation of the homologous recombination DNA double-strand break repair pathway, also sensitize breast cancer cells to PARP1i. However, unlike in cells with depletion or inactivation of ATM, where mutation or depletion of p53 enhances sensitivity to the PARP1i olaparib,[4] p53 status had little effect on PARP1i sensitivity in colon cancer cells depleted of Mre11 and/or Nbs1, either alone or in combination with DNA damaging agents, suggesting that Mre11 or Nbs1 deficiency has subtly different effects on PARP1i sensitivity compared with ATM deficiency. Second, the authors show that depletion of 53BP1 promotes PARP1i resistance, consistent with active NHEJ being required for PARP1i-induced cell death.[4,8]

The successful clinical application of PARP inhibitors will require identification of predictive markers for tumors likely to be susceptible to PARP inhibition. Oplustilova and colleagues[7] provide evidence that poly-ADP ribose, the product of PARP activity, could be a potential biomarker of cellular response to PARP inhibition. Finally, the authors address acquired resistance to PARP1i, an evolving problem clinically, by modulation of P-glycoprotein (P-gp). The authors show that the P-gp inhibitor Verapamil overcomes PARP1i efflux attributed to P-gp overexpression, thereby restoring sensitivity to PARP1i.[7]

Despite addressing these important questions, do these findings herald the arrival of a predictive marker for PARP1i? Unfortunately, the answer is probably not. Although these findings extend our understanding of the potential application of PARP1i to additional DNA repair-deficient cancers, there are several important caveats. The work described was performed on a range of different cell lines in vitro and has not been validated in in vivo models. In addition, the incomplete understanding of the influence of p53 on PARP1i in the context DNA repair deficiency limits its status as a predictor of sensitivity. Finally, overcoming resistance using P-gp inhibitors has had a disappointing course in modulating the efficacy of standard cytotoxic chemotherapy. Unless the third generation P-gp inhibitors are markedly more effective and less toxic, it seems unlikely that this is the best avenue to pursue in improving PARPi utility. As exemplified in HER2-positive breast cancer and in EGFR mutation-positive non-small cell lung cancer, it is a consistent finding that "molecular selection trumps clinical selection."[9] A validated predictive molecular marker can direct targeted therapy, ensuring that patients unlikely to respond are offered more useful intervention, and restrict expensive treatment to those most likely to benefit. While the work of Bartek et al.[7] extends our understanding of the role of DNA repair deficiency in PARPi sensitivity, it seems that the subtle nuances of DNA repair pathway modulation make it challenging to develop such a marker for PARP inhibition. In the absence of a functional assay to test tumor DNA repair capacity, more work is required to precisely define which tumor molecular marker (or combination of markers) will best serve this purpose.

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Examining the roles of DNA2 during mammalian end resection

Comment on: Karanja KK, et al. Cell Cycle 2012; 11:3983–96;
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The initiation and extension of end processing of chromosomal breaks to form single-stranded DNA (ssDNA), referred to as end resection, significantly affects the cellular consequences of such breaks.[1] Regarding repair, such ssDNA is the optimal substrate for RAD51 nucleoprotein filaments, which catalyze the strand exchange step that is central to homology-directed repair (HDR).[1] HDR that uses the identical sister chromatid as the template is relatively non-mutagenic. Alternatively, homologous segments in ssDNA flanking a chromosomal break could be annealed to each other to bridge the break, which is referred to as single-strand annealing (SSA) in the case of relatively extensive homology, or alternative/microhomology-mediated end-joining (Alt-EJ/MMEJ) involving more limited homology.[1] Given the preponderance of repetitive elements in the human genome, SSA and Alt-EJ/MMEJ repair events may be prone to causing substantial genome rearrangements. In contrast to facilitating these homology-mediated repair events, end resection likely inhibits non-homologous end joining (NHEJ), since breaks with ssDNA at the terminus are not readily repaired by simple ligation. Such inhibition of NHEJ may be inconsequential to genome stability, but only if the sister chromatid is present to facilitate HDR. Apart from affecting repair outcomes, ssDNA is a potent signal for inducing cell cycle checkpoint pathways.[2] Accordingly, examining how cells regulate the initiation and extent of end resection following induction of DNA lesions is critical for understanding the cellular consequences of such DNA lesions.

The DNA2 nuclease was initially identified in yeast as an essential factor for DNA replication.[3] During Okazaki fragment maturation, the DNA2 endonuclease activity cleaves the 5' flap DNA in the middle of the ssDNA flap, removing a portion of the flap.[4] The resulting short flap structure is then cleaved by the FEN1 nuclease to generate a DNA end that is suitable for ligation. More recently, yeast DNA2 was shown to function during DNA double-strand break (DSB) repair.[5-7] Specifically, DNA2 and RecQ helicase Sgs1 were shown to form a complex that processes 5' DNA ends to generate 3' ssDNA overhangs. Regarding its role in genome stability, DNA2 was recently shown to be overexpressed in human cancer cells, where it reduces replication stress and supports hyper-DNA replication.[7] How overexpression of DNA2 helps to reduce DNA replication stresses and promotes DNA replication in cancer cells remains far from clear.

In the study by Karanja et al.,[8] DNA2 is demonstrated to play an important role in promoting end resection following exposure to the interstrand crosslinking (ICL) agent cisplatin, as well as the topoisomerase I poison camptothecin. These defects in end resection are shown to affect many of the cellular consequences described above: DNA2-deficient cells show a decrease in SSA, a reduction in cell cycle checkpoint signaling (CHK1 phosphorylation), reduced repair of ICLs and a reduction in NHEJ (DNA-PKcs phosphorylation). Notably, both the resection defects and many of the above consequences are most severe in cells co-depleted of DNA2 and EXO1, indicating that while DNA2 itself is important to promote end resection, there is some degree of functional redundancy with EXO1. Interestingly, DNA2 depletion does not cause a defect in RAD51-dependent HDR and, furthermore, causes a lesser effect on RAD51 recruitment to DNA lesions as compared with its effect on end resection. Accordingly, the role of DNA2 during end resection appears to affect the relative balance of HDR and SSA, and hence the consequences of end resection on chromosomal stability.

In addition, Karanja et al. demonstrates that the role of DNA2 on the cellular response to ICLs is dependent on the FA/BRCA pathway, which is critical for recognition and processing of such ICLs.[9] DNA2 is shown to interact with the FA/BRCA factor FANCD2, and DNA2 depletion is shown to not clearly affect the cellular response to ICLs in FANCD2-deficient cells. These findings support the model that the FA/BRCA pathway recognizes ICLs to generate breaks that are resected via DNA2 in a manner that is partially redundant with EXO1. In the future, it will be important to elucidate the mechanisms by which DNA2 and EXO1 are regulated during resection, such as the coordination of the FA/BRCA pathway and DNA2.

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A novel link between the HER2-Akt and MDM2-p53 pathways via CSN6

Comment on: Xue Y, et al. Cell Cycle 2012; 11:4181–90;
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The constitutive photomorphogenesis 9 (COP9) signalosome (CSN) is an evolutionarily conserved multiprotein complex in plants and animals.[1] This protein complex, consisting of eight subunits (CSN1 to CSN8), is homologous with the 19S regulatory lid complex of the 26S proteasome, which plays a central role in the recognition and efficient degradation of misfolded proteins.[2] The diverse functions of the COP9 complex include regulation of several important intracellular pathways, such as the ubiquitin/proteasome system, DNA repair, cell cycle, apoptosis and tumorigenesis.[3] However, detailed mechanisms through which COP9 and its subunits contribute toward tumor development remain unclear.

Previously, Lee's laboratory demonstrated that CSN6, a subunit of the COP9 signalosome, interacts with and inhibits the degradation of an oncogene MDM2, leading to its stabilization (**Fig. 1**).[4] MDM2 is a RING domain-containing E3 ubiquitin ligase, toward the tumor suppressor p53 and itself, thereby regulating the proteolytic turnover of these proteins.[5] Overexpression of MDM2 is detected in approximately 30% of human cancers due to gene amplification and other unknown mechanisms.[5] They found that gene amplification of *CSN6* is also detected in a high percentage of human breast cancer tissues, and there is a positive correlation between copy numbers of *CSN6* gene and breast tumor size.[4] Importantly, CSN6 is concomitantly overexpressed with MDM2 in human breast cancer tissues, consistent with their observation that CSN6 stabilizes MDM2 by inhibiting its self-ubiquitination. Complete deletion of *CSN6* in mice results in early embryonic lethality, which is partially rescued by concomitant deletion of *p53*.[4] Mice heterozygous for *CSN6* (*CSN6*$^{+/-}$) exposed to high doses of γ-irradiation (IR) show decreased survival due to an increased p53 activity. However, exposure to lower doses delays the onset of tumor development, suggesting that reduced CSN6 levels result in an increase in the p53 activity and prevent tumorigenesis in vivo.[4] Thus, CSN6 plays a crucial role in the MDM2-p53 pathway and tumor development. However, the regulatory mechanisms behind the activation of the CSN6-MDM2-p53 axis are unknown.

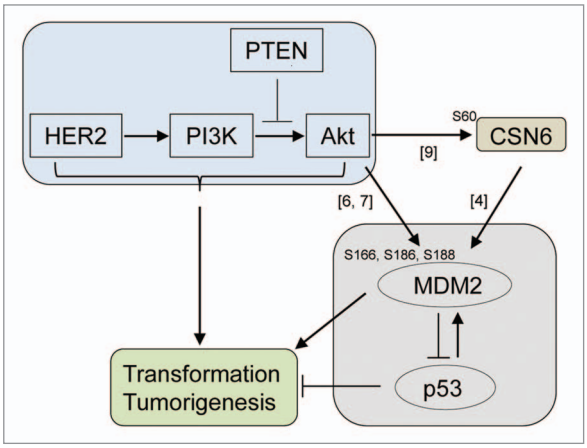

Figure 1. The HER2-Akt pathway affects the MDM2-p53 pathway by direct phosphorylation of MDM2 and via stabilization of MDM2 by CSN6. Numbers indicate the references cited.

The stability and activity of MDM2 are regulated by multiple means. One of the mechanisms is that the oncogenic HER2-Akt signaling phosphorylates and activates MDM2 (**Fig. 1**).[6,7] The HER2 oncoprotein is overexpressed in approximately 30% of breast cancers and activates Akt.[8] Although the phosphorylation of MDM2 at Ser166, Ser186 and Ser188 by Akt is involved in the subcellular localization and stabilization of MDM2,[6,7] the exact mechanisms by which HER2-Akt signaling activates MDM2 remain unclear.

A recent paper from Lee's laboratory illustrates a novel mechanism by which HER2-Akt signaling stabilizes MDM2 through CSN6 (**Fig. 1**).[9] They demonstrate that Akt directly interacts with and phosphorylates CSN6 at Ser60, which inhibits the degradation of CSN6 by reducing its ubiquitination. Phosphorylated and stabilized CSN6, as previously established, increases the level of MDM2 and subsequently reduces p53 expression.[4] Overexpression of Akt translocates CSN6 from the cytoplasm to the nucleus, which could facilitate its effects on MDM2.[9] They also show that CSN6 cooperates with Akt in cellular transformation. Hence, this study has further strengthened the significance of the MDM2-p53 pathway on tumorigenesis through a novel link of Akt-mediated CSN6 activation. Thus, MDM2 can be activated by direct phosphorylation via HER2-Akt singling and indirect stabilization via the Akt-CSN6 axis (**Fig. 1**).

This study has opened new avenues for future exploration that might advance the aspect of using CSN6 as a therapeutic target. It is important to determine a positive clinical correlation between HER2 and CSN6 expression in human tumor samples. Studies using mouse models manipulated for both HER2 and CSN6 will further provide in vivo evidence for their roles in tumorigenesis. It would be interesting to learn whether or not the Akt-mediated phosphorylation of MDM2 and the Akt-mediated stabilization of CSN6 cooperate with each other toward the Akt-mediated MDM2 activation. Further investigations to understand the effects of CSN6 phosphorylation on tumorigenesis and COP9 function should also be performed. Taken together, this study opens a new field of oncogene-mediated tumorigenesis, thus significantly accelerating the development of a novel therapeutic strategy for various types of cancer.

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FBW7-Aurora B-p53 feedback loop regulates mitosis and cell growth

Comment on: Teng CL, et al. Cell Cycle 2012; 11:4059–68; PMID:23095493; http://dx.doi.org/10.4161/cc.22381

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FBW7 (F-box and WD repeat domain-containing 7, also known as FBXW7, CDC4, AGO and SEL10) is a well-characterized tumor suppressor and is frequently mutated in a variety of cancers. As a substrate recognition component of SCF (which is a complex of SKP1, CUL1 and F-box proteins) type ubiquitin ligase, FBW7 targets several well-known oncoproteins for ubiquitination and degradation, and therefore controls diverse cellular processes, including cell cycle progression, cell proliferation, cell differentiation and maintenance of genomic stability.[1] However, the exact mechanism of FBW7-associated tumor suppression remains elusive. Although cyclin E and c-Myc have been identified as targets of FBW7, the downregulation of these two proteins cannot explain the polyploidy problems associated with FBW7 that are observed in many types of cancers.

In a recent issue, Teng et al. showed that FBW7 regulated the ubiquitination and degradation of Aurora B, a mitotic checkpoint kinase that plays a critical role in chromosome alignment, segregation and cytokinesis during mitosis.[2] Cancer cells frequently exhibit an unusually high level of Aurora B, leading to dysregulated mitosis and resulting in unequal chromosome segregation, which provides a growth advantage to cancer cells.[3] Therefore, Aurora B is an attractive target for therapeutic cancer drugs. Teng et al. demonstrated that FBW7 was a negative regulator of Aurora B, and that the expression of FBW7 suppressed Aurora B-mediated cell growth and mitotic deregulation and reduced the percentage of multinucleated cells caused by Aurora B overexpression. By mapping the interaction region for the mutual association in FBW7 and Aurora B, Teng et al. further identified that R465 and R505 residues of WD 40 domain of FBW7 within the binding pockets are necessary for binding to Aurora B.[2] Importantly, FBW7 R465 mutations are frequently observed in cancers.[4] The mutant FBW7 would not be able to interact with Aurora B and mediate its degradation, which may lead to Aurora B accumulation and mitotic defects, thereby providing a growth advantage. It has been demonstrated that Aurora B is a negative regulator of p53, and it not only phosphorylates p53, leading to enhanced p53 degradation through MDM2-mediated ubiquitination, but also suppresses p53 transcriptional activity and function.[5,6] Loss of p53 causes the downregulation of FBW7α.[7] Taken together, these findings suggest the existence of a feedback loop between FBW7, Aurora B and p53. Clearly, a fine balance is critical for maintaining correct chromosome segregation and cell progression during mitosis in normal cells. Any signaling that breaks the balance, such as FBW7 mutations, Aurora B elevation or p53 mutations, may cause mitotic catastrophe and accelerate cancer cell growth. The findings of Teng et al. not only shed a new light

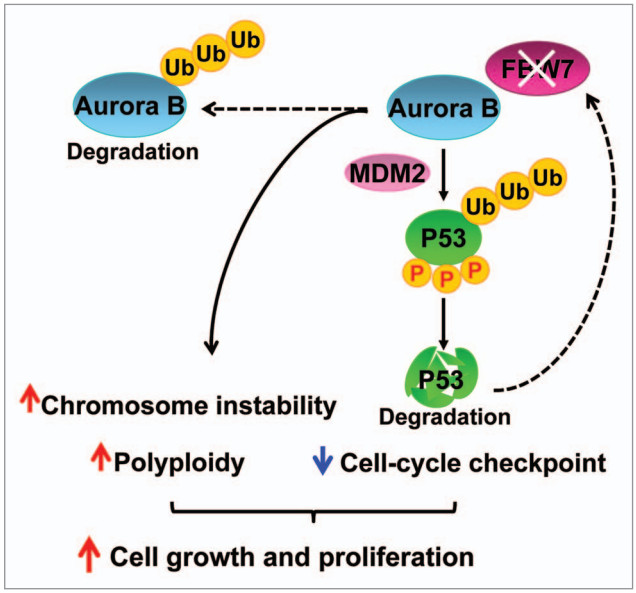

Figure 1. FBW7-Aurora B-p53 feedback loop regulates cell processes. FBW7 suppresses Aurora B expression through ubiquitination-mediated protein degradation. Loss of FBW7 leads to the accumulation of Aurora B; Aurora B phosphorylates p53 and enhances MDM2-mediated p53 degradation, resulting in consequent cancer cell growth. The deficiency of p53 causes the downregulation of FBW7α.

on the tumor suppressive functions of FBW7 in oncogenesis, but also provide therapeutic strategy for cancer treatment.

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