

Cell Cycle News & Views

A novel link between p53 and ROS

Comment on: Italiano D, et al. *Cell Cycle* 2012; 11:4589–96; PMID:23187810; <http://dx.doi.org/10.4161/cc.22853>

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As one of the most intensively studied transcription factors, it is unsurprising that p53 is involved in many biological processes, including cell cycle arrest, DNA repair, senescence and apoptosis.¹ Its activities are mainly regulated by posttranslational modifications and interactions with other cellular components. Over the past few years, p53 has also been linked to redox homeostasis, the balance between cellular pro- and antioxidant levels.² On the one hand, reactive oxygen species (ROS) can modify the cysteine residues of p53, leading to a conformational change that affects its transcriptional activities.² On the other hand, p53 also acts as an upstream regulator of ROS production by activating or repressing several ROS-regulating genes, such as glutathine peroxidase (GPX), p53-induced genes (PIGs), nitric oxide synthase 2 (NOS2) and Mn superoxide dismutase (MnSOD).² Those genes have been shown to act either in a pro- or an antioxidant context. Hence, the role of p53 in overall ROS regulation is a complex network and still needs to be investigated in depth.

ROS are generated by both mitochondrial and non-mitochondrial pathways. In the latter pathway, the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) mainly contributes to ROS production. Among many family members, NOX2 is the one which has been most extensively studied (Fig. 1). NOX2 mainly localizes on the plasma membrane and generates superoxide utilizing NADPH and molecular oxygen upon activation, e.g., in the process of phagocytosis.³ Recently, neutrophil cytosolic factor 2 (NCF2), the gene encoding p67^{phox}, which is the cytosolic subunit and activator of NOX2, has been identified as a novel target of p53.⁴ In this study, Italiano et al. have shown that p53 can bind to the promoter of NCF2 and activate gene expression, indicating that p53 is a transcription factor for NOX2. NCF2 is upregulated by doxorubicin treatment in p53-positive HCT 116 cells but

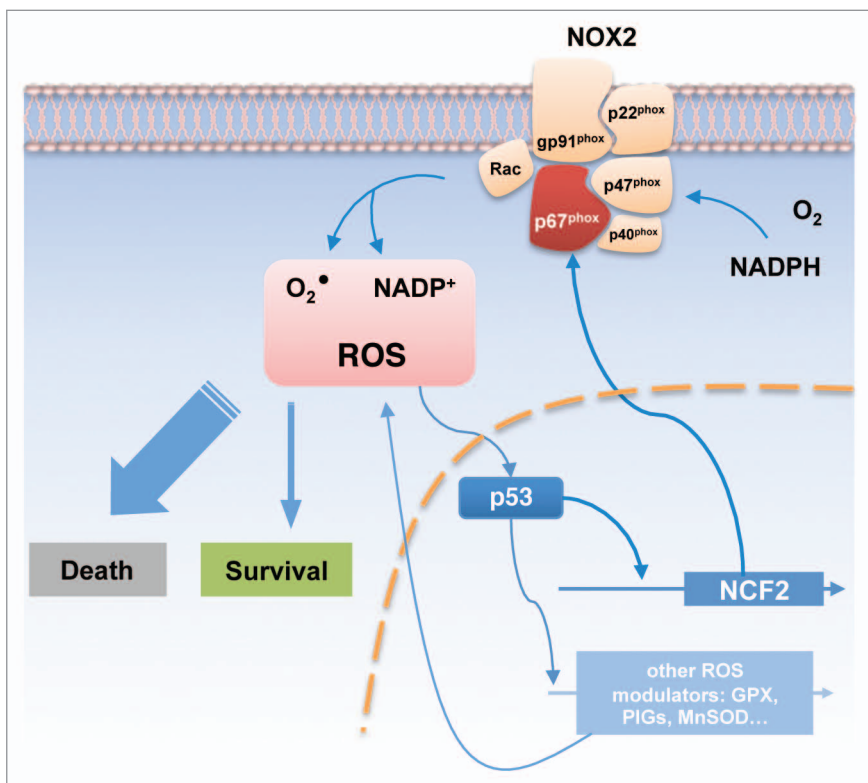


Figure 1. The network of ROS regulation by p53. Reactive oxygen species (ROS) can modulate the activity of p53, which, in turn, controls the expression of several ROS-regulating genes, such as GPX, PIGs and MnSOD. Those act as either pro- or antioxidant. NCF2, the gene encoding the intercellular subunit of NOX2 protein complex, is also transcriptional activated by p53. Upon activation, NOX2 generates ROS beneficial to cell survival. On the other hand, high ROS concentration may lead to cell death.

not in p53-negative cells. Downregulation of NCF2 with siRNA-based approach results in reduced ROS production and increased cell death in HCT 116 and HaCat cells. This suggests that NOX2 expression is a sort of ROS-dependent cell survival factor owing to the influence of ROS on p53 (Fig. 1). It should be mentioned, however, that high ROS concentrations can also kill cells.⁵ Taken together, these results provide a new insight into the network of p53 and ROS production. Since p53 can act both pro- and anti-apoptotically, the pro-oxidant NCF2/p67^{phox} can thus support the

anti-apoptotic role of p53 under certain conditions. In this case, p53 is probably required to maintain a sufficient level of NCF2/p67^{phox} for cell survival. However, under which circumstances p53 activates NOX2 and how they modulate the cell fate are still questions of interest at the moment.

In summary, the identification of NCF2/p67^{phox} as a novel target of p53 extends our understanding of the partnership between p53 and ROS production and further highlights the unknown role of p53 in inflammatory diseases, such as cardiovascular, autoimmune

and allergic diseases as well as primary and secondary immunodeficiencies.

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Linking JNK-STAT3-Akt signaling axis to EZH2 phosphorylation: A novel pathway of carcinogenesis

Comment on: Chen B, et al. *Cell Cycle* 2013; 12:112–21; PMID:23255093; <http://dx.doi.org/10.4161/cc.23030>

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Activation of JNK signaling pathway has long been viewed as a one-way road to the destination where apoptotic or non-apoptotic cell death occurs in response to a plethora of extracellular stimuli. Paradoxically, JNK has also been implicated in the proliferation of transformed and cancer cells.¹ For example, several early studies have shown that activation of JNK kinase could increase the incidence of tumor formation or tumor size of hepatocellular carcinoma (HCC), gastric cancer and lung cancer induced by chemical carcinogens or tobacco smoke. However, it is still puzzling how JNK, which is a well-studied kinase regulating cell death, acts in the opposite direction to induce proliferation of cancer cells. In both compensatory growth model in *Drosophila* and cancer model in mice, JNK was viewed as an upstream kinase of Wnt/BMP signaling and JAK/STAT3 signaling that is important in providing growth advantages for the cells. Alternatively, JNK appears to be essential for

the expression of c-myc, a tumor-promoting oncogene in human and mouse HCC.² In a recent issue of *Cell Cycle*, Chen and colleagues³ provide convincing evidence showing that activation of JNK by arsenic is an early event in the JNK-STAT3-Akt signaling axis that is linked to serine 21 (S21) phosphorylation of EZH2, an enzyme subunit of the PRC2 complex responsible for trimethylation of histone H3 lysine 27 (H3K27me3).

Previously, the Chen group demonstrated that JNK phosphorylates STAT3 at serine 727 (S727), which, in turn, activates Akt and induces VEGF expression and cell migration.⁴ In this report, they validate the JNK regulation of STAT3 via miR-21 and link the JNK-STAT3-Akt signaling axis to the phosphorylation of EZH2. In addition, they found that STAT3 upregulates Akt through miR-21-mediated silencing of *Spry2* rather than PTEN or PDCD4 as previously reported. *Spry2* is a tumor suppressor that antagonizes multiple receptor tyrosine kinases associated with the activation of Ras/ERK and PI3K/Akt is the major effect from loss of *Spry2*.^{5,6}

Akt-dependent S21 phosphorylation of EZH2 has been reported in breast cancer cells treated with IGF-1 or estrogen.⁷ It is believed that this phosphorylation weakens the association between EZH2 and other PRC2 subunits, which

results in the decrease in H3K27me3 level in the genome. Unexpectedly, this report did not show a detectable effect of S21 phosphorylation of EZH2 on H3K27me3 level. The authors attribute this finding to the small fraction of EZH2 being phosphorylated by arsenic, which may not be sufficient to affect the methyltransferase activity of EZH2. Interestingly, they observed that a substantial amount of S21-phosphorylated EZH2 is localized in the cytoplasm, which is unusual considering that EZH2 is predominantly a nuclear protein. The question to be answered is whether S21-phosphorylated EZH2 can partner with specific proteins in the cytoplasm to alter their function.

The significance of this paper is that it might reveal a novel mechanism of carcinogenesis induced by arsenic and other related metal carcinogens. It is worth noting that JNK is involved in the signaling of STAT3 and Akt that leads to EZH2 phosphorylation. The activation of JNK-STAT3-Akt signaling axis and EZH2 phosphorylation are potentially crucial steps in the generation of cancer stem cells (CSCs), since both STAT3 and EZH2 are known to be involved in the self-renewal, pluripotency and proliferation of CSCs (Fig. 1).⁸ Interestingly, a recent report suggests that Oct4, one of the four Yamanaka factors for reprogramming, is a substrate of Akt.⁹ Phosphorylation of Oct4 by Akt would enhance the transcriptional activity of Oct4 on other pluripotent or self-renewal genes, suggesting the potential new role of JNK-STAT3-Akt signaling and EZH2 phosphorylation in CSC growth and carcinogenesis.

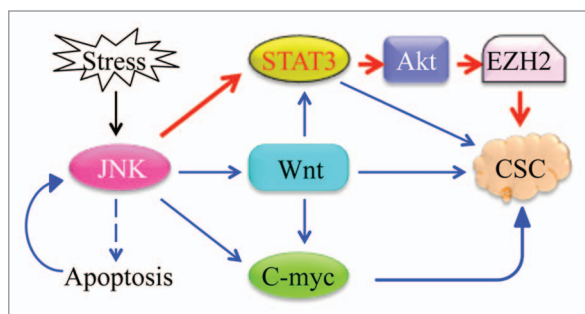


Figure 1. JNK-STAT3-Akt signaling axis in carcinogenesis.

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p53 continues to surprise: High levels of p53 can suppress apoptosis

Comment on: Chee JLY, et al. *Cell Cycle* 2013; 12:278–88; PMID:23255126; <http://dx.doi.org/10.4161/cc.23054>

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On average, p53 is mutated in 50% of tumors. As results accumulate from large-scale cancer genome sequencing approaches, it is evident that underlying this average, p53 mutation rates in different tumor subtypes are highly heterogeneous. For example, p53 is mutated in over 80% of triple-negative basal-like breast cancers and 90% of high-grade serous ovarian cancers, while, in contrast, luminal A breast tumors are 88% wild-type p53.¹ These findings suggest that the tissue-specific genetic background of the precursor cancer cell can influence the subsequent route of p53 inactivation.

Missense mutations of p53 are common. These are frequently situated in the DNA binding domain of p53 (hotspot mutations), resulting in impairment of the ability of p53 to transactivate its downstream pathways. Such mutations not only obviolate the normal functions of p53, but also result in a gain of function, a focus of current research. This gain of function is associated with mutant p53 promiscuously cooperating with other transcription factors (for example, NF- κ B, VDR³ and p63⁴) resulting in expression of genes driving metastasis.

In the 50% of tumors with wild-type p53, how are the normal responses of p53 attenuated? There are presumably upstream, downstream or a combination of factors that suppress the normal critical damage sensor roles of p53. The nature of the sensors and responses when oncogenes are overexpressed are presently being unravelled.⁵ Normal cells maintain low levels of p53 protein to prevent the activation of the downstream apoptotic and other tumor suppressor pathways.

Unexpectedly, high levels of wild-type p53 protein are found in some tumors and are associated with metastasis and poor prognosis. The cancer cell can function in the face of these high levels of wild-type p53 by excluding the protein from the nucleus and relocating to the cytoplasm (e.g., ref. 6), thus limiting the transactivation of p53 target genes. Cancer cells with mutant p53 can also show high levels of the protein located in the cytoplasm. Since transactivation activity of mutant p53 is absent, this prompted Chee et al.⁷ to speculate that high levels of cytoplasmic p53 (wild-type or mutant) provide a gain of function and therefore a selective advantage to the cancer cell. The paper by Chee et al. provides compelling evidence that this gain of function results in increased resistance of the tumor cell to chemotherapeutic drugs.

In their study, Chee et al. showed that p53 can interact with and inhibit caspase-9, one of the critical caspases in the classical apoptosis cascade. At first this appears counter intuitive as one of the major transactivation pathways of p53 targets is to drive apoptosis in response to external or internal cellular stress. However, when the unusual cytoplasmic localization of the p53 in these cancer cells is considered, this begins to make sense. Increased resistance to cisplatin, a commonly used chemotherapeutic agent, is shown to be dependent on mutant or wild-type p53. One of their approaches utilizes an ecdysone-inducible system for expression of wild-type and mutant p53 in a p53-null H1299 cancer cell. This is a particularly powerful approach due to the lack of leaky expression often seen in other inducible

expression systems. The levels of either wild-type or mutant p53 correlate with increasingly specific inhibition of caspase-9. In normal cells the interaction of caspase 9 and p53 in the cytoplasm cannot be detected as p53 is preferentially located in the nucleus.

Therefore in tumor cells the consequences of high levels of cytoplasmic p53 are a possible mechanism to circumvent the expected toxic consequences of p53 but in addition a gain of function that imparts resistance to chemotherapeutic agents. These findings highlight the amazing plasticity of p53 and its exploitation by tumor cells to positively drive their survival pathways.

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Tumors and their stroma: Mitochondria at the crossroads

Comment on: Sanchez-Alvarez R, et al. *Cell Cycle* 2013; 12:172–82;

PMID:23257779; <http://dx.doi.org/10.4161/cc.23058>

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Recent advances in cancer research has revealed that tumors should be considered as an integrated network of neoplastic and ancillary cells of the tumor microenvironment, including cancer-associated fibroblasts (CAFs), macrophages, endothelial cells, etc.¹ The cross-talk between these populations is not only merely mediated by soluble cytokines and growth factors, but is now been enlarged to metabolites, like lactate, ketone bodies or proteins.^{2,3} These metabolites are exchanged among stromal and cancer cells or using membrane solute transporters, or mediated by release of cargo-vesicles, such as exosomes or oncosomes, which can carry ATP, proteins or miRNAs.⁴

This intra-tumoral cross-talk elicits, in cancer cells, an escaping strategy called epithelial mesenchymal transition (EMT) accompanied by expression of stem-like traits and granting for successful metastases.⁵ In addition, stromal and cancer cells undergo a reciprocal

metabolic reprogramming, useful to sustain cancer cells survival and growth. In particular, in stromal cells, cancer cells induce a Warburg-like metabolism, fueling cancer cells themselves with essential metabolites such as lactate and ketone bodies. Cancer cells use these energy-rich molecules for anabolic purposes as well as to fuel ATP synthesis through respiration, undergoing the so-called "reverse Warburg" metabolism.^{3,6}

This coupling metabolism within tumor stroma, involving direct and reverse Warburg metabolism, could explain the controversial data concerning the role of mitochondria in cancer progression. Indeed, several data indicate a mandatory role of mitochondria in cancer cells, ranging from lactate respiration, to Krebs cycle fueling with ketone bodies, to citrate exportation to fuel fatty acids synthesis.⁷ In addition, mitochondrial metabolism is compulsory for glutamine-addicted cancer cells. The most likely hypothesis is that in

cancer cells, mitochondrial reprogramming leads to a shift toward ketone/glutamine utilization, leading to citrate-mediated fatty acids synthesis. This integrated behavior commits stromal cells to a less efficient metabolism (extrusion of energy-rich metabolites and mitochondrial-independent energy production), and cancer cells to exploit stromal cells to fulfill their survival and growth in ischemic environment. This interplay presumes that cancer cells rely extensively on mitochondrial functions.

The paper from Lisanti's group⁸ perfectly fits with this scenario in a breast cancer model, as it points out that the effects of inhibition of mitochondrial function are different between cancer and stromal cells, thereby giving an explanation to the antiproliferative effects of metformin. The latter is a widely used oral antidiabetic drug, endowed with promising effects for cancer prevention and treatment.⁹ Metformin is reported to inhibit mitochondrial

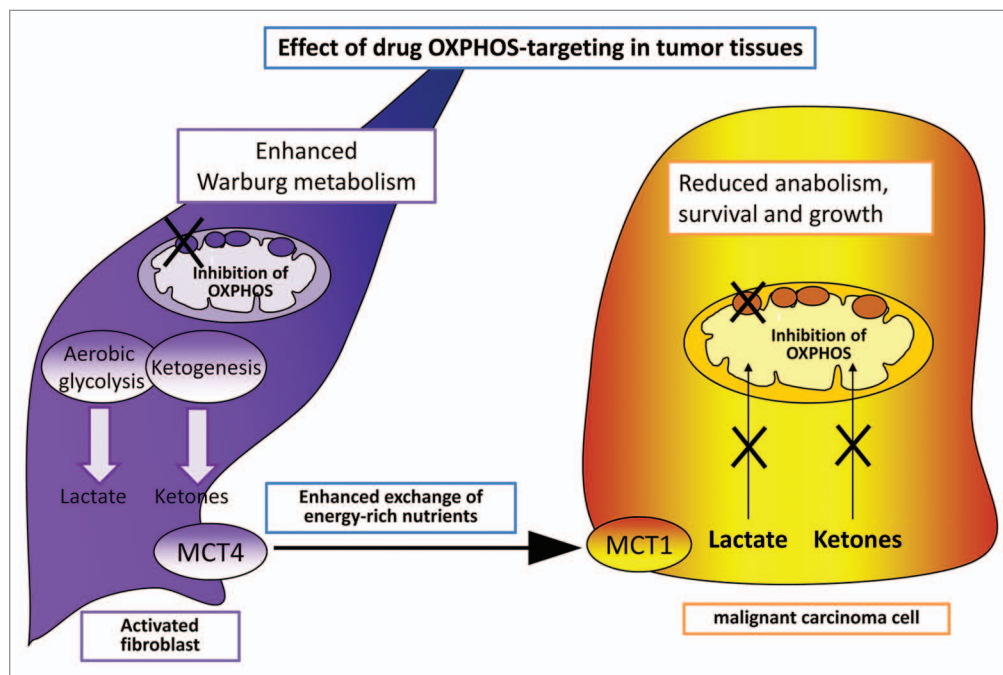


Figure 1. Targeting OXPHOS in tumor microenvironment. Inhibition of OXPHOS in the whole tumor tissue gives rise to opposite effects in tumor cells or in stromal counterparts. Indeed, the block of mitochondrial machinery in CAFs activate a Warburg-like metabolism, forcing the production of lactate and ketones, energy-rich metabolites that cancer cells are no more able to utilize for anabolic purpose due to the block of their own mitochondrial metabolism by drugs. In addition, during OXPHOS targeting of tumors, accumulating lactate and ketones likely participate to acidify the hostile tumor microenvironment.

complex I activity, thereby disrupting oxidative mitochondrial metabolism, mandatory for cancer reverse Warburg metabolism and granting survival and growth. Sanchez-Alvarez and colleagues,⁸ although not directly using metformin, reported that uncoupling protein-mediated mitochondrial dysfunction actually has compartment-specific effects. Indeed, mitochondrial dysfunction in stromal CAFs enhances their metabolic reprogramming to production of energy-rich metabolites, increasing tumor growth. On the contrary, disruption of mitochondrial function through UCP overexpression in cancer cells leads to the opposite effect, restraining tumor growth.

The outcome of these data are that, in vivo, mitochondrial functional disruption may have positive or negative effects on

cancer progression, depending on the effective addition of different cancers from their stromal counterparts. A later, with respect to the epidemiologic data on diabetic patients treated with metformin, showing a reduced risk of cancer onset, the final answer to the question on in vivo effects of mitochondrial drugs for cancer progression will arise from the several ongoing clinical trials assessing the effect of adding metformin to the existing chemotherapy regimen in the treatment of cancers (Fig. 1).

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From photomorphogenesis to cancer: A CSN journey

Comment on: Chen B, et al. *Cell Cycle* 2012; 11:4633–41; PMID:23187808; <http://dx.doi.org/10.4161/cc.22887>

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The COP9 signalosome (CSN) is an eight-subunit protein (CSN1-CSN8) complex critical for protein degradation in all eukaryotes.¹ Discovered first as a regulator of constitutive photomorphogenesis (COP) in plants, it has an intrinsic deneddylation activity that removes the ubiquitin (Ub)-like protein Nedd8 from cullin-RING Ub ligases.² Through its function to coordinate ubiquitylation and proteasome degradation, CSN plays roles in cellular processes including cell cycle control, DNA damage response, apoptosis, senescence and transcription.^{3,4} CSN has recently been implicated in tumorigenesis;³ however, the specific mechanisms are still emerging.

Mong-Hong Lee and colleagues have spearheaded recent efforts to understand roles for CSN in cancer. Studies focused on CSN5 and CSN6 suggest that expression of these CSN subunits may be elevated in several human cancers.³ Indeed, CSN components are implicated in the negative regulation of important cancer-related genes, including p53, MDM2, P27, SMAD7, RUNX3, ID1, SKP2 and HIF1.³

In studies of CSN6, Lee and colleagues have identified a role for CSN in the control of DNA damage response and cancer (Fig. 1). In addition to demonstrating amplification of the *CSN6* gene locus at 7q22.1 in human mammary

tumors,⁵ they report that AKT phosphorylation at Ser60 stabilizes CSN6.⁶ Interestingly, by promoting 14–3–3 σ degradation through stabilization of its E3-ligase COP1, CSN6 can activate AKT to create a self-propelling positive feedback loop⁷ (Fig. 1). Moreover, CSN6 promotes p53 degradation through a mechanism that stabilizes MDM2 protein by limiting its auto-ubiquitylation.⁵ Accordingly, due to elevated p53 activity, *Csn6*^{-/-} mice displayed increased apoptosis and attenuated tumorigenesis in response to irradiation.⁵ Collectively, Lee and colleagues have linked activation of the PI3K pathway to the MDM2-p53 axis through CSN, where p53 is destabilized to promote tumorigenesis (Fig. 1).

In their latest work,⁸ this group has demonstrated that CSN6 overexpression is associated with low levels of p57^{Kip2}, a cyclin-dependent kinase inhibitor (CKI) and putative tumor suppressor gene. p57^{Kip2} is known to be ubiquitylated by the Skp-Cullin-F-box (SCF) ubiquitin ligases SKP2 and FBL12.⁹ The authors provide evidence that CSN6 interacts with SKP2 to promote p57^{Kip2} polyubiquitylation. By contrast, CSN6 knockdown impaired SKP2-mediated polyubiquitylation of p57^{Kip2}. Together these findings support the existence of a CSN6-p57^{Kip2}-SKP2 complex that mediates the

destruction of p57^{Kip2}. Accordingly, the authors identified reduced levels of p57^{Kip2} in breast tumors with elevated CSN6 expression and an association between poor overall patient survival with either high or low expression levels of CSN6 and p57^{Kip2}, respectively. This study highlights the importance of a CSN6-p57^{Kip2}-SKP2 signaling axis in breast cancer and provides yet another mechanism by which CSN6 can promote cancer.

Through combinatorial effects on the MDM2-p53 signaling axis and now SKP2-mediated p57^{Kip2} degradation, it is hypothesized that CSN6 overexpression can effectively promote cell proliferation by simultaneously relieving cell cycle restraints, apoptosis, senescence, and presumably p53 functions in DNA damage repair and cell metabolism, among other important tumor suppressive mechanisms. The increasing importance of CSN6 in controlling different oncogenic pathways makes CSN targeting an attractive therapeutic opportunity in cancer. Indeed, CSN6 targeting is hypothesized to stabilize p53, p57^{Kip2} and 14–3–3 σ proteins, among others (clearly, the multiple roles of CSN make this endeavor complex). Thus, therapeutic targeting the CSN awaits characterization of other substrates for this fascinating and multifunctional complex.

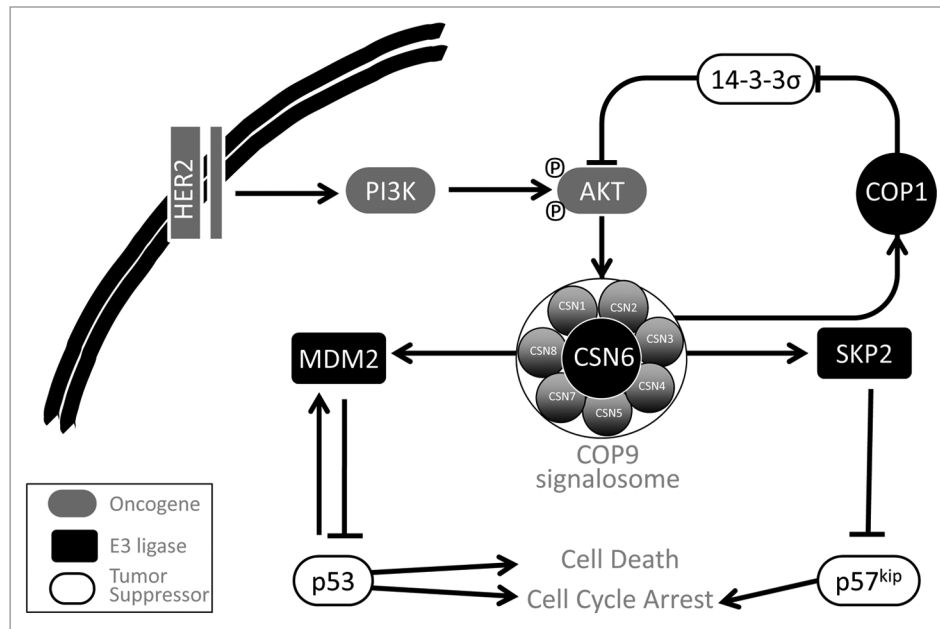


Figure 1. The COP9 signalosome (CSN) is a regulator of multiple oncogenic E3-ligases. CSN6 is activated by inputs from activated PI3K kinase pathway, as observed in breast cancers with HER2 amplification. CSN6 controls the activities of the E3 ligases COP1, MDM2 and SKP2. Through COP1, CSN mediates 14–3–3 σ degradation, thereby relieving negative regulation of AKT, which, in turn, forms a positive feedback to activate CSN6. By activating MDM2 and SKP2 activity toward their tumor suppressor substrates p53 and p57kip2, respectively, CSN is hypothesized to promote oncogenesis.

For instance, because a majority of human tumors carry inactivated p53, it will be of great interest if inactivation of any COP9 subunit is found to be effective in tumors in a p53-independent manner. In addition, there is a need to examine the effect of COP9 inactivation on normal cells, especially since gene targeting of COP9 subunits in mice (Csn2, Csn3, Csn5, Csn6 and Csn8) results in embryonic lethality.³

Overall, this study by Lee and colleagues not only opens up the attractive possibility for targeting CSN6 for cancer therapy, it also highlights the important and complex functions of the CSN, which has come a long way from its originally described repressor function of photomorphogenesis in Arabidopsis to becoming an increasingly important player in human cancer.

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