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Cell Cycle News & Views

The Herculean task of killing cancer cells: Suppression of FOXO3A in acute leukemia involves a hydra of multiple survival kinases

Comment on: Buontempo F, et al. Cell Cycle 2012; 11:2467–75; PMID:22713244; http://dx.doi.org/10.4161/cc.20859

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In Greek mythology, one of Hercules' labors was to slay the Hydra. The task seems impossible, as the creature was a multi-headed monster with the ability to grow two new heads when one was cleaved off. Oncologists face a similar daunting task in eliminating malignant cells, as each cancer appears to have its own Hydra protecting it. The suppression of the Forkhead box class O (FOXO) family of transcription factors is a common event in many cancers, including acute leukemias. FOXO3A can serve as a tumor suppressor, as it positively regulates genes that promote apoptosis (e.g., Bim, FAS ligand) and cell cycle arrest (p21 and p27).[1,2] FOXO3A phosphorylation results in the ubiquitination, nuclear expulsion and proteolysis of the transcription factor.[2-4] Inactivation of FOXO3A is complex, as the mechanism involves a number of different survival kinases, including protein kinase B (AKT), IκB kinase β (IKKβ) and extracellular receptor kinase (ERK). Further complicating matters, each kinase recognizes different sites, so suppression of FOXO3A occurs at multiple levels. Of the FOXO3A kinases, the majority of focus is on AKT. Such attention is logical, as aberrant activation of AKT by mutation of upstream regulators is common in many cancers.[5] Mutations that induce AKT activation involve inactivation of negative regulators, such phosphatase and Tensin homolog (PTEN), or constitutive activation of positive AKT regulators, such as Phosphoinositide-3 kinase (PI3 Kinase), rat sarcoma (RAS) and Fms-like tyrosine kinase receptor-3 (FLT-3). The FLT-3 internal tandem duplication mutation (FLT-3ITD) is an especially poor prognostic factor for acute myeloid leukemia (AML) patients. Kornblau and colleagues recently demonstrated that phosphorylation of FOXO3A is an adverse prognostic factor for survival and resistance to therapy for AML patients.[6] Not surprisingly, FOXO3A phosphorylation levels were higher in AML patients with abnormal FLT-3.[6] However, AKT cannot always account for FOXO3A suppression. Mien-Chi Hung's group identified IKKβ as a key suppressor of FOXO3A in breast cancer cells lacking active AKT.[7] Targeting IKK to suppress NFκB signaling became especially appealing as a novel chemotherapy strategy, with the possibility that activation of FOXO3A could occur.[3] Strategies to target IKK in T cell acute lymphoblastic leukemia (T-ALL) would seem promising, as IKK/NFκB signaling appear to be especially important in this disease. Activating Notch mutations occur in a majority of T-ALL patients and Notch signaling has been suggested to maintain T-ALL cells by activating NFκB and IKK.[8] In a recent issue of *Cell Cycle*, Buontempo and colleagues found that a novel IKKβ inhibitor, BMS-345541, effectively kills T-ALL cells that contain Notch mutations by a mechanism involving FOXO3A activation.[9] The study demonstrated that the IKK inhibitor potently suppressed IKK/NFκB signaling but did not block AKT or ERK activity. BMS-345541 was effective at inducing FOXO3A activity, as the drug induced nuclear localization of the transcription factor and increased expression of the FOXO3A gene target p21.[9] It appears, at least in T-ALL cells containing Notch mutations, that IKKβ is responsible for suppressing FOXO3A, as use of the highly specific AKT inhibitor MK-2206 had no impact on FOXO3A nuclear localization or gene expression of its target genes.[9] Importantly, Buontempo and colleagues found that BMS-345541 was efficient in killing primary T-ALL blast cells derived from pediatric patients. Targeting IKK could prove to be beneficial to these and other patients, especially if their malignant cells contain wild-type p53. FOXO3A and p53 share some common regulatory elements.[3] Nuclear export of both molecules involves Exportin-1 (CRM-1). Furthermore, proteosomal degradation of both molecules is mediated by the E3 ubiquitin ligase murine double minute 2 (MDM2).[3,4] Since MDM2 expression is mediated by IKK/NFκB, it is possible that both FOXO3A and p53 could be activated to kill tumor cells. Still, p53 mutations are common in cancer, and it is likely that at least for activation of FOXO3A, an approach to inactivate more than one of its suppressors will be likely. As Hercules was successful in slaying the Hydra with the aid of his nephew Iolaus, it is our hope that inclusion of IKK inhibitors and other agents that can activate FOXO3A as suggested by the Martelli group for T-ALL therapy will result in more effective treatments for T-ALL and other cancers.

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Protein phosphatase PP4: Role in dephosphorylation of KAP1 and DNA strand break repair

Comment on: Liu J, et al. Cell Cycle 2012; 11:2643–9;
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Repair of DNA double-strand breaks (DSB) is essential for cell survival. Two major pathways, the highly accurate homologous recombination (HR) repair and the more error-prone non-homologous end-joining (NHEJ) pathway, are engaged in these repair processes, and their relative contribution is dependent on the cell cycle. Phosphorylation events triggered by DNA damage response and checkpoint kinases, including ATM, ATR, DNA-PK, CHK1 and CHK2, are important signaling mechanisms during DSB repair. However, in order for DSB repair to proceed in a coordinated manner and to be completed, the phosphorylation of key proteins in the pathways needs to be reversed at specific steps by protein dephosphorylation. The phosphatases PP1, PP2, PP4, PP6 and PPM1D have so far been implicated in homologous recombination repair of DSBs.[1] Some of the substrates that are dephosphorylated by these phosphatases are replication protein A2 (RPA2), a single-stranded DNA binding protein and gamma-H2AX, a phosphorylated specialized histone, both proteins serving as platforms for the repair reactions.[1,2]

It has been less clear which protein phosphatases are involved in the nonhomologous end-joining pathway. In this issue of *Cell Cycle*, Liu et al. identified a PP4 phosphatase complex as an important component of NHEJ.[3] Using a GFP-based in vivo NHEJ assay and a random plasmid integration assay, the authors show that depletion of PP4, by targeting either its catalytic subunit PP4C or its regulatory subunit PP4R2 compromises NHEJ. Following immunoprecipitation of PP4R2, the authors conducted mass spectrometric analysis of proteins associating with this subunit. Besides other components of the PP4 phosphatase complex, they identified the protein KAP1 as a strongly enriched binding partner. KAP1 is a scaffold protein functioning as a transcriptional repressor in most experimental systems, owing to its ability to associate with epigenetic modulators including histone H3 lysine 9 methyltransferases, histone deacetylases and heterochromatin protein 1 (HP1).[4] KAP1 interacts with the sequence-specific KRAB zinc finger proteins and other transcription factors, facilitating its binding to specific compartments of the genome.

DSB repair needs to operate effectively throughout the entire nucleus, both within the more easily accessible active chromatin and within compacted, heterochromatinized loci. Earlier studies had indicated that KAP1 plays an important role as a phosphorylation target during the DNA damage response and in DSB processing in heterochromatin.[5-7] Serine 824, which is near the C-terminal bromodomain of KAP1, becomes phosphorylated by ATM upon treatment of cells with DNA damaging agents that produce DSBs. Liu et al. now show that depletion of PP4C leads to an increase of KAP1 serine-824 phosphorylation, and that PP4 can dephosphorylate KAP1 in vitro. Similar results were reported recently by Lee et al.[8] Liu et al. also found that KAP1 promotes NHEJ in vivo, and that it seems to be in the same pathway with PP4, although the effect of PP4 depletion on NHEJ efficiency was stronger, suggesting that this phosphatase also dephosphorylates other proteins involved in this repair pathway.[3] The current data suggest that appropriate phosphorylation of KAP1 may enable DSB repair, whereas hyper- or hypo-phosphorylation could be detrimental to the repair process. Interestingly, KAP1 has been hypothesized to prevent homologous recombination at certain loci. Chromatin-immunoprecipitation studies have suggested that prevalent genomic targets of KAP1 are near the 3′ ends of many zinc finger genes,[4] although it has not been possible to identify a transcriptional role for KAP1 at these binding sites. These ZNF genes contain blocks of high sequence homology that could be lost during recombination processes. Future studies will need to determine if unphosphorylated KAP1 indeed functions as

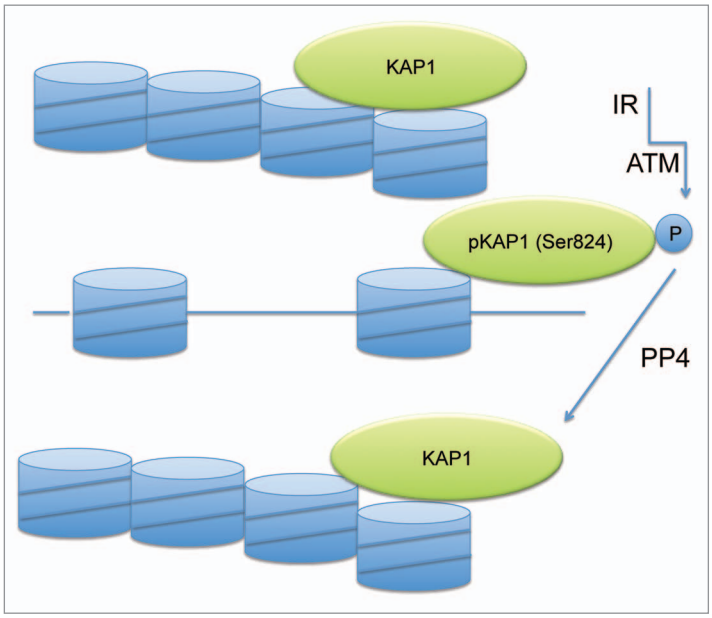

Figure 1. Schematic diagram of KAP1 phosphorylation and dephosphorylation. ATM-mediated phosphorylation of KAP1 on serine 824 leads to transient relaxation of chromatin allowing double-strand break repair processes to operate more easily within inactive chromatin domains. KAP1 phosphorylation is reversed by the PP4 phosphatase complex before completion of the repair process.

a sequence-specific repressor of homologous recombination in the absence of DNA damage.

The study by Liu et al. provides important initial insights into the role of the PP4 phosphatase complex in this major DSB repair process.[3] One target of the phosphatase has been identified as the co-repressor KAP1, the phosphorylation of which is thought to promote relaxation of inaccessible chromatin. Besides having a direct role at DNA damage sites, KAP1 phosphorylation and dephosphorylation are also thought to have a transcriptional role in the DNA damage response.[9] Future studies will determine the functional details of the KAP1 phosphorylation-dephosphorylation cycle in the NHEJ pathway of DNA strand break repair.

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p53-dependent growth arrest and induction of p21: A critical role for PCAF-mediated histone acetylation

Comment on: Love IM, et al. Cell Cycle 2012; 11:2458–66; PMID: 22713239; http://dx.doi.org/10.4161/cc.20864

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The tumor suppressor protein p53 acts as a guardian of genomic integrity and protects cells against a wide variety of stress conditions. Upon moderate DNA damage or certain stress signals, p53 induces a growth arrest in either G_1 or G_2 phase of the cell cycle. A key event leading to this growth arrest is the direct transcriptional activation of the cell cycle-dependent kinase (cdk) inhibitor p21 by p53.

Previous studies have identified histone acetyltransferase (HAT) proteins assisting p53 in binding to the transcriptional control region of p53 target genes and in creating a chromatin environment, including histone and p53 acetylation, permissive for gene transcription.[1-4]

Three major groups of HATs have been shown to modify p53 lysine residues located in the central DNA binding domain, its nuclear location signal or its multifunctional C-terminal regulatory domain. The MYST family members TIP60 and hMOF acetylate lysine K120 in the DNA binding domain, an event that controls the ability of p53 to induce transcription-dependent and -independent apoptosis.[5-7] GNAT family members PCAF and GCN5 primarily acetylate K320 in the nuclear location signal of p53. This modification occurs after DNA damage and contributes to the stabilization of p53 and enhances its ability to bind DNA.[2,3,8] The third group of HATs, p300 and CBP, modifies several lysine residues in the C terminus, including K373 and K382, and K164 in the DNA binding domain.[1,3,4] Acetylation by p300/CBP stimulates high affinity DNA binding of p53[1,2] and shields it from the repressive function of mdm2.[4]

An important question is to what extent histone acetylation, occurring sequentially or in parallel to p53 acetylation, contributes to target gene activation. The manuscript by Love et al. in a recent issue of *Cell Cycle* addresses this question for PCAF in the context of the p21 promoter.[8] Using siRNA-mediated knockdown of PCAF, the authors show that the p21 gene is no longer inducible by p14ARF expression in either U2OS osteosarcoma or diploid RPE1 cells. By contrast, interference with p300 or CBP expression led to p53 stabilization and increased levels of constitutevly expressed p21 protein in both cell types. Therefore, PCAF function is essential for inducible expression of p21, while p300 and CBP appear to negatively regulate p21 expression in the absence of a stimulus, perhaps due to their ability to promote p53 ubiquitylation and degradation.

As a functional consequence of PCAF siRNA treatment, cells fail to arrest the cell cycle in response to p14ARF expression or treatment with nutlin3a, an inhibitor of the p53-mdm2 interaction.[8] Acetylation of p53 K320 by PCAF is not required for p21 gene induction, since a mutant p53 carrying a K(319–321)R substitution was fully capable of inducing p21. These findings raised the possibility that the critical substrates for PCAF acetylation were in fact the nucleosomal histones bound to the p21 promoter. Indeed, chromatin immunoprecipitation experiments performed by Love et al. showed that acetylation of histone H3 K9 and K14 was increased upon p53 activation, an effect that required the presence of enzymatically active PCAF.[8] These two histone H3 residues were previously demonstrated to be the preferred histone substrates of PCAF. The authors also showed that p53 is recruited in vivo to the distal p53 response element of the p21 promoter following doxorubicin treatment, while PCAF was constitutively present at that region.[8]

Taken together, the results of Love et al. reveal that PCAF acts as a true HAT, acetylating two lysine residues in the histone H3 tail of nucleosomes at the p21 promoter in response to a diverse array of stimuli leading to p53 activation.

No matter whether genotoxic or non-genotoxic stimuli were used, PCAF was always required for full inducible expression of p21. By contrast, p300 or CBP were not required for p21 stimulation, but rather appeared to repress basal p21 levels. A recent study by Kasper et al. showed that both p21 and mdm2 expression was inducible in cells double null

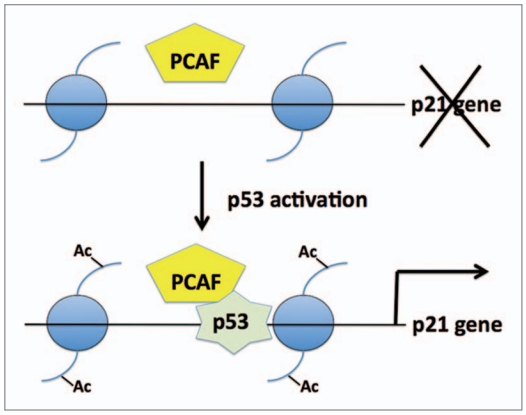

Figure 1. PCAF appears to be present constitutively at the p21 promoter. Top of the panel, in the absence of a stimulus, PCAF cannot acetylate histones in the promoter bound nucleosomes (blue). Upon activating signals, p53 binds to the p21 promoter, triggering PCAF-dependent histone H3 acetylation and expression of the p21 gene, see bottom part of figure.

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for p300 and CBP in response to etoposide or doxorubicin.[9] Interestingly, basal levels of p21 and mdm2 were also slightly increased in the absence of p300 and CBP, although not as much as in the study by Love et al.[8] Thus, two independent reports agree that p300 and CBP are dispensable for p53-dependent activation of p21.

CTGF-mediated autophagy-senescence transition in tumor stroma promotes anabolic tumor growth and metastasis

Comment on: Capparelli C, et al. Cell Cycle 2012; 11:2272-84; PMID:22684333; and Capparelli C, et al. Cell Cycle 2012; 11:2285-302; PMID:22684298

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Otto Warburg first observed that cancer cells preferentially undergo glycolysis instead of the mitochondrial TCA cycle even under oxygen-rich conditions. This form of energy metabolism in cancer cells is called "aerobic glycolysis" or the "Warburg effect."[1] Lisanti and colleagues have previously proposed an alternative model called the "the reverse Warburg effect," in which aerobic glycolysis predominantly occurs in stromal fibroblasts.[2] During this process, cancer cells secrete oxidative stress factors, such as hydrogen peroxide, into the tumor microenvironment, which induces autophagy. This leads to degradation of mitochondria (mitophagy) and elevated glycolysis in cancer-associated fibroblasts.[3] Aerobic glycolysis results in the elevated production of pyruvate, ketone bodies and L-lactate, which can be utilized by cancer cells for anabolic growth and metastasis. At the molecular level, stromal fibroblasts lose expression of caveolin-1 and activate HIF-1α (**Fig. 1**), TGFβ and NFκB signaling.[4] Stromal caveolin-1 expression predicts clinical outcome in breast cancer patients.[5]

In the June 15, 2012 issue of *Cell Cycle*, two studies by Capparelli et al. further validate the "autophagic tumor stroma model of cancer" described above, as well as identify novel mechanisms involved in this process.[6,7] Autophagy and senescence are induced by the same stimuli and are known to occur simultaneously in cells. In the first study, the authors hypothesize that the onset of senescence in the tumor stroma in response to autophagy/mitophagy contributes to mitochondrial dysfunction and aerobic glycolysis. In order to genetically validate this process of autophagy-senescence transition (AST) (**Fig. 1**), Capparelli et al. overexpressed several autophagy-promoting factors (BNIP3, cathepsin B, Beclin-1 and ATG16L1) in hTERT fibroblasts to constitutively induce autophagy. Autophagic fibroblasts lost caveolin-1 expression and displayed enhanced tumor growth and metastasis when co-injected with breast cancer cells in mice, without an increase in angiogenesis. In contrast, constitutive activation of autophagy in breast cancer cells inhibited in vivo tumor growth. Autophagic fibroblasts also showed mitochondrial dysfunction, increased production of nutrients (L-lactate and ketone bodies) and features of senescence (β-galactosidase activity and p21 activation). AST was also demonstrated in human breast cancer patient samples.[7] In the second study, using a similar experimental approach, the authors evaluated the role of the TGFβ target gene, connective tissue growth factor (CTGF), in the induction of AST and aerobic glycolysis in cancer-associated fibroblasts. CTGF would be activated in the tumor stroma upon loss of caveolin-1. CTGF overexpression in fibroblasts induced autophagy/mitophagy, glycolysis and L-lactate production in a HIF-1α-dependent manner along with features of senescence and oxidative

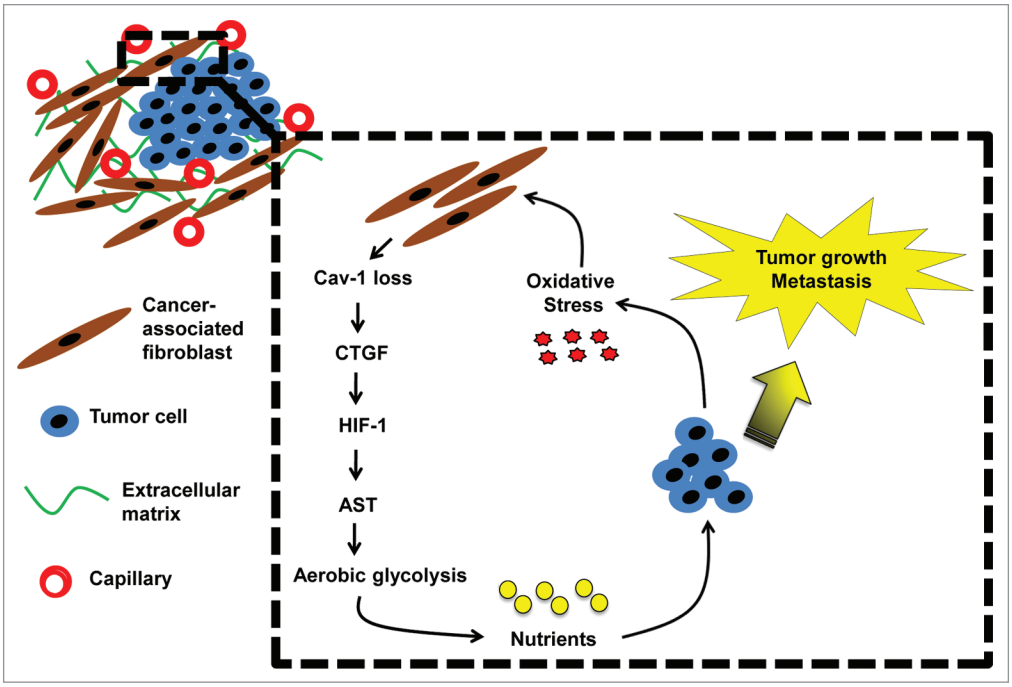

Figure 1. CTGF-mediated autophagy-senescence transition in tumor stroma promotes anabolic tumor growth and metastasis. Cancer cells secrete oxidative stress factors (H2O2) that induce autophagy in cancer-associated fibroblasts. Additionally, caveolin-1 (cav-1) loss leads to activation of connective tissue growth factor (CTGF) and HIF-1α that mediate autophagy and senescence in these stromal cells. This is called the autophagy-senescence transition (AST). AST leads to mitophagy and elevated glycolysis in cancer-associated fibroblasts. Aerobic glycolysis results in the elevated production of several nutrients (pyruvate, ketone bodies and L-lactate), which can be utilized by cancer cells for tumor growth and metastasis.

stress. CTGF overexpression in fibroblasts also promoted tumor growth when co-injected with breast cancer cells in mice (**Fig. 1**), independent of angiogenesis. As expected, CTGF overexpression in breast cancer cells inhibited tumor growth. CTGF is known to be involved in extracellular matrix synthesis; however, the effects of CTGF overexpression in fibroblasts and tumor cells were found to be independent of this function.[6]

Overall, the authors have identified a novel mechanism by which CTGF promotes AST and aerobic glycolysis in cancer-associated fibroblasts. In turn, the stromal cells stimulate anabolic tumor growth and metastasis. The authors also genetically validate the two-compartment model of cancer metabolism, whereby autophagy genes and CTGF have differential effects in stromal cells and tumor cells. The current studies have several implications for cancer therapy. The finding that HIF-1 activation is necessary for the induction of autophagy and senescence downstream of caveolin-1 loss and CTGF activation in stromal fibroblasts is intriguing. Activation of HIF-1 in the hypoxic tumor microenvironment is known to promote tumor cell growth, survival and therapeutic resistance.[8] Therefore, targeting HIF-1 has the potential to block tumor progression through dual inhibitory effects on hypoxic cancer cell growth and survival as well as the induction of autophagy in stromal fibroblasts. CTGF and AST in the tumor stroma could serve as biomarkers for predicting clinical outcome, therapy response and metastasis. The two-compartment model of tumor metabolism raises further questions regarding the use of antioxidants and autophagy inhibitors/inducers for cancer therapy. The use of these agents in the clinic should be carefully evaluated considering their differential effects on stromal cells and cancer cells.

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