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RNF8 links nucleosomal and cytoskeletal ubiquitylation of higher order protein structures

Comment on: Chahwan R, et al. Cell Cycle 2013; 12:1000–8; PMID:23442799; http://dx.doi.org/10.4161/cc.23947

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Increasing evidence for the role of histone-modifying enzymes on non-histone substrates, including those in the cytoplasm, has been emerging in recent years. Some chromatin-modifying proteins, such as the histone methyl transferase EZH2, compartmentalize to both the nucleus and cytoplasm, whereby EZH2 can methylate histones and actin, respectively.[1] Alternatively, the mammalian nuclear membrane disintegrates during mitosis, and the structural boundary separating nuclear and cytoplasmic proteins breaks down. This allows nuclear proteins to diffuse into the cytoplasm and potentially catalyze non-nuclear substrates. Evidence suggests that the Gcn5 containing histone acetyl transferase complex ATAC controls mitotic progression through the modification on non-histone targets during mitosis.[2] And more recently, studies have shown that the HIPK2 kinase controls cytokinesis through the phosphorylation of histone H2B localized at the midbody, the site of cell abscission at the end of mitosis.[3] What these and other studies suggest is that coordination and crosstalk between the chromatin and cytoskeletal structures is much more intertwined than previously appreciated.

In a recent issue of *Cell Cycle*, we showed that the histone ubiquitin ligase RNF8, which orchestrates the mammalian DNA damage response (DDR) following DNA double-strand break (DSB) formation, also controls mitotic progression through the ubiquitylation of septins in cells[4] (**Fig. 1**). Furthermore, we provided evidence that this novel role of RNF8 in mitosis is conserved from budding yeast to humans. On the contrary, support for a direct role of the yeast RNF8 orthologs Dma1 and Dma2 in the DDR or in histone ubiquitylation remains lacking. This is partly due to the compartmentalization of yeast Dma proteins to the cytoplasm,[5,6] and partly because Dma-null yeast strains lack documented hypersensitivity to DNA damaging agents.[5] Our preliminary studies suggest that Dma1 and Dma2 double-null yeast strains are hypersensitive to the DNA damaging agents hydroxyurea and bleomycin, but this has been attributed to a defect in Swe1 protein levels or efficiency of drug uptake (cells might be more permeable) and not necessarily to a defect in the DDR per se (Gravel S, unpublished). Since the phosphorylation of the histone variant H2AX and the subsequent recruitment of the MDC1 adaptor protein is required for mammalian RNF8 localization to DSB sites—and since these proteins have conserved homologs in yeast—it is possible that the lack of localization of yeast Dma proteins to the nucleus might be a critical hindrance from them acting on histones. This is especially pertinent, because budding yeast cells, unlike higher eukaryotic cells, do not disintegrate their nuclear membrane during mitosis. In light of this, it would be interesting to see whether adding a nuclear localization signal to yeast Dma proteins could promote their activity on nucleosomes following DNA damage.

Taken together, our study suggests that RNF8 may have originally arisen to mediate functions in mitosis and was only later co-opted to act on histones. Remarkably, in both the nucleus and cytoplasm, RNF8 seems
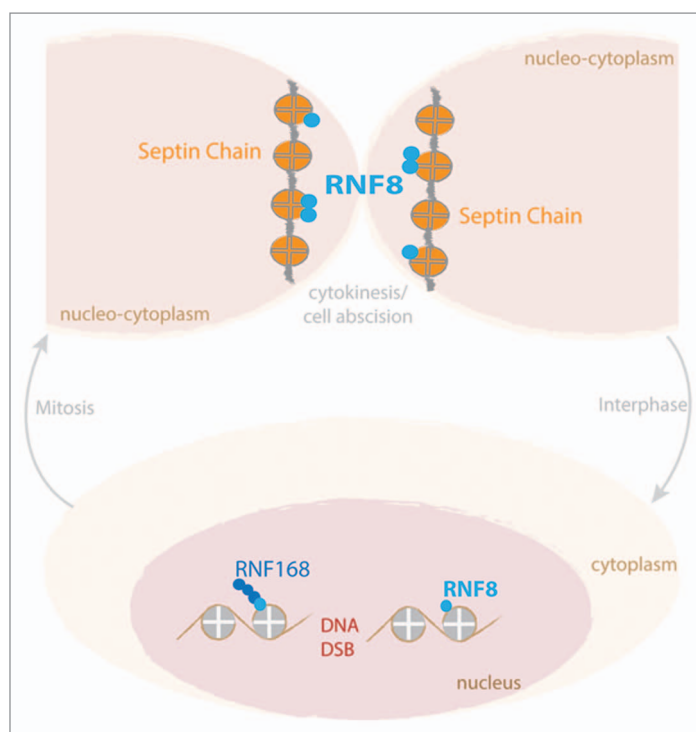

Figure 1. Cartoon depicting the differential localization and function of RNF8 at nucleosomal and cytoskeletal higher order structures during interphase and mitosis, respectively.

to target proteins that form poly-octameric higher-order structures (**Fig. 1**). These are the histones, which constitute nucleosomes, and septins, which form cytoskeletal filaments. With their ability to form higher-order chains, septins have been described as the "fourth component of the cytoskeleton."[7] Septin filaments have also been compared with nucleosomes, not only because of their structural similarity, but also due to their long half-life, heavy and reversible post-translational modifications, and their mode of inheritance during cell division.[8] It is worth noting that our work suggests that, in some particular cases, the

"histone code" might have evolved to mimic post-translational modifications occurring in cytoskeletal structures rather than the other way around. It would be intriguing in the future to address such a possibility and ascertain whether RNF168, a ubiquitin E3 ligase that works in synergy with RNF8 during the DDR, can recognize and mediate subsequent septin ubiquitylation events during mitosis. More broadly, it will be interesting to determine whether and how nucleosomal and cytoskeletal post-translational modifications are coordinated and what the functions for such coordination might be.

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ATM targets hnRNPK to control p53

Comment on: Moumen A, et al. Cell Cycle 2013; 12:698–704; PMID:23343766; http://dx.doi.org/10.4161/cc.23592

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To deal with DNA lesions, cells activate the DNA damage response (DDR) network.[1] DDR activation results in cell cycle delay to allow time for DNA repair. Upon excessive damage, the cell cycle checkpoint arrest will become permanent (a state known as senescence), or cells will undergo cell death (apoptosis). A key player controlling these cell fate decisions is the transcription factor p53. In response to genotoxic stress, p53 becomes modified and stabilized by different pathways and initially induces the expression of genes involved in DNA repair and cell cycle arrest. Prolonged p53 stabilization, however, also induces the expression of pro-apoptotic genes. This, together with the prominent role of p53 in tumor suppression[2] highlights the importance of a tight control of p53 activity. An exciting new aspect of p53 regulation in response to DNA double-strand breaks (DSBs), the most toxic DNA lesions,[1] has now been reported by Moumen et al.[3]

DSBs activate three of the phosphatidylinositol 3-kinase-related kinases (PIKKs), namely ataxia telangiectasia mutated (ATM), ataxia and Rad3-related (ATR) as well as the DNA-dependent protein kinase (DNA-PK). These kinases phosphorylate a large number of proteins involved in DNA repair, cell cycle checkpoints and transcription.[1] ATM phosphorylates p53 on serine 15 upon DNA damage, thereby contributing to p53 activation. ATM also
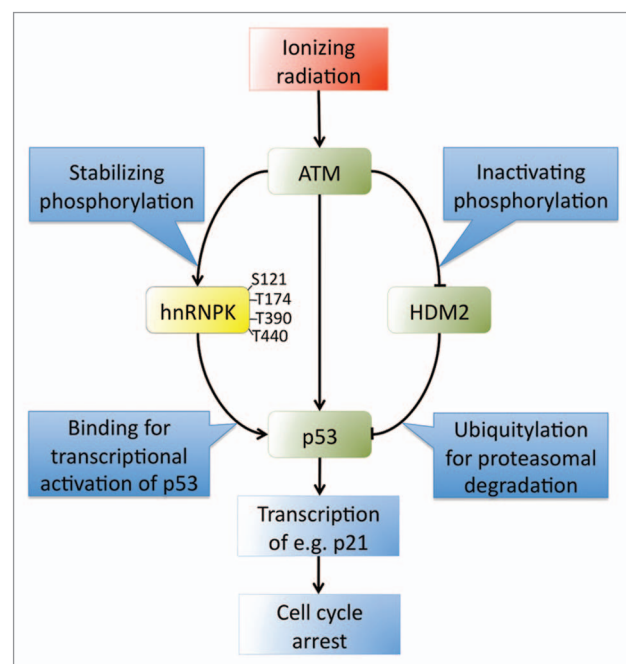

Figure 1. Pathways through which ATM activates p53-dependent transcription in response to ionizing radiation. ATM-targeted phosphorylation sites of hnRNPK identified by Moumen et al.[3] are indicated.

phosphorylates HDM2, an ubiquitin E3-ligase that regulates p53 protein levels by proteasomal degradation. Upon DNA damage HDM2 ubiquitylation of p53 is greatly reduced, leading to p53 accumulation and p53-dependent transcription.[2]

Heterogeneous nuclear ribonucleoprotein K (hnRNPK) was originally characterized as a protein of the ribonucleoprotein complex with a strong binding preference for poly(C)-sequences in RNA.[4] hnRNPK has diverse functions, including a role as a

transcriptional co-activator of p53.[5] Previous work by Moumen et al. showed that hnRNPK is stabilized upon ionizing radiation (IR) due to a reduction in its HDM2-dependent ubiquitylation, thus enhancing p53-dependent transcription after DNA damage.[5] To gain deeper mechanistic insight into hnRNPK stabilization, Moumen et al. have now shown that upon IR treatment, ATM also phosphorylates hnRNPK, on 4 serine/threonine residues (**Fig. 1**).[3] Phosphorylation by ATM reduced hnRNPK ubiquitylation, suggesting that such phosphorylation prevents HDM2-dependent ubiquitylation and subsequent degradation of hnRNPK. The importance of ATM-dependent phosphorylation of hnRNPK is illustrated by the DNA damage-induced p53-dependent transcription of the cell cycle inhibitor p21 (**Fig. 1**). Downregulation of hnRNPK with RNAi and complementation of its deficiency revealed that unlike wild-type hnRNPK, the mutant hnRNPK protein that cannot be phosphorylated by ATM does not facilitate p21 expression upon DNA damage.[3]

Despite the long-term focus on p53 biology, many aspects of p53 regulation remain unexplained at the molecular level. It remains unclear whether ATM-dependent phosphorylation of p53 directly disrupts the p53-HDM2 interaction. Also, while p53 is modified by several post-translational modifications upon DNA damage, the significance of a potential crosstalk between these modifications in regulation of the abundance and activity of p53 remains largely unexplored. For example, Aurora A, a mitotic protein kinase, phosphorylates both p53 and hnRNPK in the absence of DNA damage, leading to a destabilization of their interaction. Reduced Aurora A activity upon DNA damage therefore stabilizes the hnRNPK-p53 interaction, thus increasing p53 transcriptional activity.[6] hnRNPK is also SUMOylated upon DNA damage, a modification that is required for p53 transcriptional activation,[7] and it is methylated on several arginine residues, which also seems crucial for p53 activity.[8] Do all of these modifications work in an additive manner, or is each of them sufficient for a full p53-dependent cell cycle arrest?

To further complicate things, there are different cellular pools and isoforms of hnRNPK performing various functions,[9] and it is unclear whether ATM phosphorylates all hnRNPK molecules and which of hnRNPK's functions are affected by this modification. We also do not know whether the hnRNPK that is phosphorylated by ATM is bound to RNA, or whether such phosphorylation affects hnRNPK binding to RNA and vice versa. It also remains to be tested if hnRNPK becomes phosphorylated on the same residues in response to other types of genotoxic stress, and whether this is then mediated by different protein kinases such as ATR.

The new study by Moumen et al.[3] opens the way to answer these questions and help better understand the protein network surrounding p53, its physiological roles and malfunction in cancer cells.

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Compensation, crosstalk and sequestering: The currency of checkpoints in cancer

Comment on: Palii SS, et al. Cell Cycle 2013; 12;1105–18; PMID:23462183; http://dx.doi.org/10.4161/cc.24127

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Cells are constantly exposed to both endogenous and exogenous stresses that lead directly or indirectly to DNA damage. Cell survival is dependent on two interrelated processes, cell cycle checkpoints and DNA repair; the G_1, intra-S and G_2 checkpoints block cell cycle progression after DNA damage to provide more time for DNA repair. Cell cycle checkpoints and DNA repair are integrated through a series of signaling networks that involve numerous protein posttranslational modifications (e.g., phosphorylation, acetylation, methylation, ubiquitination) that modulate protein stability, catalytic activity and other properties. Most cancer cells have one or more defects in cell cycle checkpoints and often defects in some aspect of DNA repair. As a consequence, they become addicted to the remaining checkpoint and repair mechanisms. Tumor therapy often involves treatments that cause DNA strand breaks or replication stress. The G_1, G_2 and intra-S checkpoints are activated in response to DNA strand breaks primarily through the ATM-CHK2 pathway and to DNA replication stresses through the ATR-CHK1 pathway. Thus, disrupting these pathways potentially can enhance the therapeutic effectiveness of cancer treatments.

In a recent issue of *Cell Cycle*, Palli et al. report[1] on the interactions between CHK1, PP2A and ATM during the G_2 checkpoint response to IR-induced DNA damage (**Fig. 1**). This analysis was motivated by studies showing that chemical inhibition of CHK1 can enhance chemotherapy for cancer (e.g., see ref. 2), and that chemical inhibition of CHK1 kinase activity does not fully mimic depletion of CHK1 protein. Palli et al. compared and contrasted the effects of CHK1 inhibition in human cell lines by stable depletion with shRNA, transient depletion with siRNA and chemical inhibition. They found that stable depletion of CHK1 in 293T cells enhanced cellular radiosensitivity in colony-formation assays by about 4-fold. As mutation of ATM in ataxia telangiectasia enhances radiosensitivity about 3-fold, this sensitization by CHK1 depletion is remarkable. Depletion or inhibition of CHK1 enhanced phosphorylation at S1981 of ATM after IR, but ATM-dependent G_2 checkpoint function was modestly attenuated. This

phenomenology was linked to PP2A, a phosphatase that acts on ATM and CHK1, and which is regulated by CHK1.[3,4] Depletion or inhibition of CHK1 reduced (sequestered) nuclear PP2A protein levels and enhanced an inhibitory phosphorylation of PP2A on Tyr307. The consequence of inhibition of PP2A was increased basal and IR-induced phosphorylations on the activating S1981 of ATM as well as on S345 and S296 of the remaining CHK1. Cellular growth assays using human mammary epithelial cells with depletion of CHK1 and/or ATM showed that combined depletion of CHK1 and ATM enhanced radiosensitivity, supporting the rationale to use CHK1 inhibitors to increase cancer cure rates using adjuvant radio- and chemotherapies.[2,5]

The work by Palii and colleagues highlights the cross-talk between different elements of the DNA damage response that can produce compensatory conditions that mitigate cell killing and compromise therapeutic efficacy. While crosstalk between the ATM and ATR pathways has been known for some time, recent proteome-wide analyses of the kinase landscape in the DNA damage response implicate the involvement of dozens of kinases and highlight how extensive and interlaced the pathways in the DNA damage response are (reviewed in ref. 6). Although less is known about the roles of phosphatases, several in addition to the many forms of PP2A, including PP1, PP5 and WIP1 (PP2C), are clearly involved in the DNA damage response. We note, however, that inhibition of PP2A with okadaic acid prior to IR treatment blocked activation of the G_2 checkpoint as well as activation of ATR, CHK1 and CHK2,[7] indicating that the relationship between ATR, CHK1 and G_2 arrest is more complex than shown in **Figure 1**. Other posttranslational modifications (e.g., acetylation, ubiquitination) also play important, if less well-studied, roles as well. Furthermore, each of the major DNA damage response sensor, transducer and effector enzymes serve cellular
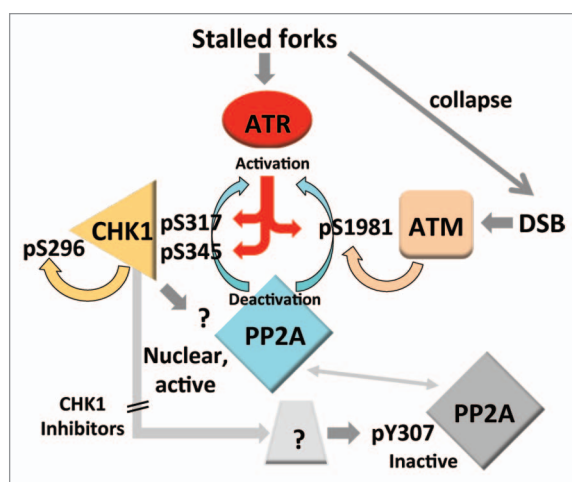

Figure 1. Pathways that can contribute to cancer cell survival. Replication stress activates the ATR pathway, leading to activation of CHK1 through phosphorylation of Ser345 and Ser317; Ser296 is autophosphorylated and serves as a marker of activated CHK1. ATR also phosphorylates ATM on Ser1981. CHK1 activity is required for active nuclear PP2A. Inhibition or depletion of CHK1 decreases nuclear PP2A and increases (through unknown mechanisms) an inhibitory phosphorylation of PP2A on Tyr307. Inhibition of PP2A results in enhanced phosphorylation of CHK1 on Ser235 and S296 and ATM on Ser1981. Basal signals that activate ATM may come from ATR acting at replication forks that are stalled at natural barriers or, after collapse of stalled forks, auto-activation by DNA double-strand breaks.

functions outside the DNA damage response that also must be understood. Thus, a deeper understanding of the pathways and mechanisms by which the DNA damage checkpoint and repair systems are regulated clearly will be important to developing more effective cancer therapeutics and therapies.

The Palii et al. study complements several recent studies that are attempting to dissect these cell survival mechanisms, determine how they can be modulated to selectively effect death in tumor cells, and how tumor cells compensate for the loss of these survival mechanisms. For example, a recent report in *Cell Cycle* by McNeely et al.[8] described the effect of CHK1 inhibition on ATM and DNA-PK activity. As oncologists move to targeted anticancer therapies, drug-combination cocktails will be needed to squelch compensatory events that reduce efficacy.

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Differences in regulation and function of E-cyclins in human cancer cells

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Mammalian cyclin E was cloned by groups of James Roberts and Steven Reed in a screen for human cDNAs can complement mutant G_1 cyclin genes *CLN1, CLN2* and *CLN3* in yeast *Sacaromyces cerevisiae*.[1] The flurry of studies that followed this discovery demonstrated that in mammalian cells cyclin E is induced in late G_1 phase, when it activates cyclin-dependent kinase CDK2, and also CDK1 and CDK3. During G_1 phase progression, cyclin E-CDK2 kinase phosphorylates and inactivates the retinoblastoma protein pRB, leading to activation of E2F transcription factors. Since the *cyclin E* gene represents one of E2F's transcriptional targets, this mechanism creates a positive feedback loop, which leads to full activation of cyclin E-CDK2 kinase. Once induced, cyclin E-CDK2 phosphorylates proteins governing cell cycle progression (pRB, p27[Kip1], E2F5), centrosome duplication (NPM, CP110), histone gene transcription (NPAT) and others. Cyclin E and cyclin E-CDK2 kinase activity is essential for assembly of DNA pre-replication complexes and for firing of DNA replication origins. As the S phase progresses, cyclin E becomes phosphorylated by cyclin E-CDK2 and by GSK3 and is then targeted for proteosomal degradation by the SCF[Fbw7] ubiquitin ligase.[1]

Subsequently, groups of Bruno Amati, Yue Xiong and Steve Coats isolated the second mammalian E-type cyclin, which was termed cyclin E2, while the protein known as "cyclin E" was renamed as cyclin E1. The two E-cyclins show substantial aminoacid similarity, associate with the same CDK partners and appear to perform similar biological functions.[1] Their regulation seems to be similar, including transcriptional activation by E2F and protein degradation through SCF[Fbw7] ubiquitin ligase. Also in vivo, the two E-type cyclins seem to perform highly overlapping set of functions. Thus, genetic ablation of cyclins E1 or E2 resulted in no major phenotypes, whereas combined loss of both E-cyclins led to an early embryonic lethality due to placental abnormalities.[2] In adult mice, combined ablation of cyclins E1 and E2 impairs neuronal synaptic function and leads to memory deficits due to a function of cyclin E in regulating synaptic plasticity.[3] Collectively, all these observations suggested that cyclins E1 and E2 are functionally equivalent.

A recent study from Elizabeth Musgrove's group[4] indicates that this prevailing view may need revisions. The authors focused on the function of overexpressed cyclin E in breast cancer cells. Cyclins E1 and E2 are overexpressed in a substantial number of human cancers, where they contribute to tumorigenesis, likely by driving uncontrolled cell cycle progression.[1] Moreover, overexpression of cyclin E1 was shown to result in chromosome instability in in vitro-cultured cells, and in vivo in mouse tumors.[5,6] While the exact molecular mechanism remains to be elucidated, this role of cyclin E1 is mediated, at least in part, by binding and phosphorylating the anaphase-promoting complex (APC) regulatory subunit, Cdh1.[7] This, in turn, inhibits APC activity, and results in impaired mitotic progression of cyclin E1-overexpressing cells.[7] Unexpectedly, Caldon et al.[4] demonstrated that cyclin E2, when overexpressed, does not interact with Cdh1, does not inhibit APC and does not impair mitotic progression. Yet cyclin E2 overexpression still triggers genomic instability, as evidenced by increased fraction of abnormal mitoses, as well as the presence of chromosomal aberrations, such as chromosome breaks and end-to-end fusions in cyclin E2-overexpressing cells. While the mechanism through which cyclin E2 causes these abnormalities remains unclear, Caldon et al.[4] propose that this effect is mediated through inactivation of pRB and pRB-like p107 and p130 proteins by hyperactive cyclin E2-CDK2. Intriguingly, the same group demonstrated that the levels of cyclin E2 in cancer cells are controlled via a distinct mechanism from that operating in normal cells.[8] Specifically, while in non-transformed cells, the levels of cyclins E1 and E2 are regulated by SCF[Fbw7], in breast cancer cells, depletion of Fbw7 affects the levels of cyclin E1 but not E2.[8]

These finding lead to several questions. Are results of Caldon et al.[4,8] generalizable across different types of human cancers? How is the stability of cyclin E2 controlled in cancer cells, and how, mechanistically, does cyclin E2 expression shift from Fbw7-dependent to -independent mode? How does cyclin E2 trigger chromosomal instability? Analyses of the endogenous protein complexes associated with cyclins E1 and E2 in cancer cells may help to unravel molecular differences between these two related, but apparently distinct, proteins.

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