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Cell Cycle News & Views

A new layer of regulation is required to silence the DNA damage checkpoint

Comment on: Wood MD, et al. Cell Cycle 2010; 9:3354-64.

Yanchang Wang; Florida State University; Tallahassee, FL USA; Email: yanchang.wang@med.fsu.edu; DOI: 10.4161/cc.9.18.13180

The regulation and function of the DNA damage checkpoint have been extensively studied during the last two decades. The activation of Chk1 and Rad53/Chk2 kinases is central to the checkpoint response to damaged DNA in all eukaryotic cells. After the priming phosphorylation by Mec1/ATM, Rad53 becomes dimerized and autophosphorylated, which frees Rad53 from auto-inhibition. Recent studies shed light on the molecular basis for the deactivation of the DNA damage checkpoint after the damage is repaired. Accumulating evidence suggests that protein phosphatases PP2A and PP2C play critical role in the silence of DNA damage checkpoint by directly dephosphorylating Rad53.[1] It appears that Chk1 is also subjected to dephosphorylation by protein phosphatase 1 during the recovery from the DNA damage-induced cell cycle arrest.[2]

In response to DNA damage, the central checkpoint kinases Chk1 and Chk2 become active to block anaphase entry by phosphorylating and stabilizing the anaphase inhibitor Pds1.[3,4] In addition to Chk1 and Rad53, cAMP-dependent protein kinase (PKA) phosphorylates Cdc20, one of the activator of anaphase promoting complex (APC) required for Pds1 degradation. This PKA-dependent Cdc20 phosphorylation assists Chk1 to restrain anaphase entry in the presence of DNA damage.[5] An interesting question is how cells reverse this phosphorylation once the damaged DNA is repaired. In a previous issue of *Cell Cycle*, Wood and Sanchez demonstrated that yeast cells lacking Ira1 and Ira2, the negative regulators of cAMP/Ras/PKA signaling pathway, exhibited obvious defect in recovery from DNA damage-induced cell cycle arrest. Moreover, the Cdc20 mutant that is resistant to the phosphorylation by PKA suppressed the recovery defect in ira1Δ ira2Δ mutant cells.[6] These observations indicate that the activity of Ira1 and Ira2 is required to reverse PKA-dependent Cdc20 phosphorylation and restart cell cycle progression after checkpoint arrest. Therefore, in addition to the dephosphorylation and inactivation of Rad53 and Chk1 checkpoint kinases, the PKA-induced phosphorylation of Cdc20 needs to be reversed for DNA damage checkpoint recovery.

These results raise many interesting questions. First, how does the phosphorylation of Cdc20 orchestrate with DNA damage? It has been shown that Mec1/ATM checkpoint kinase is essential for the phosphorylation of Cdc20 by PKA in response to DNA damage. Thus, activated DNA damage checkpoint could either reduce the activity of the negative regulators of cAMP/Ras/PKA pathway, such as Ira1 and Ira2, or up-regulate the PKA activity. Moreover, it will be interesting to identify the protein phosphatase responsible for the dephosphorylation of Cdc20 during checkpoint recovery.

In summary, multiple pathways are involved in checkpoint response to DNA damage to ensure the efficiency of cell cycle arrest. On the other hand, each pathway needs to be silenced for checkpoint recovery. The research work by Wood and Sanchez demonstrates that Ira1 and Ira2, the negative regulator of Ras, is required for the efficient checkpoint recovery. Given the fact that the yeast IRA genes are the homologs of human NF1, a tumor suppressor gene, this discovery provides a new angle to explain the role of NF1 in tumor development. It is possible that the uncoordinated cell cycle progression in NF1-deficient cells after DNA damage contributes to tumor formation.

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A sliding scale: The many faces of Ctf7/Eco1 cohesion establishment factor in DNA repair

Comment on: Lu S, et al. Cell Cycle 2010; 9:3316-28.

Robert V. Skibbens; Lehigh University; Bethlehem, PA USA; Email: RVS3@Lehigh.edu; DOI: 10.4161/cc.9.18.13181

A baker desired to open a second factory from which to prepare her wares. The issue of course was the revered but single recipe book. She painstakingly reproduced each page and, for safekeeping, clipped together each original and page-copy pair. When the process was complete, each pair was unclipped and then separated to form two recipe books. So it is with chromosomes—the revered instructions of life. Each chromosome is faithfully replicated during S phase to produce two identical sister chromatids which are later segregated during mitosis into the newly-forming daughter cells. To identify chromatids as sisters between S phase and mitosis, replication products are "clipped" together (**Fig. 1**). In budding yeast, sister chromatid clips (termed cohesins) are composed of Mcd1/Scc1, Irr1/Scc3, Smc1 and Smc3. Higher eukaryotes also require Sororin to maintain pairing, highlighting the complexity of cohesin structure.[1] Further obscuring interpretations are findings that cohesins function in chromosome condensation, DNA replication fork progression, DNA repair and transcription regulation. How separable are these roles? At the heart of cohesion is Establishment—a process by which cohesins

are converted to a pairing competent state. Establishment requires the acetyltransferase Ctf7/Eco1 (ESCO1 and ESCO2 in humans) that modifies Smc3 specifically during S phase in unperturbed cells and Mcd1/Scc1 in response to DNA damage during G_2/M.[2] Ctf7/Eco1 is critical for chromosome condensation, DNA replication fork progression, DNA repair and transcription regulation—providing a target from which to test whether these functions are indeed separable.

In a previous issue of *Cell Cycle*, lead authors Lu and Goering head a collaborative effort from the laboratories of Jennifer Gerton and Sue Jaspersen (Stowers Institute of Medical Research) regarding just this issue.[3] These authors explored the effects of several ctf7/eco1 alleles in budding yeast - focusing on a ctf7/eco1^{W216G} mutation, which they report phenocopies the acteyltransferase-deficient human ESCO2^{W539G} allele responsible for the developmental malady Roberts Syndrome (RS).[4] Lu, Goering and colleagues performed in vivo cohesion assays at discrete loci along the chromosome length and report that ctf7/eco1^{W216G} cells are predominantly sister chromatid-pairing competent but exhibit extreme sensitivity to double-strand breaks induced by X-ray. In part, this study extends a report on Roberts Syndrome patient cells that contain paired sisters but exhibit sensitivity to a subset of genotoxic agents (sister chromatids in RS patient cells exhibit a railroad configuration in which only heterochromatic regions appear unpaired).[5] A comparison of these cell context sensitivities will be immensely informative.

Two additional findings attest to this separation of Ctf7/Eco1 function. The first concerns RAD61 (WAPL in humans). Rad61 is an anti-establishment factor in that RAD61 deletion bypasses the need for Ctf7/Eco1 in cohesion establishment.[2] However, RAD61 deletion fails to suppress X-ray sensitivity in ctf7/eco1^{W216G} cells—highlight diverse roles for Rad61 and Ctf7/Eco1 in both cohesion and DNA damage.[3] The second finding concerns targets: neither Smc3 nor Mcd1/Scc1 over-expression rescued ctf7/eco1^{W216G} cell sensitivity to double strand breaks, despite numerous findings attesting to the identity of these Ctf7/Eco1 targets.[6] While several alternate explanations are certainly plausible, these findings raise the possibility that neither is the target of interest under the conditions tested.

A molecular explanation may lie in dosage. In a wonderful convergence of studies, Heidinger-Pauli and colleagues found a continuum of function depending on cohesin dosage. Adapting a clever tRNA nonsense suppressor system to eukarotic cells, these researchers reported that DNA repair (and chromosome condensation) appear exquisitely sensitive to even moderate decreases in cohesin levels while sister chromatid pairing appears unperturbed—the latter requiring a dramatic reduction in cohesin levels.[7] This dosage dependency for cohesins likely parallels ever-decreasing Ctf7/Eco1 function in which DNA damage capabilities are the first to go.[3,7]

Double-strand breaks can be resolved by homologous recombination (HR): in mitotic cells the template being the sister chromatid. In this fashion, heterozygosity is maintained and haplo-insufficiency averted. Lu, Goering and colleagues found reduced levels of reciprocal crossovers in ctf7/eco1^{W216G} cells, suggesting that this mutation reduces sister exchanges, which might then lead to repair mechanisms that promote loss of heterozygosity. A similar outcome was reported by Covo and colleagues, except in that study the role of Mcd1/Scc1 was found to be a critical factor in promoting sister chromatid exchange and maintaining heterozygosity.[8] In combination, these studies provide important insights into mechanisms of cancer progression, genome instability and even developmental maladies.

Acknowledgements

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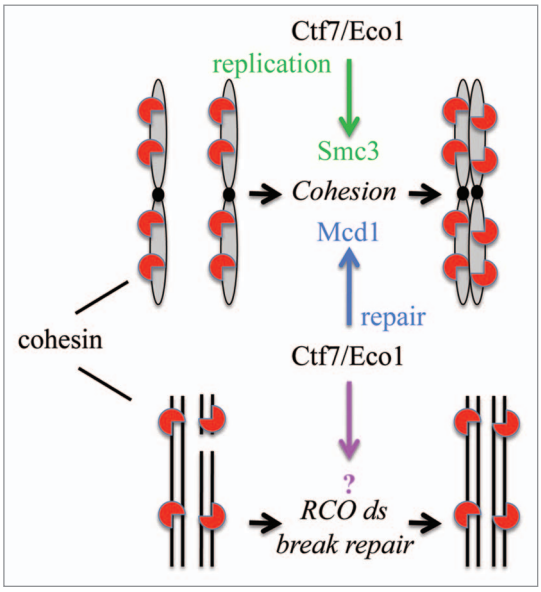

Figure 1. Sister chromatid pairing (cohesion) can occur through Ctf7/Eco1-dependent acetylation of Smc3 during DNA replication (top portion, green) or through Ctf7/Eco1-dependent acetylation of Mcd1/Scc1 in response to DNA damage repair pathways (middle portion, blue). New findings raise an interesting possibility that Reciprocal Crossover (RCO)-based repair through mitotic recombination between sister chromatids (homologous chromosomes not shown) might occur through Ctf7/Eco1-dependent acetylation of an as yet unidentified factor (lower portion, purple).

Additional proof for the importance of Eco1 for DNA double strand break repair

Comment on: Lu S, et al. Cell Cycle 2010; 9:3316-28.

Lena Ström; Karolinska Institute; Stockholm, Sweden; Email: lena.strom@ki.se; DOI: 10.4161/cc.9.18.13182

DNA double strand breaks (DSBs) are a serious threat to the genome, rendering correct DSB repair extremely important.[1] In the manuscript "Eco1 is important for DNA damage repair in *S. cerevisiae*" by Lu et al., in a previous issue of *Cell Cycle*, a new aspect of the DNA repair function for the acetyltransferase Eco1, a component of the cohesion network, is analyzed. Here, the recombination outcome after induction of DSBs in cells harboring a mutation in the gene for Eco1 is investigated.[2]

Eco1 (*Saccharomyces cerevisiae*) is an essential and conserved protein (human ESCO1 and 2) and mutations in the gene for the human ESCO2 gene cause Roberts Syndrome (RBS) a severe developmental disorder. RBS is, in addition to multiple severe physical and mental damages, characterized by repulsion between sister chromatid centromeric regions, and their cells are sensitive to certain types of DNA damages.[3] Cohesion is what holds sister chromatids together from their formation during S-phase until anaphase and is made possible by the Cohesin complex. Cohesion has been found to be instrumental for DSB repair in addition to its importance for correct chromosome segregation. Acetylation of a Cohesin sub-component by Eco1 is required for establishment of cohesion during S-phase.[4] That S-phase cohesion is essential for DSB repair is a well established fact and consequently Eco1 ,the main cohesion establisher, is fundamental for DNA repair.[5] Cohesin localization at DSB in G2 has later been shown to be required for repair of DSB. It has also been demonstrated that in response to such DSBs, new cohesion [damage-induced (DI-) cohesion], is formed. Cohesin components are targets for acetylation by Eco1 also for this type of cohesion, for which Eco1 was found to be the limiting factor. Thus, if overexpressed cohesion can be formed post-S-phase also in the absence of DSBs. Inactivation of Eco1 showed that DI-cohesion, in addition to S-phase cohesion, is required for post-replicative DSB repair. The molecular mechanism for DI-cohesion during repair has however remained unclear. How important DI-cohesion actually is for DSB repair can also be questioned since factors needed for break localization of Cohesin and for formation of DI-cohesion have been shown to be dispensable for DSB repair. Also, the reverse has been shown; DI-cohesion formed but no repair, indicating that DI-cohesion is not sufficient for DSB-repair. As stated, inactivation of Eco1 completely abrogates both DI-cohesion and DSB repair, which reopens the question of what Eco1 does to promote postreplicative DSB repair. Possibly it has other repair functions besides establishment of DI-cohesion and new targets for acetylation might await discovery.[6]

Lu et al. set out to test a series of eco1 mutations in *S. cerevisiae*, and focus mainly on a modification that mimics a mutation in the human ESCO2 gene, affecting the acetyltransferase activity of the protein, and being associated with RBS. The mutations tested only mildly affect S-phase cohesion at permissive temperature, but are to different extents sensitive to DNA-damaging agents, which was not caused by a lack of checkpoint activation. Surprisingly, the authors discover that Eco1, as shown by the RBS mutation, seems to promote reciprocal exchange of chromosome arms (crossing over), following treatment with Bleomycin in mitosis, but not during meiosis. These results do suggest an important specificity in function for Eco1 at various types of DSBs, and it would be very interesting to analyze whether this depends on ability to activate DI-cohesion or if it is an additional DNA repair utility of Eco1. Even though the RBS mutation is in the acetyltransferase region of the protein and reduce the acetylase activity, it is not absolutely clear that the defect in reciprocal cross over depends on acetylation since overexpression of the mutated allele in a background with the same mutation rescues acetylation of a known acetylation target.[2] But one can also argue that this motivates a search for additional targets for Eco1 acetylation to further increase the understanding of the multifunctional Cohesin complex. Reciprocal crossover is important to avoid loss of heterozygosity, a hallmark of cancer. Thus the data described by Lu et al. adds a new perspective on the cohesion pathway and its importance for genome integrity.

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Incapacitating CtBP to kill cancer

Comment on: Straza MW, et al. Cell Cycle 2010; 9:3740-50.

Ling-zun Zhao and G. Chinnadurai; St. Louis University Medical Center; St. Louis, MO USA; Email: chinnag@slu.edu; DOI: 10.4161/cc.9.18.13221

In this issue of *Cell Cycle*, Straza et al.[1] report therapeutic targeting of the transcriptional compressor C-terminal binding protein (CtBP) with a small molecule to specifically induce apoptosis in transformed cells and in cancer cells. Although CtBP has been associated with tumor promotion as a negative regulator of several tumor suppressors,[2] the present study is significant since it is the first report on exploiting CtBP as an anti-cancer target.

The vertebrate CtBP family proteins consist of two major related proteins, CtBP1 and CtBP2 (collectively referred as CtBP) that function as transcriptional corepressors for a large number of repressors. Both proteins exhibit overall sequence and structural similarity to the D-isomer specific 2-hydroxy acid dehydrogenases (D2-HDH).[3] The role of the dehydrogenase activity in CtBP-mediated transcriptional repression remains controversial. Although CtBP1 was shown to possess a slow dehydrogenase activity,[4,5] the cognate "substrate" for the CtBP dehydrogenase activity remained obscure until an intermediate of the methionine salvage pathway, 2-keto-4-methylthio-2-oxo butyrate (MTOB) was identified as a good substrate for CtBP1 dehydrogenase.[6] The analysis of the constituents of the CtBP1 protein complex has helped to establish a general mechanism of transcriptional repression by CtBP[7] (**Fig.1**). A DNA-binding transcriptional repressor recruits CtBP to the target promoter through a PLDLS-like motif first identified in adenovirus E1A. Using the individual subunits in the CtBP dimer, CtBP simultaneously interacts with a transcriptional repressor and a chromatin-modifying protein complex that consists of enzymes such as histone deacetylases (HDAC) 1/2 and lysine specific demethylase-1 (LSD-1)[4] that suppress gene transcription. By structural and biochemical studies, an NAD(H)-binding domain in CtBP has been found to be a redox sensor of the cellular NAD+/NADH ratio, altering CtBP conformation and/or dimerization to regulate CtBP interaction with repressors/chromatin modifying enzymes.

The present study by Straza et al. has revealed an important clue to the role of the dehydrogenase "substrate"-binding domain in CtBP function. In the CtBP structure, the substrate-binding domain and the PLDLS-binding cleft are physically very close to the dehydrogenase catalytic center.[8,9] Although PLDLS-binding does not seem to compete with substrate binding in vitro,[8] data by Straza et al. suggest that substrate loading can exert a significant impact on CtBP recruitment to target promoters. The CtBP substrate MTOB was shown to relieve CtBP2-mediated repression of a pro-apoptotic gene Bik at high concentrations, resulting in enhanced apoptosis of transformed cells and cancer cells in contrast to the relative resistance of normal cells to MTOB. This effect was correlated with reduced recruitment of CtBPs, especially CtBP2, to the Bik promoter. Although CtBP1/2 were previously reported to repress several pro-apoptotic genes including Noxa, Perp, Bax and Bik,[10,11] Bik appears to be most critical for MTOB-induced apoptosis since shRNA-mediated depletion of Bik relieved most of MTOB-induced apoptosis in colorectal cancer cells. This result suggests that molecules that maximize the cell killing

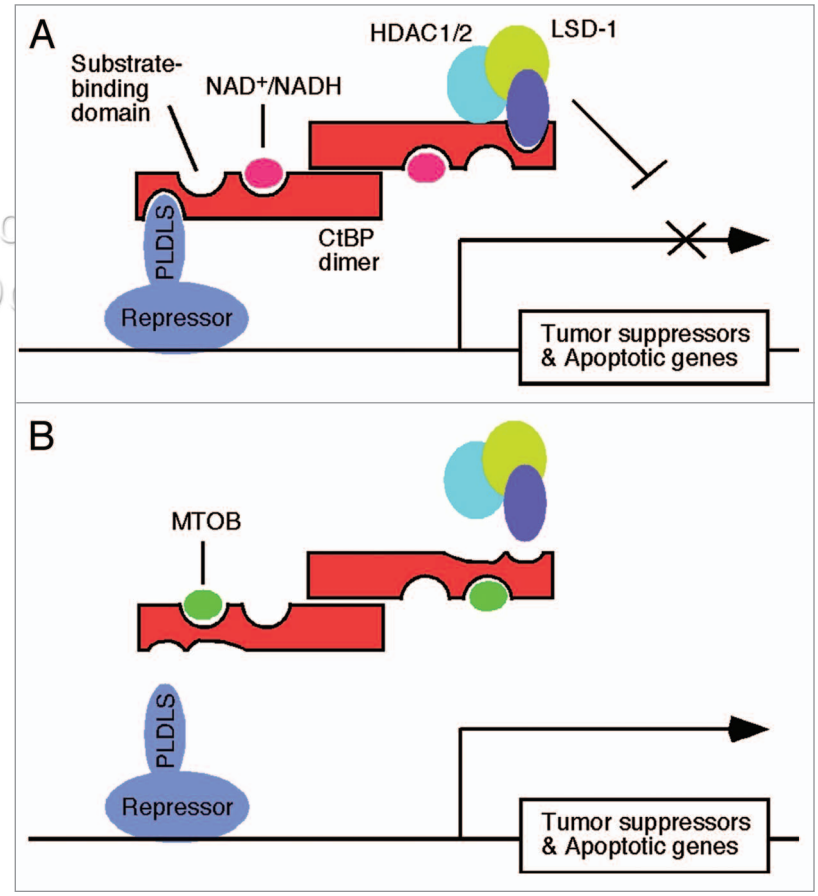

Figure 1. (A) Transcriptional repression of tumor suppressors and apoptotic genes by the CtBP dimer under normal conditions. CtBP is recruited to the target promoter through interaction with the PLDLS-like motif in the repressor which is anchored to the target promoter. The second subunit in the CtBP dimer interacts with DNA-modifying enzymes including HDACs and LSD-1. Epigenetic modifications of the chromatin by the CtBP complex result in gene silencing. NAD+/NADH binding domain and substrate (MTOB)-binding domain are illustrated. (B) Transcriptional activation of tumor suppressors and apoptotic genes after binding of MTOB to CtBP. MTOB binding to the substrate-binding domain of CtBP might induce conformational changes in the PLDLS-binding cleft and cause dissociation of the CtBP complex from the repressor, resulting in derepression of the target genes.

activity of Bik may constitute attractive anti-cancer agents. Although no detailed mechanism of MTOB-suppression of CtBP recruitment to target promoters has been provided by the authors, one possibility might be that MTOB loading to the CtBP substrate-binding domain causes conformational changes in the PLDLS-binding cleft, resulting in reduced CtBP interaction with promoter-bound transcriptional repressors (**Fig.1**). Should this be the case, then experiments with mutants in the substrate-binding dozmain of CtBP could be performed to show resistance of the mutants to inhibition by MTOB. It is of high significance that this study also showed that CtBP is over-expressed in many primary colon tumors and CtBP expression appears to be inversely correlated with expression of tumor suppressor ARF. More detailed expression profiling of CtBP, tumor suppressors, and apoptosis-regulatory genes including Bik in various tumor samples may help uncover new correlations between these genes and help better understand the mutual regulations and roles of these genes during tumorigenesis.

The authors demonstrated the utility of MTOB as an anti-cancer agent in cell culture as well as in the mouse xenograft model. Since MTOB appears to inhibit the transcriptional activity of CtBP at relatively high concentrations, identification of new generation CtBP substrate molecules that function at relatively low concentrations might constitute more effective anti-cancer drugs. Should the biochemical mechanism of MTOB-mediated inhibition of CtBP be clarified further, there might be MTOB derivatives that could bind to the CtBP substrate-binding domain and inhibit CtBP function more specifically and more efficiently.

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The role of p53 in nutrients levels

Comment on: Ashur-Fabian O, et al. Cell Cycle 2010; 9:446-7.

Yosef Shaul and Nina Reuven; Weizmann Institute of Science; Rehovot, Israel; Email: yosef.shaul@weizmann.ac.il;

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The tumor suppressor p53, a sequence specific transcription activator, binds and regulates the transcription of a large number of genes. The level of p53 protein is largely determined at the level of p53 modification and escaping degradation. A large number of p53 modifiers were identified and most clustered into the group of stress responding effectors. Signals from multiple stresses triggered by genotoxic, metabolic, oxidative and oncogenic insults give rise to p53 accumulation and activation.

Lately, the linkage between p53 and metabolism has attracted many studies that by large are based on revealing new target genes.[1,2] In these cases cell-autonomous mechanisms are described to regulate mitochondrial respiration, autophagy, glycolysis, fatty acid oxidation and the creatine pathway controlling ATP homeostasis.[3] In addition to this level of regulation Ashur-Fabian et al.[4] show that p53 may have a non-cell-autonomous role in regulating nutrient transport and uptake. They have identified ApoB and Apobec1 as new p53 target genes. ApoB is involved in the formation of the LDL spherical particles in transporting the absorbed dietary lipids from the digestive tract to the liver. Apobec1 is an RNA editing enzyme that modifies apoB mRNA to translate a C terminus truncated version of apoB.

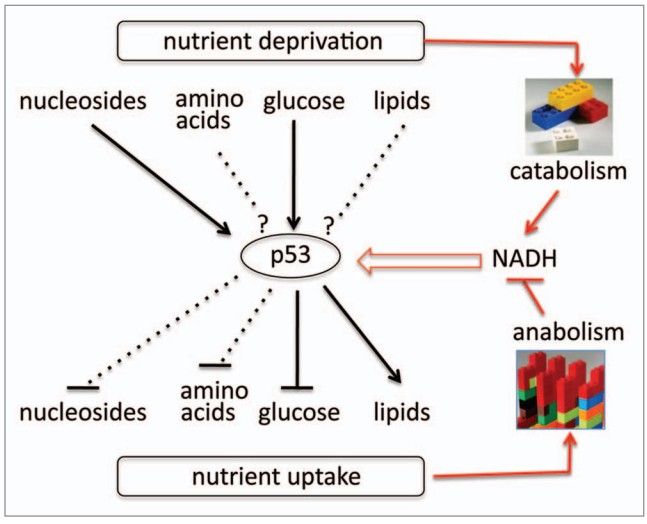

Figure 1. A model: p53 nutrient response and regulation. The dotted lines are a likely assumption.

Ashur-Fabian et al.[4] first demonstrated that both Apobec1 and apoB genes contain p53 response elements that bind p53, as has been shown by ChIP analysis. Using the luciferase reporter assay they have shown that p53 activates these promoters provided that the identified p53 response elements are intact. They found an increase in the level of Apobec1 and apoB mRNA after adriamycin treatment of HepG2 cells, a genotoxic drug that induces p53 accumulation. The authors then used C57b1/6 mice and showed a significant increase in the apoB mRNA level in response to adriamycin treatment in the small intestine, where apoB is normally expressed. The liver of the treated mice showed an induction in the level of apobec1 expression. The authors went on to demonstrate that the adiramycin treated mice are indeed more active in RNA editing but only in the liver. Finally, the authors validated the role of p53 in regulating apoB in mice by

demonstrating that apoB transcription was induced in the liver and in the small intestine of γ-irradiated wt but not p53 knockout mice.

The underlying molecular mechanisms of the pleiotropic role of p53 in metabolism and nutrient supplies are not adequately understood. How nutrient deficiencies regulate p53 level and why lipid metabolism is linked to the p53 network remain open questions. Glucose deprivation induces p53 accumulation but p53 inhibits the glucose transporters GLUT1 and GLUT4 (see the model).[2] The level of p53 is also induced by nucleoside deprivation[5] and p53 is expected to reduce nucleoside uptake (due to its blocking function of cell division). Ashur-Fabian et al.[4] show that p53 increase lipids and cholesterol uptake but we do not know whether p53 level is affected by lipid scarcity. NADH regulates p53 level[6,7] and therefore might be a general regulator. Nutrients deprivation is expected to stimulate catabolic activity whereas excess of nutrients reached by excessive uptake may support anabolic activity. The former increases NADH level whereas and the latter process consumes NADH. Nucleotides metabolism may not fit this principle; nevertheless, a recent report shows that pyrimidine biosynthesis is regulated by p53 via NQO1,[8] an NADH dependent process.

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