levels fall toward evening, *TOC1* expression rises. TOC1 then directly or indirectly induces expression of *CCA1* and *LHY*.

In summary, the two papers discussed here bring us closer to fully understanding the molecular components of the plant circadian system. Are CCA1, LHY, and TOC1/APRR1 the whole story of the plant central oscillator? Begging forgiveness in advance, we conclude by saying that time will tell.

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# Cyclin G: A Regulator of the p53-Mdm2 Network

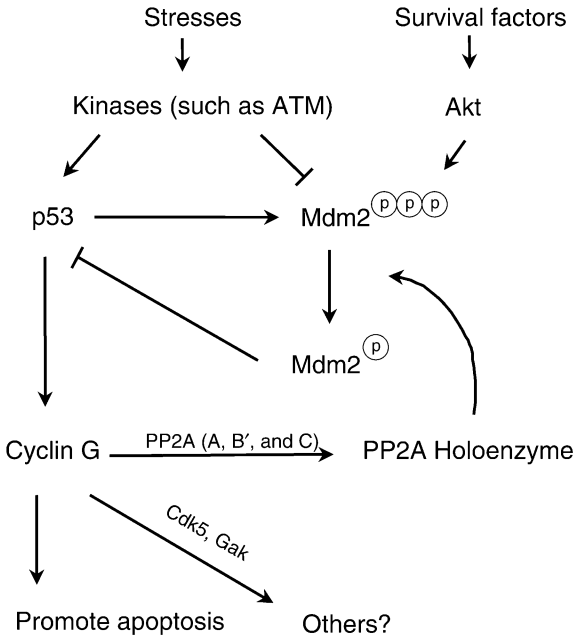
**A recent study published in the April issue of *Molecular Cell* has shown that cyclin G, a p53 target, is a regulatory component of the active PP2A holoenzyme, which activates Mdm2 through dephosphorylation. These findings suggest that cyclin G is a key regulator of the p53-Mdm2 network.**

p53 is a stress sensor and is activated in response to a variety of stress stimuli. Activated p53 then regulates a diverse array of target genes, which mediate p53 activity in the control of cell cycle arrest, apoptosis, and DNA repair (Ko and Prives, 1996). Many cellular genes have been identified, including p21, 14-3-3$\sigma$, and MCG10, which induce cell cycle arrest; Bax, Puma, and Killer/Dr5, which induce apoptosis; and p53R2 and GADD45, which participate in DNA repair. However, after stress subsides and cellular damage such as damaged DNA is repaired, the activated p53 becomes harmful to normal cell growth and needs to be eliminated. It has been clearly demonstrated that the main negative regulator of p53 is Mdm2, which is itself a p53 target gene (Michael and Oren, 2002).

In response to various stress conditions, stress kinases such as ATM are activated, which then phosphorylate and activate p53 (see Figure). Recent studies have shown that some of these stress kinases also phosphorylate Mdm2, and phosphorylated Mdm2 has a reduced ability to interact with, and inhibit, p53 (Michael and Oren, 2002). Therefore, removal of an inhibitory phosphate from Mdm2 is necessary for its activation. In addition, recent evidence indicates that prosurvival kinases, such as AKT, can phosphorylate Mdm2 and increase its ability to target p53 (Michael and Oren, 2002). Therefore, the activity of Mdm2 appears to be regulated by phosphorylation in a manner similar to that of cyclin-dependent kinases (CDKs).

Cyclin G was one of the earliest p53 target genes to be identified, but its function in the p53 pathway has been elusive (Okamoto and Beach, 1994). A number of studies have shown that cyclin G has growth-promoting functions and is highly expressed in regenerating hepatocytes and motoneurons and in rapidly growing cancer cells (Morita et al., 1996; Skotzko et al., 1995). In addition, cyclin G can also increase the sensitivity of cancer cells to TNF$\alpha$-induced apoptosis (Okamoto and Prives, 1999). As a cyclin, cyclin G can associate with cdk5 and GAK, a cyclin G-associated kinase (Kanaoka et al., 1997), but the significance of these associations is unclear. Cyclin G was also known to interact with the B′ subclass of PP2A phosphatase (Okamoto et al., 1996). PP2A is a serine/threonine phosphatase, consisting of a catalytic (C), a structural (A), and a regulatory (B) subunit. Until the recent Okamoto et al. study, the significance of the cyclin G-PP2A interaction was also not clear. Their new data have provided convincing evidence that cyclin G interacts with the enzymatically active PP2A phosphatase (Okamoto et al., 2002). In addition, cyclin G directly interacts with Mdm2 and can stimulate the ability of PP2A to dephosphorylate Mdm2, and thus serves as a recruitment factor. Specifically, they provide strong evidence that the PP2A holoenzyme is capable of dephosphorylating two sites in Mdm2 (S166 and T216) both in vitro and in vivo.

These data raise an important question: does cyclin G have an impact on the activity of Mdm2 toward p53? Using mouse embryo fibroblasts (MEF) that are deficient in cyclin G, Prives and colleagues provide the most interesting and compelling evidence that in the absence




The p53-Mdm2 Network and Its Regulation by Cyclin G-PP2A Phosphatase

of cyclin G, PP2A dephosphorylates Mdm2 less efficiently, and the resulting hyperphosphorylated Mdm2 is less efficient in destabilizing p53 (Okamoto et al., 2002). Addition of cyclin G to cyclin $G^{-/-}$ MEF cells restores the activity of PP2A, and subsequently the activity of Mdm2 in degradation of p53 (Okamoto et al., 2002). These data suggest that cyclin G serves as a negative regulator of p53 by activating Mdm2 through dephosphorylation (see Figure). This also provides a mechanistic explanation for the observation that cyclin G expression is associated with growth promotion rather than arrest (Skotzko et al., 1995).

These new observations provide insight into the function of cyclin G in the p53 pathway, and also raise other interesting questions that need to be addressed in the future. For example, what are the phosphorylation sites in Mdm2 that are specifically targeted by cyclin G-PP2A? Does cyclin G-PP2A, through dephosphorylation, activate MdmX, which is a member of the Mdm family (Michael and Oren, 2002) and a regulator of the p53-Mdm2 network? What are other cellular proteins that interact with cyclin G and are also a substrate for cyclin G-PP2A? Do cyclin G-cdk5 and cyclin G-GAK serve as a kinase to phosphorylate Mdm2 and activate Mdm2 to inhibit p53? Why do cyclin G null mice develop normally (Kimura et al., 2001)? Do cyclin G-related cyclins, that is, cyclin G2 and cyclin I, have similar activity? Is cyclin G-PP2A phosphatase activity necessary for sensitizing cancer cells to TNF$\alpha$-induced apoptosis? Finally, the new findings raise the possibility that cyclin G could be exploited for the development of cancer therapeutic agents. For example, potential strategies could include inhibition of cyclin G expression, blocking the interaction of cyclin G with the B′ subunit of PP2A and Mdm2, and inhibition of PP2A phosphatase activity toward Mdm2.

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## Unexpected Twist to the Z Ring

**Development in *Bacillus subtilis* involves a switch in the location of the cytokinetic Z ring from midcell to the pole. Time lapse photography of an FtsZ-GFP fusion reveals that this switch involves a spiral intermediate and allows identification of the specific sporulation functions involved.**

The Z ring is a cytoskeletal structure formed by the self-assembly of FtsZ, the ancestral homolog of eukaryotic tubulins. In most prokaryotes, cell division depends upon the Z ring, so the problem of how the cell positions the division site can be reduced to how the Z ring is positioned (Lutkenhaus and Addinall, 1997). The developmental program in *Bacillus subtilis* that results in sporulation offers a unique window on this problem. During vegetative growth, the Z ring is positioned at midcell and two equal-sized progeny cells are produced. However, during sporulation, an alternative, asymmetric form of cell division is induced by nutrient deprivation, yielding two cells of different sizes, the forespore and the mother cell, with different developmental fates. A few years ago it was demonstrated by immunofluorescence that Z rings form at each cell pole early in sporulation (Levin and Losick, 1996). One of these is used for the asymmetric division, while the other is eventually discarded.