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evance of the association of spChk1 with spWee1 is as yet unknown (*14*)]. Chk1 probably acts directly on Cdc25: spChk1 and hChk1 proteins (*5–7*) can bind to and phosphorylate spCdc25 and hCdc25 in vivo and in vitro. The sites of phosphorylation on hCdc25 by hChk1 is the same Ser^{216} (*5*, *7*) that is required for arrest in vivo (*7*).

How does phosphorylation inhibit Cdc25? Cdc25 phosphorylation itself does not appear to directly inactivate Cdc25 (*7*). Rather, Peng *et al.* found that only the species of Cdc25 phosphorylated on Ser^{216} (and not the unphosphorylated species) binds to 14-3-3 proteins, a class of molecules that bind to signaling molecules including phosphatases (*15*). Peng *et al.*, therefore, propose that the 14-3-3 protein sequesters Ser^{216}-phosphorylated Cdc25, thereby preventing it from activating Cdc2 by dephosphorylation. Supporting this scheme is the observation that 14-3-3 proteins encoded by the *rad24* and *rad25* genes are involved in arrest after damage in fission yeast (*16*, *17*).

Taken together, these results suggest that after damage, Chk1 becomes active, phosphorylates Cdc25 on Ser^{216}, which promotes the binding of Cdc25 to 14-3-3 protein and therefore its sequestration. In this state, Cdc25 cannot activate Cdc2. The activation of Chk1 after DNA damage appears to involve phosphorylation mediated by other checkpoint proteins, including spRad3 in fission yeast (*13*) and probably related Rad3-like proteins in other cell types (*3*).

This hypothesis now connects the function of checkpoint protein kinase Chk1 to cell cycle regulators Cdc25 and Cdc2. Because this model is based on a number of inferences and depends on the conservation of pathways in different cell types, several points remain to be directly tested. The roles of the putative Chk1 and 14-3-3 proteins in mammalian cells in arrest have yet to be established. The model predicts that the fission yeast Rad24 and Rad25 proteins will bind to and sequester Cdc25 phosphorylated on Ser^{216} and thereby somehow prevent activation of Cdc2. If and how that occurs is unknown. The mechanism of activation of Chk1 remains to be determined as well.

These findings suggesting a specific mechanism for cell cycle arrest at G_2 (see the figure) are a substantial advance in the field. Nevertheless, additional mechanisms of regulation for G_2 arrest apparently exist. Human cells with a nonphosphorylatable Cdc2 subunit are only partially defective in G_2 arrest, leading to speculation that other mechanisms (such as localization of cyclin B) may also be involved in arrest (*9*). In budding yeast, inhibitory phosphorylation of Cdc28, the homolog of Cdc2, is not sufficient to explain G_2 arrest (*20*, *21*). Finally, arrest in S phase when DNA replication is blocked may in some cell types also require Cdc2 phosphorylation (*7*), but in some cases S-phase arrest involves additional mechanisms unrelated to Cdc2 phosphorylation (*18–20*). Indeed, arrest in G_1 after DNA damage in mammalian cells may be regulated by both an inhibitor of Cdk activity, p21 (*23*, *24*), and an inhibitory tyrosine phosphorylation of Cdk4 (*25*) (possibly by the same Chk1-dependent pathway discussed here).

Next, the field will want to inactivate the checkpoint pathways for cancer therapy by targeting components like Chk1 (*26*). Cancer cells treated with drugs that inactivate Chk1, for example, may render those cells more sensitive to DNA damaging agents already widely used in therapy. Whether the resulting increase in sensitivity will affect cancer cells more than normal cells in one of several important issues. Ultimately, to manipulate checkpoint pathways we will need to know yet more molecular details of those pathways, how the pathways are changed in cancer cells, and what else the specific proteins in those pathways do in a cell.

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