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CELL CYCLE

# A WEE pointer

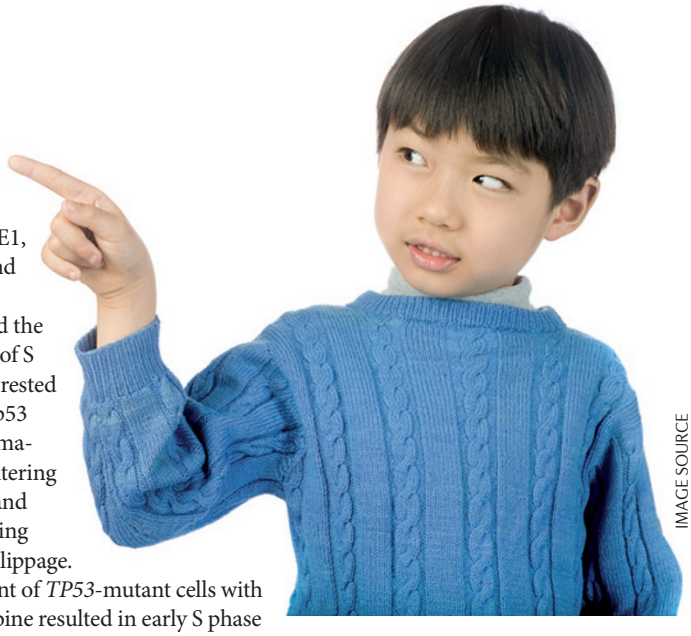

IMAGE SOURCE

Nicholas Turner, Marieke Aarts and colleagues have investigated the mechanism through which inhibition of the mitotic regulator WEE1 sends S phase-arrested cancer cells into a premature mitosis.

Small-molecule inhibitors of the kinase WEE1, which phosphorylates cyclin-dependent kinase 1 (CDK1) and so inhibits the mitosis-promoting cyclin B (CCNB)–CDK1 kinase complex, have been shown to synergize with chemotherapeutic agents by promoting an early entry into mitosis. On screening 23 breast cancer cell lines and two breast epithelial cell lines, the authors found that, in the presence of both gemcitabine, which induces an S phase arrest, and the WEE1 inhibitor MK-1775, only cells with mutated *TP53* prematurely entered mitosis before they had completed S phase. Cells were able to exit mitosis after prolonged arrest without dividing properly (known as mitotic slippage) and many then either arrested or underwent apoptosis. Inhibition of CDK1 activity prevented the effect of WEE1 inhibitors, indicating that CDK1 activity is crucial for the induction of premature mitosis from S phase by WEE1 inhibition. The kinase CHK1 can also indirectly regulate CDK1 phosphorylation as part of the intra-S phase checkpoint, so the authors inhibited both CHK1 and WEE1, and found that this increased the number of S phase-arrested mutant p53 cells prematurely entering mitosis and undergoing mitotic slippage. Treatment of *TP53*-mutant cells with gemcitabine resulted in early S phase arrest and induction of cyclin B1 and CDK1 expression, as well as activation of CHK1, indicating that S phase-arrested cancer cells with mutated *TP53* might be reliant on CHK1–WEE1 function to prevent premature entry into mitosis.

> “S phase-arrested cancer cells with mutated *TP53* might be reliant on CHK1–WEE1 function to prevent premature entry into mitosis”

Preliminary gene expression analyses in 20 *TP53*-mutant breast cancer cell lines indicate that those with high expression levels of mitotic cyclins (cyclin E1 and B-type cyclins) are likely to be more susceptible to the effects of WEE1 inhibition than those that have high levels of cyclin D1 (a G1–S cyclin). Increased expression of the Polycomb gene *EZH2* was also associated with gemcitabine and MK-1775 synergy. Breast cancers that grow aggressively can have high expression levels of *EZH2* and *CCNB1*, implying that they may be particularly sensitive to WEE1 inhibition combined with chemotherapeutics that induce an S phase arrest.

Although experiments using colon cancer xenografts indicated that the combination of gemcitabine with MK-1775 shows some efficacy *in vivo*, further experiments in more informative mouse models are needed to better understand which tumours are most likely to respond to DNA damage-induced S phase arrest and WEE1 inhibition-induced premature entry into mitosis.

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**ORIGINAL RESEARCH PAPER** Aarts, M. *et al.* Forced mitotic entry of S-phase cells as a therapeutic strategy induced by inhbition of WEE1. *Cancer Discov.* 23 Apr 2012 (doi:10.1158/2159-8290.CD-11-0320)