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Bypassing The Spindle Assembly Checkpoint In Vertebrates

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Checkpoints are signal transduction pathways that monitor key events of the cell cycle and give the cell enough time to complete or correct detected errors. The spindle assembly checkpoint (SAC) ensures the equal partition of chromosomes between two daughter cells. Failure to satisfy the SAC can irreversibly alter the cell's ploidy, leading to genome instability, and ultimately, tumorigenesis. In the presence of unattached or weakly attached kinetochores the SAC delays mitotic exit by preventing the anaphase promoting complex (APC)-mediated proteolysis of cyclin B, a regulatory subunit of cyclin-dependent kinase 1 (Cdk1). Like all checkpoints, an active SAC does not normally arrest cells permanently, and escape from mitosis with an unsatisfied SAC requires that cyclin B/Cdk1 activity be inhibited. While in yeast, and likely Drosophila, this occurs through an "adaptation" process involving a Cdk1-inhibitory phosphorylation or activation of a cyclin-dependent kinase inhibitor (Cdki), in vertebrate cells the mechanism is unknown. We conducted a series of fluorescence microscopy studies on rat kangaroo (PtK1) and normal human (RPE1) cells dividing in the presence of nocodazole. We found that escape from mitosis in the absence of microtubules occurs in the presence of kinetochore-associated SAC proteins and requires both proteolysis and cyclin B destruction. Also, in the presence of a functional SAC, cyclin B is progressively destroyed by a proteosome-dependent mechanism. Thus vertebrate cells do not adapt to the SAC. Rather, our data suggest that the SAC cannot prevent a slow but continuous degradation of cyclin B that ultimately drives the cell out of mitosis.