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Separase cooperates with Zds1 and Zds2 to activate Cdc14 phosphatase in early anaphase.

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Completion of mitotic exit and cytokinesis requires the inactivation of mitotic cyclin-dependent kinase (Cdk) activity. A key enzyme that counteracts Cdk during budding yeast mitotic exit is the Cdc14 phosphatase. Cdc14 is inactive for much of the cell cycle, sequestered by its inhibitor Net1 in the nucleolus. At anaphase onset, separase-dependent down-regulation of PP2A(Cdc55) allows phosphorylation of Net1 and consequent Cdc14 release. How separase causes PP2A(Cdc55) down-regulation is not known. Here, we show that two Cdc55-interacting proteins, Zds1 and Zds2, contribute to timely Cdc14 activation during mitotic exit. Zds1 and Zds2 are required downstream of separase to facilitate nucleolar Cdc14 release. Ectopic Zds1 expression in turn is sufficient to down-regulate PP2A(Cdc55) and promote Net1 phosphorylation. These findings identify Zds1 and Zds2 as new components of the mitotic exit machinery, involved in activation of the Cdc14 phosphatase at anaphase onset. Our results suggest that these proteins may act as separase-regulated PP2A(Cdc55) inhibitors.