Opinion

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The Mitotic Exit Network: new turns on old pathways

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In budding yeast, the Mitotic Exit Network (MEN) is a signaling pathway known to drive cells out of mitosis and promote the faithful division of cells. The MEN triggers inactivation of cyclin-dependent kinase (Cdk1), the master regulator of mitosis, and the onset of cytokinesis after segregation of the daughter nuclei. The current model of the MEN suggests that MEN activity is restricted to late anaphase and coordinated with proper alignment of the spindle pole bodies (SPBs) with the division axis. However, recent evidence suggests that MEN activity may function earlier in mitosis, prompting re-evaluation of the current model. Here we attempt to integrate this recent progress into the current view of mitotic exit.

Mitotic exit in budding yeast

The division of the cell involves its transient but profound reorganization to ensure the coordinated distribution of cellular material between the daughter cells. On completion, mitotic structures disassemble, mitotic regulators are inactivated, and interphase is reinstated. This process, termed mitotic exit, starts with the inactivation of Cdk1, the master regulator of mitosis, and the dephosphorylation of its substrates. As a consequence, the mitotic spindle breaks down, cytokinesis occurs, chromosomes decondense, and interphase functions resume. Importantly, faithful cell division requires tight coordination of mitotic exit with chromosome segregation. Although little is known about how mitotic exit is controlled in most systems, budding yeast is an exception. In this organism, a dedicated pathway – the MEN – triggers Cdk1 inactivation and the onset of cytokinesis on segregation of the daughter nuclei.

The MEN (reviewed in [1,2]) is a signaling pathway driven by the GTPase Tem1, which signals through the Hippo-related kinase Cdc15 (Figure 1A) [3–7]. Cdc15 activates two LATS-related MEN kinases, Dbf2 and Dbf20, which work in concert with the coactivator Mob1 to release the phosphatase Cdc14 from the nucleolus, from where it redistributes throughout the cell [4,7–12]. Cdc14 then antagonizes and inactivates Cdk1 by dephosphorylating its targets, promoting cyclin destruction and mediating the accumulation of the Cdk1 inhibitor Sic1 [13,14]. In parallel, the Dbf2 kinase phosphorylates components of the cytokinesis machinery, such as the F-BAR protein Hof1, thereby promoting cytokinesis onset [15]. Thus, activation of the MEN and Cdc14 promotes Cdk1 inactivation and cell cleavage concomitantly.

It is widely accepted that MEN activity is coordinated with proper mitotic progression. This concept stems from the observation that mitotic exit does not occur if the mitotic spindle is misaligned with respect to the division axis of the cell [16–23]. These arrested cells lack MEN activity, thereby preventing the release of Cdc14 from the nucleolus. However, inactivation of a Tem1 inhibitor, the bipartite GTPase-activating protein (GAP) comprising the proteins Bub2 and Bfa1, bypasses this telophase arrest. As a consequence, cells with a mispositioned spindle and lacking either Bub2 or Bfa1 divide into binucleate mother cells and anucleate daughters [16–19,21,22]. Thus, MEN regulation ensures the coordination of mitotic exit with proper anaphase completion.

In the past few years, numerous studies have added to our knowledge about mitotic exit and the MEN, challenging some of the classical views. In this review, we discuss this recent progress and try to integrate these observations with current knowledge to provide a more comprehensive view of mitotic exit.

Regulation of MEN activity

A large body of work has established that the MEN signals the proper positioning of the SPBs, the yeast equivalent of centrosomes, with respect to the dividing cell. SPBs are embedded in the nuclear envelope and face the cytoplasm with their outer plaque, from which they nucleate astral microtubules (reviewed in [24]). At the SPBs, the MEN proteins interact with the centriolin-related factor Nud1 [25,26]. Throughout mitosis, Tem1, Bfa1, and Bub2 localize to SPBs and most strongly to the SPB directed toward the bud [17,21,27]. In late anaphase, most of the Bub2 and Bfa1 pools gather on the SPB in the bud, while Tem1 is released from their inhibition, thereby promoting activation of Cdc15 and Dbf2/20 and mitotic exit.

Thus, one interpretation of these data is that Tem1, and hence the MEN, is kept inactive by Bub2 and Bfa1 as long as no SPB has entered the bud, after which Tem1 is released from inhibition and triggers mitotic exit (reviewed in [1]). However, several studies in different model organisms suggest that it is not that simple. First, numerous

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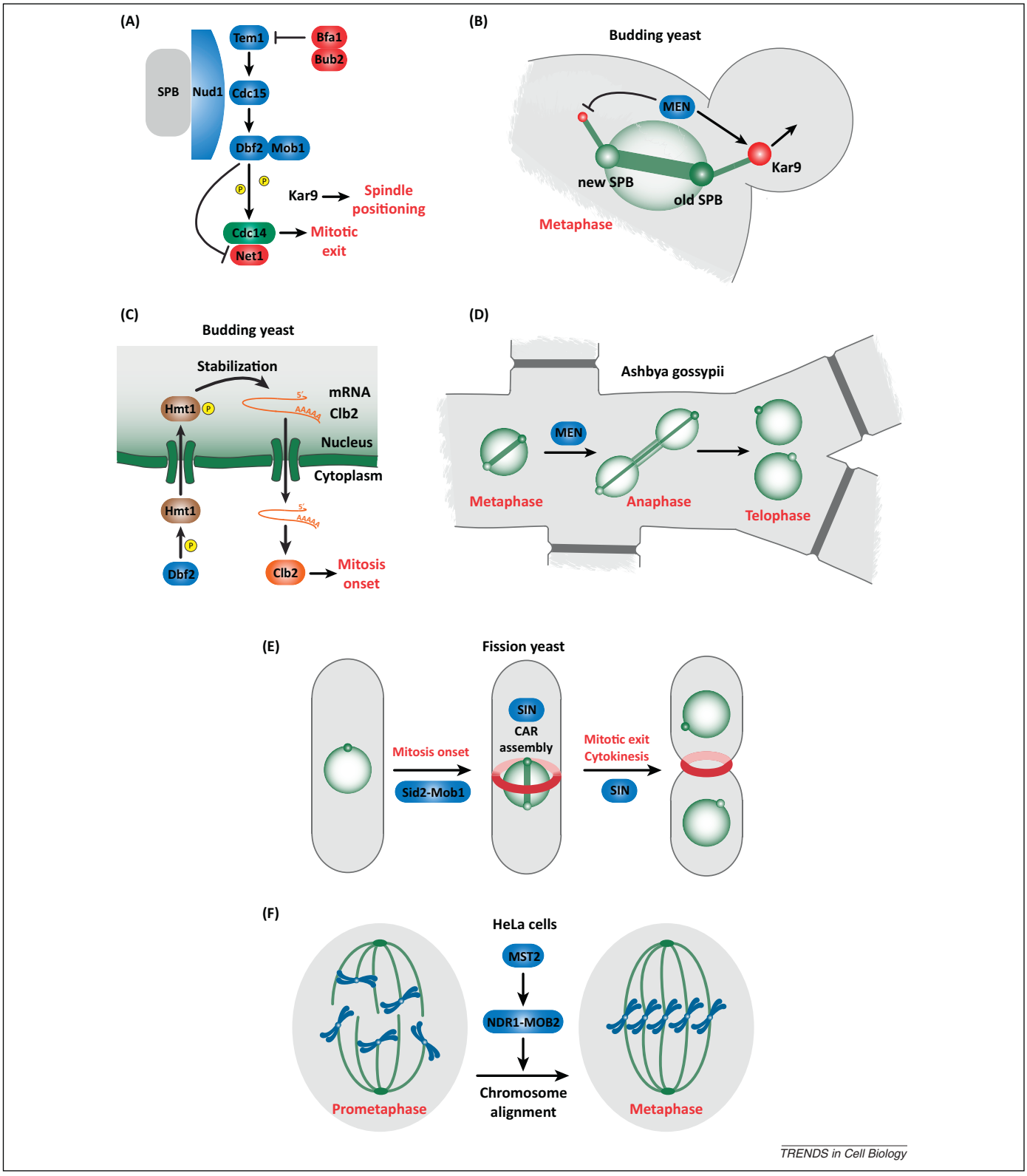

Figure 1. Functions of the Mitotic Exit Network (MEN) and its homologs throughout the cell cycle. (**A**) The MEN (blue) in budding yeast ensures spindle positioning through Kar9 and mitotic exit by activation of Cdc14. (**B**) The MEN promotes specification of spindle pole body (SPB) fate and the asymmetric accumulation of Kar9 with respect to old and new SPBs in metaphase. (**C**) Before the onset of mitosis, the MEN kinase Dbf2 activates the methyltransferase Hmt1, which enters the nucleus and promotes the stabilization and export of Clb2 mRNA into the cytoplasm. Subsequent translation and accumulation of Clb2 protein is required for progression into mitosis. (**D**) In *Ashbya gossypii*, the MEN promotes the progression from metaphase to anaphase, but not mitotic exit. (**E**) The homologous Septation Initiation Network (SIN) in fission yeast controls both the onset of mitosis through the Dbf2 homolog Sid2 and the assembly of the contractile actomyosin ring. These functions occur before the role of the SIN in mitotic exit and cytokinesis. (**F**) In HeLa cells, the Cdc15 homolog MST2 and the Dbf2-related protein NDR1 promote chromosome alignment in prometaphase.