Cell Cycle 13:5, 693–694; March 1, 2014; © 2014 Landes Bioscience

Cell-size control: Complicated

Comment on: Bhatia P, et al. Cell Cycle 2014; 13: 538–52; PMID:24316795; http://dx.doi.org/10.4161/cc.27411

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Cells usually grow to a proper size before they divide. To ensure an optimal size for cell survival and function, it is crucial that cells develop efficient and sensitive mechanisms for cell-size control. In 2009, 2 independent studies proposed that the DYRK-family kinase Pom1 could serve as a cell-length sensor to negatively regulate mitotic entry through SAD-like kinase Cdr2 in fission yeast.[1,2] Pom1 forms concentration gradients with highest concentration at the cell tips. As the cell grows, Pom1 concentration at the cell center decreases continuously until it is too low to maintain the inhibition on Cdr2, whose activation promotes mitotic entry by regulating (directly or indirectly) downstream kinases Cdr1, Wee1, and Cdk1. In addition, Pom1 is also a negative regulator of division-site positioning. However, it remains unclear how Pom1 and Cdr2 cooperate in temporal and spatial regulation of cell division.

To answer this question, Bhatia et al.[3] set out to further evaluate the Pom1 gradient model on cell-size control and published their work in the February 15, 2014 issue of *Cell Cycle*. The previous model utilizes Pom1 global protein level along the cell long axis as a cell length indicator.[1,2] However, local protein concentrations define protein functions and behaviors more accurately in a biological process. Since Pom1 and Cdr2 concentrate on the plasma membrane, they quantitatively measured Pom1 and Cdr2 fluorescence intensity along the cell cortex. Contrary to the previous model,[1,2] Pom1 level at mid-cortex is much lower and does not change as cells elongate. More surprisingly, the overlap between Pom1 and Cdr2 distribution is small and continues to decrease.[3] These findings contradict the assumptions and predictions in the previous model, where there is a larger Pom1 and Cdr2 overlap, and the Pom1 concentration at cell center decreases during cell growth.

Alternatively, the authors provided 3 lines of evidence to show that partial loss of Pom1 protein level or activity, while not affecting division-site positioning, displays premature mitotic entry.[3] Pom1's function in division-site positioning needs much less Pom1 than cell-size control. Temporal regulation on cell division, however, requires higher Pom1 concentration and activity, and is more sensitive to protein level alterations. Cdr2 is the substrate for both Pom1 functions, although Cdr2 only plays a minor role in division-site selection, as anillin Mid1 still forms cytokinesis nodes, and a majority of cells place the division site normally without Cdr2.[4] Pom1 inhibits Cdr2 by phosphorylation on its C-terminal tail.[2,3] While the inhibition is important for timing of mitotic entry, it does not affect Cdr2 distribution on the cell cortex or its interaction with Mid1. The increasing Cdr2 level with cell length at medial cortex may contain distinct information for mitotic entry itself, although this effect may be minor, as moderate overexpression of Cdr2 weakly promotes premature mitotic entry only when Pom1 is absent.[3]

To add more layers of complexity, Pom1 is not the only input of mitotic entry, nor even the Cdr2-regulatory network (**Fig. 1**). Multiple mechanisms that function through Cdr2/Cdr1 (Cdr1 inhibitor Nif1, cell polarity component Skb1, and NIMA kinase Fin1) or via parallel pathways (stress responses and Cdc14 family phosphatase Clp1) promote or inhibit mitotic entry, leading to variations in cell lengths. However, the relationship between these pathways is largely unknown. It would be especially interesting to see how the levels and functions of Pom1 and Cdr2 are affected by these other inputs.

The observation that Pom1 functions are dosage-dependent is also found in some of other cell cycle regulators. For example, Polo kinase Plo1 accumulates at spindle pole bodies (SPBs) and promotes mitotic entry. Its concentration on SPB is responsive to cell stresses conducted by MAPK stress response pathway and target of rapamycin (TOR) signaling pathway, which would result in premature mitotic entry (**Fig. 1**).[5] It is possible that Pom1 also responds to certain stress by altering its protein levels on the cell cortex. Interestingly, Tea1 and Tea4, which recruit Pom1 to the cell cortex, also participate in the MAPK stress response pathway.[6]

In summary, the mechanism underlying how cell controls its size during the cell cycle is much more complicated than our current understanding. The redundancy of multiple pathways provides fertile ground for future studies. Studies on budding yeast suggested no definite "cell sizer" that triggers mitotic entry.[7] A recent publication in *Cell Cycle* by

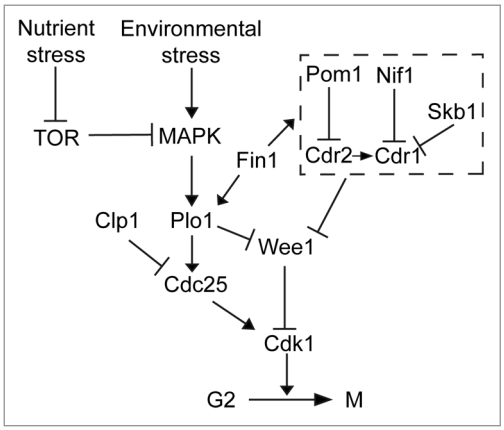

Figure 1. Current understanding of regulations on mitotic entry. Cdr1 and Cdr2 kinases are inhibited by Cdr1 inhibitor Nif1, cell polarity component Skb1, and Pom1 kinase, whereas the NIMA kinase Fin1 positively regulates the whole pathway (dashed box) through an unknown mechanism. Activated Cdr1/Cdr2 phosphor-inhibit Wee1 kinase, which in turn relieves Cdk1 inactivation. The Polo kinase Plo1 accumulates on the SPB to promote mitotic entry. Its localization also responds to stress signals from MAPK and TOR, as well as Fin1. Clp1 phosphatase controls the mitotic timing by dephosphorylating Cdc25 phosphatase. All the inputs control the balance between Cdc25 and Wee1 to ensure a proper cell size and timing of cell division.

Wood and Nurse also challenged the model that Pom1 is a cell-size sensor.[8] Nevertheless, the dosage effect of Pom1 concentration remains crucial for temporal and spatial regulations of cell division.

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