Review

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Inability to regulate cell wall integrity and cell cycle progression in *smi1-Δ* mutant cells in *Saccharomyces cerevisiae*

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Abstract

Saccharomyces cerevisiae is a yeast species often used as a model for eukaryotic organisms. In *S. cerevisiae*, the *SMI1* gene and resulting protein, Smi1p, have been found to have an important role in controlling cell wall integrity by regulating cell cycle progression. Smi1p is a key coordinator between the cell wall integrity pathway and the cell cycle progression pathway. Here, we review the effects of a *SMI1* gene knockout, cells with the *smi1-Δ* allele, to further learn about the function of the *SMI1* gene in yeast cells. Mutant *smi1-Δ* cells experience challenges mediating cell cycle progression and regulating cell wall integrity leading to decreased cell reproduction and cell wall defects. The *smi1-Δ* cells have reduced (1,3)-beta-glucan synthesis causing higher sensitivity to cell wall damaging agents. This review synthesizes research from eight studies to describe what is already known about the *SMI1* gene, the role of Smi1p in biochemical cell pathways, and *smi1-Δ* mutant cells. As well, the review offers direction for further research on *smi1-Δ* cells that could lead to a better understanding of the *SMI1* gene function in *S. cerevisiae*.

Introduction

In *S. cerevisiae*, the *SMI1* gene codes for a protein that transcriptionally regulates cell wall integrity and synthesis through the coordination of cell cycle progression (Hong & Huh, 2021; Martin-Yken et al., 2003; Samakkarn et al., 2021). A 2006 study by Basmaji et al. found that the *SMI1* gene is expressed constitutively. Smi1p, however, is an unstable protein that is degraded when the cell enters the stationary phase of the cell cycle (Basmaji et al., 2006). Smi1p, while not essential for cell growth under normal conditions, has an important role in maintaining the stability of the cell wall under stressful conditions (Martin-Yken et al., 2016; Samakkarn et al., 2021). A 2002 study by Martin-Yken et al. found that the overexpression of *SMI1* in cells resulted in increased resistance to cell wall affecting drugs compared to wildtype cells with regular levels of *SMI1* expression. Research done by Samakkarn et al. found that increased levels of *SMI1* expression resulted in higher glycerol production in cells and thus improved osmoregulation in cells (2021).

Smi1p is involved in three biological pathways: cell wall synthesis, cell polarity and budding during mitosis, and protein degradation in the cell (Basmaji et al., 2006). A paper by Martin-Yken et al. in 2016 found that Smi1p acts to directly coordinate between the cell wall integrity (Pkc1-Slt2 mitogen-activated protein kinase) pathway and the cell cycle progression (calcium calcineurin) pathway as seen in Figure 1A. This literature review will summarize the challenges encountered by *smi1-Δ* mutant cells

related to cell wall integrity and cell cycle progression.

Literature Summary

The *SMI1* gene knockout results in *smi1-Δ* mutant cells that encounter numerous issues in regulating cell wall structure and cell cycle progression (Basmaji et al., 2006). Samakkarn et al. (2021) and Hong et al. (1994) confirm that the deletion of the *SMI1* gene results in cells with multiple cell wall defects and decreased cell reproduction. Defects in mutant cells have been found to include cell wall osmotic sensitivity (Hong et al., 1994). It was found that *smi1-Δ* mutants experience a reduction of (1,3)-beta-glucan, a major component of yeast cell walls (Basmaji et al., 2006; Hong et al., 1994). The lack of the *SMI1* gene leads to decreased levels of (1,3)-beta-glucan synthesis activity and less stable cell walls (Basmaji et al., 2006). The *smi1-Δ* mutant cells can survive; however, the cell walls of mutants have higher sensitivity to damaging agents leaving cells

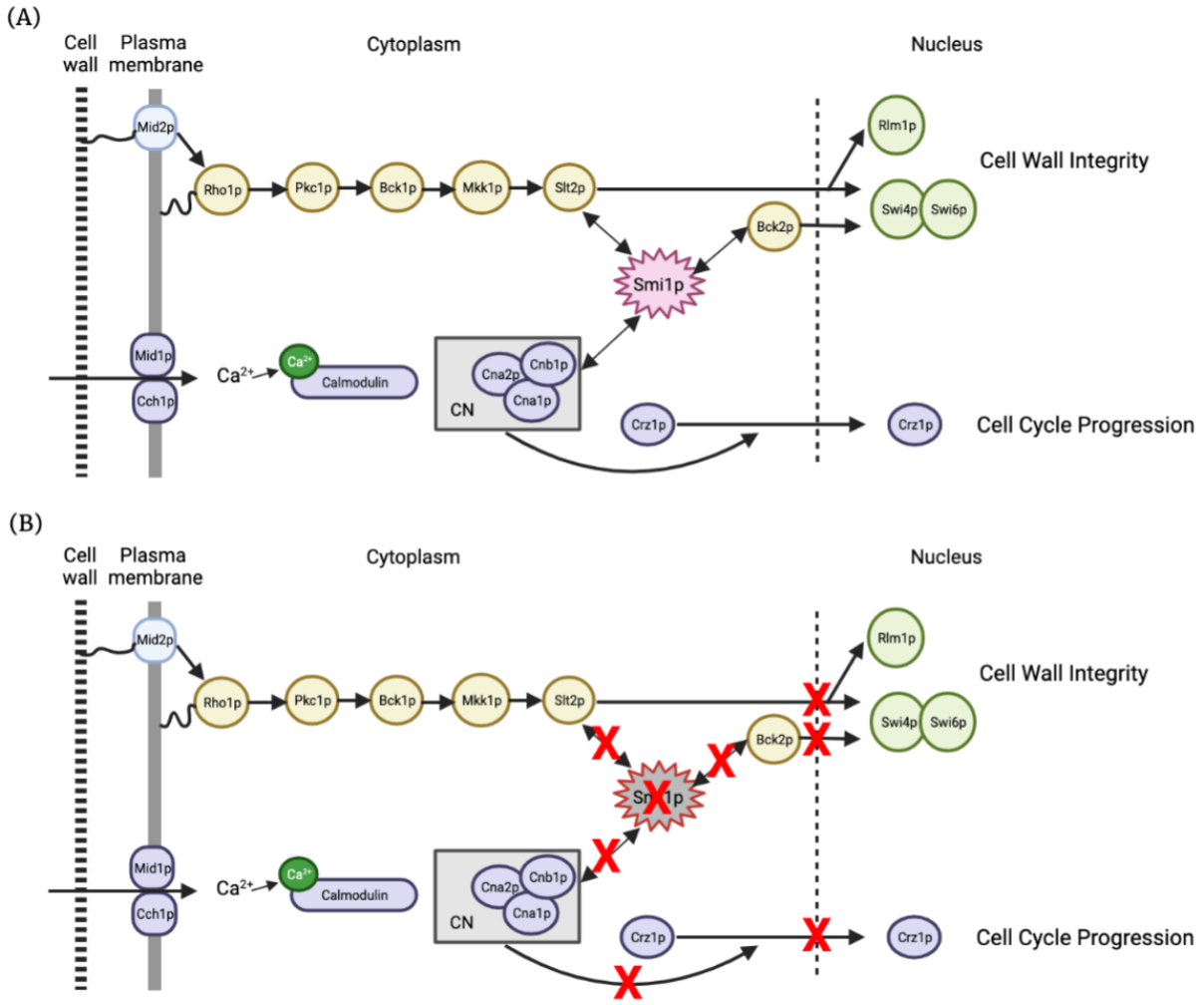

Figure 1. Smi1p in the cell wall integrity (Pkc1-Slt2 mitogen-activated protein kinase) pathway (yellow) and cell cycle regulation (calcium calcineurin) pathway (purple). (A) The functioning cell wall integrity and cell cycle regulation pathways coordinated by Smi1p. In the cell wall integrity pathway, the activation of Smi1p by Slt2p coordinates the Swi4p/Swi6p complex and Rlm1p. The Swi4p/Swi6p complex mediates cell growth through cell cycle coordination of the G1 cell phase progression. Rlm1p mediates transcription of cell wall components. In the cell cycle progression pathway, Smi1p contributes to the calcineurin (CN) complex to activate Crz1p. Crz1p is a transcription factor that helps regulate G2-M cell cycle progression. **(B)** The smi1-Δ pathway showing the terminated pathways due to lack of Smi1p. There is no activation of Rlm1p, the SWi4p/Swi6p complex or Crz1p leading to a lack of transcription factors required for cell wall growth and cell cycle progression. (Figure adapted from Basmaji et al., 2006, Martin-Yken et al, 2003, and Villa-García et al., 2011).

unable to regulate the cell wall integrity pathway (Martin-Yken et al., 2003; Hong & Huh, 2021) as illustrated in Figure 1B. Samakkarn et al. tested *smi1-Δ* cells in the presence of high ethanol as well as high temperatures (2021). Under these conditions, *smi1-Δ* cells had both reduced growth and cell wall biosynthesis leading to an increased frequency of cell wall defects compared to wildtype cells (Samakkarn et al., 2021).

Mutant cells lacking the *SMI1* gene experience dysfunction at two stages of the cell cycle (Martin-Yken et al., 2016). Martin-Yken et al. note that smi1-Δ cells experience dysfunction at the morphogenesis checkpoint, which involves the cell wall integrity and calcium calcineurin pathways, as well as the part of the cell cycle that determines the size of daughter cells at cytokinesis (2016). In Figure 1B, the calcium calcineurin pathway is shown to be interrupted by the knockout out of *SMI1*. Interestingly, a 2021 paper by Hong and Huh found that *smi1-Δ* cells have a longer replicative life span than wildtype cells due to higher stability of rDNA caused by deletion of the *SMI1* gene in mutant cells.

Many questions remain about how the *SMI1* gene interacts with such a high number of different processes controlling cellular regulation (Basmaji et al., 2006). There is little known about the 3D structure of Smi1p in different complexes and how its domains interact with other proteins (Martin-Yken et al., 2016). Basmaji et al. conclude that the role of the Smi1p is understood to be important for cell wall integrity, however, the mechanisms of how it regulates the cell to maintain integrity, and at what point in the cell cycle it acts, is less well known (2006). Additionally, Hong and Huh suggest that more research needs to be performed to determine the mechanism behind how the loss of the Smi1p activates other proteins to increase the replicative life span of cells (2021).

Summary and Conclusion

As was illustrated in the literature for *smi1-Δ* cells, it is clear that the *SMI1* gene in S. cerevisiae codes for a protein responsible for cell wall integrity regulation by its involvement in coordinating cell cycle progression (Martin-Yken et al., 2016; Samakkarn et al., 2021). Smi1p plays a crucial role in regulating the cell under stressful conditions as seen in the inability of *smi1-Δ* cells to maintain a strong cell wall while under stress (Samakkarn et al., 2021). Due to the *SMI1* gene knockout, cells are interrupted in their ability to coordinate the cell wall integrity and cell cycle progression pathways (Martin-Yken et al., 2016). Research has been done to identify the various pathways that Smi1p interacts with, however, to fully understand the effects of the *smi1-Δ* mutation and how it affects cell life cycles, more research needs to be done to determine how the Smi1p domains interact with other proteins and at what point in the cell cycle Smi1p acts (Basmaji et al., 2006; Martin-Yken et al., 2016).

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