The dynamics of cell wall biogenesis in yeast
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GENERAL DISCUSSION

When I started this research five years ago, the catalytic subunit of β-1,3-glucan synthase had just been cloned, independently by a number of groups. Until that time, the cell wall of yeast and other fungi had of course been the focus of study. However, the approaches had typically been based on analyzing the composition of the wall, and by purifying proteins involved in cell wall metabolism, supplemented with cytological studies of cells and regenerating protoplasts. Molecular biology had not really found its way into the study of the cell wall.

Several reasons can be found to explain this. First, when cell biologists look at yeast mutants to understand the function of the gene mutated, they will often get rid of the wall, since it hinders, for example, the entry of antibodies. Cell wall phenotypes are not easily found if one is not explicitly looking, and as the wall hadn’t yet been “discovered” as an interesting organelle, not many people were looking. Second, many mutations in many genes important for cell wall biogenesis do not have strong phenotypes. Often, several homologues are present that are normally expressed under different conditions, but that can take over each other’s functions if one is absent. The Bgl family of endoglucanases or transglucosylases, for example, has four members, the Gas family five, and the β-1,3-glucan synthase Fks1p has a very close homologue that prevents lethality of a fks1 mutant. It is even worse in the case of the GPI-dependent cell wall proteins, mutants in which often have no detectable phenotype. The last reason why the cell wall is not easy to study with conventional genetics and molecular biology is that very many genes affect the cell wall, and often in an indirect manner. Among the thousand deletion mutants studied in the EUROFAN project, approximately 200 are hypersensitive to Calcofluor white, SDS or sonication, indicating defects in the cell wall. In retrospect, this could have been expected; all genes involved in cell polarity, secretion, cell cycle progression, and even carbon source metabolism, can be expected to have some effect on the cell wall, because it is such a huge organelle and its synthesis has to be so well coordinated with cell cycle progression and nutrient availability, and because it is generated extracellularly, so that all components or synthetic machinery must be directed to the right place in or through the plasma membrane.

In the mean time, several developments have increased interest in the cell wall. First, detailed understanding of the exact make-up of the wall has made it possible to ask and answer new and more accurate questions about, for example,
the incorporation of proteins, and different modes of synthesis in response to varying conditions. Second, the completion of the yeast genome project has made it possible to easily identify genes involved in cell wall biosynthesis, and to study their effects. For example, the in silico identification of all potential GPI-proteins has much facilitated the study of cell wall proteins. Also, the development of databases containing information ordered by gene or protein has created greater awareness of other fields than one's own, and following the example of the GPI-proteins, induces researchers to look at phenotypes they would not formerly have been aware of. Possibly the most important consequence of the completion of the genome project is the development of whole-genome techniques, and particularly the incredible amount of whole-genome expression data that have become available to the entire yeast community, providing clues as to when and in which cells genes might fulfill their functions. A third, unfortunate, development is the fact that the human pathogenic yeasts, such as Candida albicans, are gaining ground, because of the increased number of immuno-compromised patients. The cell wall is a preferred target for antifungal drugs, since it is unique for the fungus and essential to it. In that respect, the study of the cell wall of pseudohyphally growing Saccharomyces cerevisiae should be a focus of attention, since hyphal Candida is infectious. The, also recently, increased understanding of mechanisms leading to the pseudohyphal switch should much facilitate this work, and we already know that a cell wall protein is imperative to invasive growth.

One of the most apparent aspects of regulation of cell wall biosynthesis is its coordination with the cell division cycle. Simply by looking at growing yeast, one can see that there are events, such as bud emergence, cell separation, growth of the bud and not of the mother, where cell wall biosynthesis or breakdown must be strictly controlled. Indeed, when genes encoding cell wall biosynthetic enzymes were cloned, in many cases they were found to be transcribed in a cell cycle dependent manner. The same holds true for covalently incorporated cell wall proteins, transcription of more than half of which is cell cycle regulated. Since it is impossible to separate mothers and buds in amounts sufficient for biochemical or enzymatic analyses, we have never been able to study the differences between bud walls and mother walls. The identification of many of the participants in cell wall biogenesis (different cell wall proteins, Fks1p, Rho1p, actin, cell wall sensors such as Wsc1p), has allowed us to determine their locations. Additionally, the now widespread use of GFP, has allowed us to follow the movements of the ones that are not fixed in
position, and to understand interactions, cause and effect. Therefore, we can now study the cell wall and cell wall biosynthesis in detail, and start looking at its specific functions.

One of these functions is the generation or maintenance of cellular polarity. Intracellularly, several systems cooperate to generate polarity. However, these systems can be depolarized and repolarized, seemingly remembering the situation as it was. Therefore, a mechanism must exist that provides fixed landmarks for polarity. The cell wall would be an ideal candidate, as proteins or structures incorporated in the wall remain fixed. Known examples are of course bud scars and the birth scar, that mark the distal and proximal pole, respectively. However, what component in birth and bud scar interacts with intracellular components is unknown. The fact that cell wall proteins are not uniformly distributed, and can be very specifically localized, suggests their involvement in establishment or maintenance of cellular polarity. Although we have not yet been able to show such a function of any specific cell wall protein, the involvement of the cell wall in the generation or maintenance of polarity, and its potential in fixing landmarks that can be used for this process, warrants thorough investigation.
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