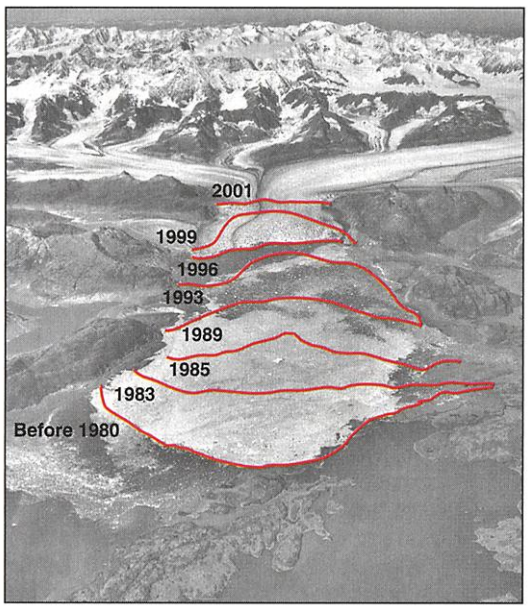


**Recent wastage of Columbia Glacier, Alaska.** This large glacier is rapidly losing mass by thinning and the discharge of icebergs into the sea. Aerial photograph taken in September 1996.

tion and geodynamic data suggest that a eustatic component is necessary to explain the data (*13*). The new glaciological results of Arendt *et al.* (*1*) provide support for a eustatic contribution. They identify a major eustatic contribution to sea level change near the Gulf of Alaska, probably the largest in the world.

To make confident projections for the course of sea level rise in the 21st century, we must first understand its causes in the past century. The work of Arendt *et al.* shows the way ahead. We need more laser-altimeter studies of glaciers in areas where mass-balance observations are few. We also need better climate-glacier synthesis models and improved parameterization of atmospheric general circulation models for mountain regions, especially maritime areas such as coastal Alaska. Satellite geodesy, oceanography, glaciology, geodynamics, and climate change must all contribute if this important aim is to be achieved.

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14. In (A), laser-altimeter results were arbitrarily cumulated from 1965 to be comparable with the surface balance observations. In (B), the data on Alaska from (*5*) have been multiplied by the ratio 90,000/74,000 because of the larger area considered in (*3*).

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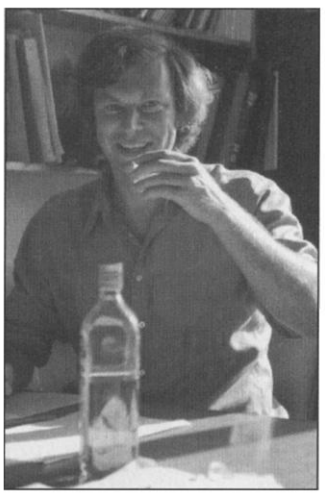
PERSPECTIVES: CELL BIOLOGY

# When Wee Meets Whi

**Peter Sudbery**

Most cell types maintain a constant size over many generations and must reach a critical size before they can divide. This suggests that cells must have a mechanism to coordinate cell division (mitosis) with attainment of the critical size (*1*). Working with the fission yeast *Schizosaccharomyces pombe* in the 1970s, Paul Nurse and his colleagues identified mutants that divided at an abnormally small size and called them "*wee*" mutants after the Scottish word for small. Analysis of these mutants was instrumental in elucidating regulation of the cell cycle in fission yeast by the cyclin-dependent kinase (Cdk) encoded by the *cdc2* gene (*2*). Later, small-size mutants were discovered in the budding yeast, *Saccharomyces cerevisiae*, and were promptly given the moniker *whi*, pronounced "wee" (see the photograph, this page). The *WHI1-1* allele isolated in the budding yeast screen (*3*) helped to identify the $G_1$ cyclins, which associate with Cdks to promote commitment to cell division in most eukaryotic cells (*4*).

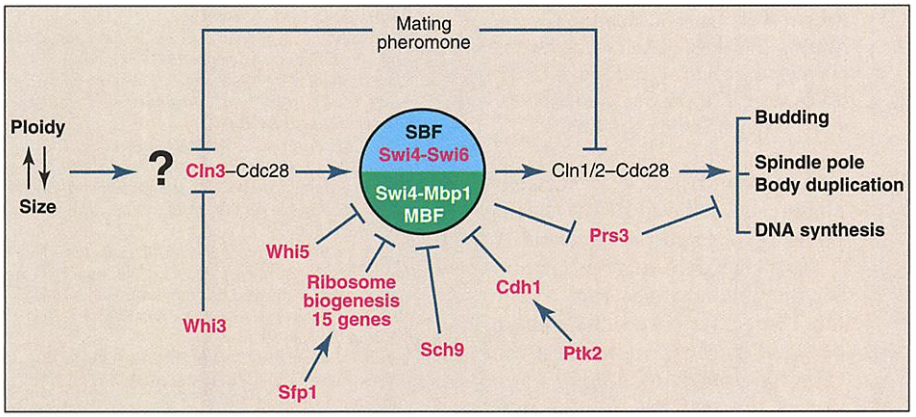
Yeast size mutants are difficult to isolate because there is no obvious difference between the colonies they form and those formed by wild-type cells (for example, in terms of growth rate). In fact, some mutations may even alter cell size without affecting the size control mechanism itself, making it even more difficult to identify those genes involved in size homeostasis. One way to identify genes genuinely involved in the size control mechanism is to assess the effect of mutating each gene in the yeast genome. This is precisely the approach taken by Jorgensen *et al.* (*5*) and presented on page 395 of this issue. Their comprehensive screen of all 6000 gene deletion mutants in *S. cerevisiae* yielded 500 mutants with altered cell size. From their screen, these authors identified a number of genes that seemed to be genuinely involved in size homeostasis, including, unexpectedly, 15 genes that are important for ribosome biogenesis.



**A Whi dram.** The isolation of the *S. pombe wee* mutants by Paul Nurse and Peter Fantes spurred Bruce Carter and me to screen for small-size mutants in *S. cerevisiae*. I bet Bruce a bottle of the best Irish Whiskey that we would not be able to isolate such mutants. Happily, I lost the bet, and we identified *S. cerevisiae* small-size mutants, which we called *Whi* in honor of the bet. Bruce can be seen here enjoying the spoils of victory, a bottle of Black Bushmills.

Analysis of budding yeast mutants defined a checkpoint in late $G_1$ phase of the cell cycle called Start (*6*). Once cells pass Start, they are committed to mitosis, but in order to divide, they must have reached a critical size (*7*). The critical size is sensitive to growth rate, so that slow-growing cells pass Start at a smaller size than fast-growing cells. Start is initiated by Cln3p, the protein encoded by the *WHI1-1* gene (subsequently renamed *CLN3*). Cln3p integrates signals about cell size and growth rate. When the critical size is reached, Cln3p associates with a Cdk called Cdc28p, which activates two transcription factors, SBF (Swi4p-Swi6p) and MBF (Mbp1p and Swi4p) (*8*). These transcription factors drive the expression

The author is in the Department of Molecular Biology and Biotechnology, University of Sheffield, Sheffield, S10 2TN, UK. E-mail: p.sudbery@sheffield.ac.uk




**A great Start.** The Start network in *S. cerevisiae*. Proteins identified in the screen of 6000 *S. cerevisiae* gene deletion mutants by Jorgensen *et al.* (*5*) are shown in red. The molecular mechanisms that enable yeast cells to measure their size against DNA content and then transmit this information to the Start network, which initiates mitotic cell division, are still not understood. Proteins implicated in this process include those involved in ribosome biogenesis.

of the $G_1$ cyclins *CLN1* and *CLN2*, which associate with Cdc28p to program steps in the Start process, such as bud emergence, DNA synthesis, and spindle pole body duplication (see the figure, this page). A critical feature of Start regulation is the instability of $G_1$ cyclins. The *WHI1-1* allele causes a decrease in cell size because the Cln3p it encodes is abnormally stable and so reaches high levels resulting in prolonged activation of the $G_1$ cyclins and an aberrant Start (*4*).

Mutations that subvert the size control process yield two phenotypes in *S. cerevisiae*—small mutants (*whi*) in which Start is initiated too soon, and large mutants (*lge*) in which Start initiation is prevented even when the yeast have attained the appropriate size. In the first stage of their gene deletion screen, Jorgensen *et al.* ranked the size of 4812 viable haploid deletion mutants and selected the largest and smallest 5% of the population for further study. They also determined the size of mutants containing heterozygous deletion of essential genes, because a size control gene may act in a dosage-dependent manner. Any mutation that directly interferes with the cell cycle without affecting growth will cause yeast to be large. Many of the 249 *lge* mutants did indeed contain mutations in predicted cell cycle genes. In addition, among *lge* mutants were those with mutations in genes that would be expected to delay Start when deleted (*cln3*Δ, *swi4*Δ, *swi6*Δ, and so forth). To identify other genes affecting cell size control, Jorgensen *et al.* tested the set of *lge* mutants for genetic interactions with known regulators of Start. The authors identified a new gene, *LGE1*, that when deleted together with the *swi4* gene killed the yeast.

Small size can result from any mutation that reduces the growth rate, because the size control mechanism operates so that slower growing cells divide at a smaller size. Most of the mutations producing the small (*whi*) phenotype affected genes involved in respiration or ribosome biogenesis. The remaining 61 *whi* mutants were screened for a growth rate effect by plotting their doubling time against size and selecting only those that fell below the baseline obtained from wild-type cells and a panel of slow-growing ribosomal gene deletion strains. Twenty-five *whi* mutants that may be genuinely involved in size control were identified in this way. Two of the affected genes are known to be involved in Start. The first, *WHI3*, is a negative regulator of *CLN3* (*9*), whereas the second, *CDH1*, encodes an activator of the anaphase-promoting complex (*10*) that degrades the mitotic cyclin Clb2, enabling exit of cells from mitosis and their maintenance in $G_1$. From genetic interactions the authors pinpointed two other genes in the Start network, *WHI5* and *PKT2*. *WHI5* probably acts upstream of *SWI4*, and *PKT2* acts upstream of *CDH1*. Another *whi* mutant, *prs3*Δ, was already known to be lethal when deleted in tandem with *whi2*Δ (*11*). *PRS3* encodes a key enzyme in the biosynthesis of purines, pyrimidines, and the amino acids histidine and tryptophan. Both *whi2*Δ and *prs3*Δ mutants have the interesting property that they fail to respond to nutrient depletion by preventing Start. Unlike all other *whi* mutants, the small size of the *prs3*Δ mutant was independent of mutations in other known Start regulators. This mutant may be part of a new Start initiation pathway.

Mutations in 15 genes involved in ribosome biogenesis caused a reduction in size, and had either no effect on growth rate or a disproportionate effect on size relative to the change in growth rate. Other ribosome biogenesis genes that were deleted were not classed as size-control genes because they had a large effect on growth rate. Five of the 15 genes were nonessential and were part of the set of 25 *whi* haploid deletion mutants. Ten of the 15 genes were essential and resulted in a size reduction in heterozygous deletion mutants.

Mutation of *sfp1* resulted in one of the smallest phenotypes observed in the *whi* mutant set. *SFP1* encodes a zinc finger transcription factor that controls expression of a wide range of genes encoding proteins involved in biogenesis of ribosomes or other components of the translation machinery. Another recent report identifies a yeast protein, Yph1p, that links control of cell proliferation to DNA replication, ribosome biogenesis, and mRNA translation (*12*). Thus, ribosome biogenesis appears to be directly linked to the commitment to cell division. As the rate of ribosome biogenesis is proportional to cell size, it could be the measure that cells use to assess how big they are. In *Drosophila* and mouse, cell size control involves the protein kinase B (PKB) pathway that regulates the rate at which ribosomal components are produced (*13*). Intriguingly, another very small *whi* mutant lacks the *sch9* gene, which encodes a protein that is 49% identical to PKB in its carboxyl-terminal kinase domain. Thus, ribosome biogenesis as a regulator of size control may be an evolutionarily conserved phenomenon.

It is well established that cells do not simply seek to maintain a constant absolute size. Rather, they maintain a constant relation between cell size and the amount of DNA or ploidy (*1*). So cells must be able to monitor both their size and DNA content and adjust the timing of mitosis accordingly. To monitor DNA content, it is necessary to postulate that a gene or genes act in a dosage-dependent manner (*1*). A strong prediction is that such genes will induce a size change in heterozygous diploids. A number of *whi* mutants, including *sch9*Δ, did indeed exhibit size reduction in their heterozygotes and may identify proteins that report the status of DNA content to the cell. The big problem is to understand exactly how the protein products of the genes identified in the Jorgensen *et al.* study are able to measure cell size against DNA content, and are then able to transduce the resulting signal to the Start network. The tantalizing results of Jorgensen *et al.*'s ambitious screen have made this big problem just a wee bit smaller.

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