under different demographic histories.

Coalescent theory states that all genes in a population share a common ancestor. How long ago that common ancestor existed is the time to coalescence, or the time to the most recent common ancestor. When a single population diverges into two, initially many genes lineages will have common ancestors that existed prior to divergence of the populations; that is, the time to coalescence of any particular gene lineage will be greater than the time to divergence. These are termed 'deep coalescence' events. As the time since divergence increases, the expected number of deep coalescence events declines, until all of the gene copies in each population share a common ancestor that existed more recently than the divergence between the two populations (Figure 1).

Using data simulations, Carstens *et al.* [8] compared the number of deep coalescence events seen in their data with the number that would be expected if populations diverged either at the onset of the last ice age (~100,000 years ago), or since the ice age ended (~17,000 years ago). These data simulations showed that, if the grasshopper populations had diverged after the last ice age, there should have been many more deep coalescence events than were actually observed in DNA sequence data from the grasshoppers.

Although phylogeography has fallen out of fashion in recent years, the emerging climate crisis has made understanding past climate changes more important than ever. By integrating palaeoclimatology with coalescent theory, Carstens *et al.* [8] have set a new benchmark for historical biogeography that foreshadows an exciting future for the field. This new synthesis will unite investigators from population genetics, ecology, and climatology into a new science of biogeography that will continue to flourish through the next century.

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Department of Biological Sciences, University of Idaho, Moscow, Idaho 83844-3051, USA.
E-mail: csmith@uidaho.edu

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Polarized Cell Growth: Double Grip by CDK1

Precise coupling of cell growth and cell-cycle progression is crucial for achieving cell homeostasis. A recent study sheds light on two distinct roles of cyclin-dependent kinase 1 (CDK1) in promoting polarized cell growth in budding yeast.

Giulia Rancati and Rong Li

Cell-size homeostasis is an important requirement for cell proliferation. Many efforts have been devoted to tackling this classic problem, but it remains unclear how cell growth is coordinated with cell division [1]. In the current view, cell growth and cell-cycle control are considered separate processes that are linked through dependency mechanisms. Most published studies have focused primarily on two questions: how a cell-size threshold is set; and how this threshold impinges upon the cell-cycle regulatory system governed by cyclin–CDK complexes. The budding yeast *Saccharomyces cerevisiae* has been a useful model for studying the coupling between growth and cell-cycle progression. Existing evidence suggests that yeast cells assess their growth status by measuring the rate of translation as a function of cell volume [1]. A threshold translation rate allows accumulation of G1 cyclin, which leads to activation of CDK1 and entry into S phase through complex mechanisms. In addition, inhibition of CDK1 activity before S-phase entry permits cell growth, albeit in an isotropic fashion [2,3].

Therefore, CDK1 was not previously implicated in the regulation of cell growth and the coordination between cell growth and cell-cycle control appeared to be a one-way street.

An aspect of *S. cerevisiae* cell growth/division that has not been considered extensively in the study of cell-size control is the fact that nearly half of the cell growth required for the generation of two daughter cells occurs after G1. Yeast cells divide through bud formation and cell growth is therefore polarized along a vectorial axis toward the bud to allow delivery of various constituents to the newly forming cell surface [4–6]. The cell has limited time to complete this growth, as a near doubling of cell volume and surface area must occur within a short window of ~30 min during S–G2 phases. It has been shown that CDK1 orchestrates the switch between isotropic growth and polarized growth. In particular, when CDK1 is bound to G1 cyclins, it triggers the transition from isotropic growth in G1 to polarized growth in S–G2; however, when bound to mitotic cyclins, CDK1 activity switches the cell back to isotropic growth during M phase [7] (Figure 1). It is thought that most targets of CDK1 during these transitions are components of the core signaling machinery, centered on the Rho-type Cdc42 GTPase, which controls the establishment of cell polarity.

Recent work from McCusker *et al.* [8] now reveals previously unrecognized roles for CDK1 in promoting different aspects of polarized cell growth. To dissect the role of CDK1 in polarized cell growth, this group took advantage of an analogue-sensitive allele of CDK1 (*cdk1-as*) that was previously shown to be rapidly inactivated upon addition of an adenine analogue, 1NM-PP1, and found, surprisingly, that an acute inhibition of CDK1 caused an immediate arrest of bud enlargement. This result implied that CDK1 activity is continuously required for bud growth after the onset of S phase. A critical process in bud growth is the polarized delivery of Golgi-derived secretory vesicles along actin cables via a myosin V motor protein [9]. Secretory vesicles fuse at the bud tip to insert the material for building the new cell surface, composed of plasma membrane and cell wall. CDK1 inactivation promptly delocalized all the components of this machinery from the bud tip, including the exocyst complex required for vesicle fusion, the myosin V motor protein, and even components of the endocytic complexes required for recycling. It is unlikely, however, that the observed growth arrest was a consequence of depolarization of growth, since neither the mother cell nor the bud increased in size upon CDK1 inhibition, whereas blocking actomyosin-based transport primarily affects growth polarity, as opposed to growth *per se* [10,11]. Thus, the growth inhibition was likely to be due to a direct inhibition of some steps along the secretory pathway.

What might be the advantage of CDK1 assuming growth control of the bud after G1? One possibility is that phosphorylation by CDK1 maintains the efficiency of the exocytic machinery to ensure the growth required for achieving a bud size that is large enough to accommodate the incoming nucleus and all the organelles required for survival after cytokinesis. In other words, like the chromosomal events in the cell cycle, the generation of the new cell compartment (bud) is driven by the CDK1 cell-cycle engine. Remarkably, there is even a checkpoint that delays mitotic entry by the activation of the CDK1 inhibitor, Swe1, in response to defects in polarized growth [12]. Still, it remains unclear why growth is permitted in G1 without CDK1 activity. It is tempting to speculate that a growth inhibitor is allowed to accumulate after the G1/S transition, possibly due to inactivation of APC-dependent proteolysis. CDK1 activity would therefore be required to counteract this growth inhibitor during S phase (Figure 2).

The second part of the study by McCusker *et al.* [8] investigates how CDK1 activity triggers the establishment of cell polarity, which occurs at the G1–S transition and is governed by Cdc42. Polarized assembly of the actin cytoskeleton and localization of the vesicle fusion machinery to the site of bud emergence are regulated by Cdc42 and several other Rho GTPases [4,5,13]. Activation of Cdc42 requires the guanine nucleotide exchange factor (GEF) Cdc24. In G1 cells, Cdc24 is sequestered in the nucleus in an inactive form, and G1 cyclin–CDK1 complexes trigger Cdc24 activation and relocation from the nucleus to the site of budding. There are few insights, however, into how CDK1 activates Cdc24 at the molecular level. To elucidate

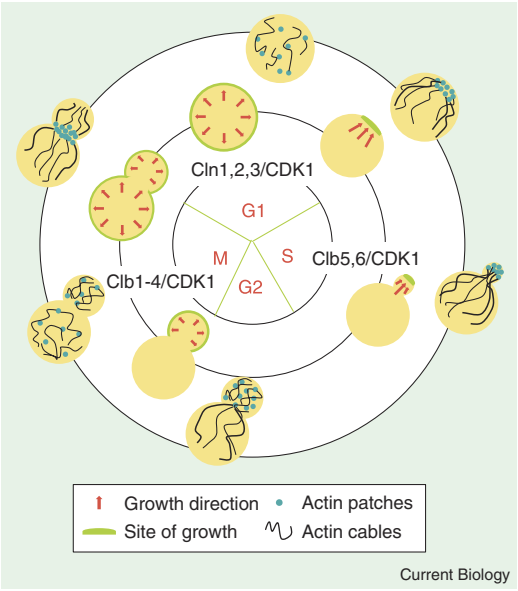

Figure 1. Coordination between cell-cycle progression, actin organization and cell-surface growth.

During budding yeast mitotic cell divisions, the CDK1–cyclin complexes couple cell-cycle progression with growth and actin cytoskeleton rearrangements. Cell-cycle progression is represented in the core of the diagram. Polarized and isotropic growth is represented as direction and site of growth. Actin cytoskeleton rearrangements are described through the reorganization of its major components: actin patches and cables.

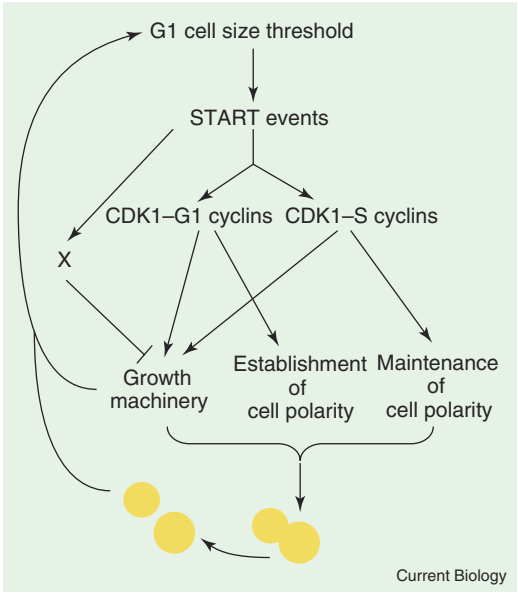

Figure 2. A schematic model for coupling growth and cell cycle in the control of cell size in budding yeast.

In G1, active growth machinery and isotropic growth allow the mother cell to reach a certain size threshold which triggers START events. CDK1 activation by G1 cyclins leads to the establishment of cell polarity and promotes rapid growth. Hereafter, growth becomes dependent on CDK1, possibly due to accumulation of a growth inhibitor (X) after START. Active CDK1–S cyclin complexes sustain polarized growth through S and G2, enabling the bud to reach an appropriate size for cell division.

this point, McCusker *et al.* [8] sought for possible CDK1 targets among the Cdc24-interacting proteins. Purification of Cdc24 in cells undergoing bud growth led the authors to identify Bem1, Rga1 and Boi1/2 as Cdc24-interacting partners, though it was unclear whether these proteins exist in a single complex. Rga1 is one of the Cdc42 GTPase-activating proteins (GAPs) [14], whereas Bem1 and Boi1/Boi2 are multi-domain adaptor-like proteins [13,15]. Bem1 was previously shown to form a complex with Cdc42–GTP and Cdc24. This complex is thought to constitute a positive feedback loop for the establishment of Cdc42 polarization [16,17].

Cdc24 and its interacting partners show cell-cycle-dependent phosphorylation, the onset of which roughly correlated with the peak of the protein level of the G1 cyclin Cln2. CDK1 inactivation using the *cdk1-as* allele resulted in delocalization of these proteins and Cdc42 from the incipient bud tip at apparently different rates, suggesting that CDK1 is continuously required for the maintenance of the polarized state. The authors further characterized the function of Boi1 phosphorylation by CDK1. Mass spectrometry led to the identification of 29 phosphorylation sites in Boi1, 12 of which matched the minimum consensus site for CDK1. Mutagenesis of these consensus sites caused temperature-sensitive growth. The terminal phenotype at the restrictive temperature was characterized by the presence of large unbudded cells and small budded cells with large mothers. The function of CDK1-mediated Boi1 phosphorylation is therefore more consistent with a role in the establishment and maintenance of cell polarity, as opposed to a role in the growth control operated by CDK1. Much remains to be elucidated at a mechanistic level on how CDK1-induced phosphorylation of Cdc24 and its interacting partners affect the biochemical activities of these proteins.

The observation that CDK1 activity is continuously required for the polarized state has an interesting implication on the design principle of cell-polarity control in yeast. The burst of G1 cyclin–CDK activity is thought to trigger the establishment of cell polarity at the G1–S transition. Whereas G1 cyclin–CDK activity is short-lived, the polarized state must be sustained through the whole period of bud growth. In engineering terms, this may be explained by system hysteresis, where the switch that controls cell polarization is intrinsically bistable and the polarized state is able to sustain even after the inductive signal diminishes [18]. Alternatively, the G1 cyclins may simply pass the torch on to other CDK1 activators to maintain the polarized state. The findings of McCusker *et al.* [8] suggest that G1 cyclin–CDK activity is unlikely to be sufficient for sustaining polarized growth and these authors propose that the S-phase cyclins, Clb5/6, may be the subsequent torch bearer. The lack of temporal bistability in the polarity regulatory network may allow growth polarity to be tightly coordinated with cell-cycle progression, enabling precise bud-size control and reorganization of the growth machinery to the bud neck later in the cell cycle.

In summary, existing data now indicate that cell-size homeostasis during vegetative growth in yeast is achieved at two levels: a G1 restriction point that ensures the appropriate size of the mother cell; and a ‘double-grip control’ by CDK1 during polarized growth to achieve sufficient bud size in a short period. This double-grip control refers to the dual function of CDK1 in controlling first the establishment and maintenance of cell polarity and then in sustaining the activity of the growth machinery, possibly by modulating the activity of the secretory components. A question of interest is whether the mechanism underlying the control of polarized growth by CDK1 is relevant to other eukaryotes. Since budding yeast cell division is intrinsically asymmetric and shares some of the common principles governing asymmetric cell divisions in multicellular organisms, it would not be surprising to find conserved features in the molecular pathways that connect CDKs to cell polarity and polarized membrane trafficking. Next summer will be the 25th anniversary of the discovery of cyclins [19], and it seems clear that we are still scratching the surface of cyclin–CDK’s functionality.

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The Stowers Institute for Medical Research, 1000 East 50th Street, Kansas City, Missouri 64110, USA.
E-mail: RLI@Stowers-Institute.org

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Cell Signalling: The Merry Lives of BAK1

Plant receptor-like kinases characterised by leucine-rich repeats have been shown to play dual roles in seemingly unrelated biological processes, inviting comparison with TOLL-like receptors of animals.

Gwyneth C. Ingram

The plant protein kinase BRI1-ASSOCIATED RECEPTOR KINASE1 (BAK1) plays a key role in the perception of growth-promoting phytosteroids such as brassinolide. In addition to its role in the control of plant growth, brassinolide perception has been shown to promote cell death both during senescence, and during tracheary element development in xylem tissue [1,2]. The discovery then, in two independent studies [3,4] reported recently in *Current Biology*, that BAK1 also plays a key role in negatively regulating plant cell death, comes as rather a surprise.

BAK1, like the cognate brassinolide receptor BRASSINOSTEROID INSENSITIVE1 (BRI1), is one of more than 200 receptor-like kinases encoded by the *Arabidopsis* genome which have extracellular domains containing leucine-rich repeats (LRRs) [5]. Few of these LRR receptor-like kinases have been assigned biological functions, possibly because of extensive functional redundancy. Of these few, BRI1 is undoubtedly the best characterised at the molecular level (reviewed in [6]). The association of BRI1 with BAK1 during brassinolide perception has also been investigated in considerable detail [7–10]. In line with its role in brassinolide perception, loss of BAK1 function causes a brassinolide-insensitive phenotype. However, compared to that of *bri1* mutants, the *bak1* phenotype is weak, suggesting that BAK1 acts redundantly.

BAK1 belongs to a five-member clade of LRR receptor-like kinases named after SOMATIC EMBRYOGENSIS RECEPTOR KINASE (SERK) [11]. Do members of the SERK clade act redundantly with BAK1? He *et al.* [3] found that *BAK-LIKE1* (*BKK1*), like *BAK1* [9], can suppress the phenotype of the weak *bri1-5* allele when over-expressed. Furthermore, they demonstrated both genetic and physical interactions of BKK1 with BRI1, suggesting true functional redundancy of BKK1 with BAK1. Null alleles of *BKK1* show no visible phenotype [3].

If BAK1 and BKK1 act redundantly in brassinolide perception, *bak1; bkk1* double mutants might be expected to show an enhanced brassinosteroid-insensitive phenotype compared to *bak1* mutants. Instead, He *et al.* [3] observed post-embryonic seedling lethality of the double mutant due to spontaneous cell death. Transcriptome analyses of the double mutant showed increased expression of defence and senescence related genes which, in *bri1* mutants, show either no change from wild type, or decreased expression.

A role for BAK1 in suppressing cell death is supported by the work of Kemmerling *et al.* [4]. Their independent study identified BAK1 as one of 32 LRR receptor-like kinase encoding genes whose expression is up-regulated by infection with avirulent *Pseudomonas syringae* strains, and suppressed by infection with a virulent strain. When challenged with the virulent strain, instead of the restricted infection-site lesions observed in wild-type plants, *bak1*