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# Synthetically engineered *rpb1* alleles altering RNA polymerase II carboxy terminal domain phosphorylation induce discrete morphogenetic defects in *Schizosaccharomyces pombe*

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In this report the phenotypic effects of systematic site-directed mutations in the fission yeast RNA pol II carboxy terminal domain (CTD) are investigated. Remarkably, we find that alterations in CTD structure and/or phosphorylation result in distinct phenotypic changes related to morphogenetic control. A hypothesis based upon the concepts of "informational entropy" and "algorithmic transformation" is developed to explicate/rationalize these results.

Of particular importance to the regulation of transcription in eukaryotes is the dynamic modulation of the phosphorylation status of the largest sub-unit of RNA polymerase II, Rpb1p.[1-4] This sub-unit is catalytically essential for transcription and has long been known to be a substrate of kinases and phosphatases which function in pre-mRNA processing.[1,3-7] While the importance of this dynamic regulation is well documented, the portion of the Rpb1p molecule subject to these modifications—the C-terminal domain or CTD—remains the subject of much fascination.[7-16] This interest is due in part to the fact that the CTD possesses a unique repetitive structure consisting of multiple copies of the heptad, $Y_1S_2P_3T_4S_5P_6S_7$ (each heptad being phosphorylatable on $Y_1$, $S_2$, $T_4$, $S_5$ and/or $S_7$ residues). Furthermore, although the heptad repeats of the CTD are essential for life in all organisms examined to date, they are also clearly not required for basal transcriptional activity in vitro.[1,3,6,8,10] This suggests that while not catalytically essential, the CTD must perform other critical functions in eukaryotes.

Given the ease with which simple combinatorial symbolic systems can function as universal Turing machines, it has been suggested that algorithmic information theory might provide a useful and logical framework for understanding these functions.[15] Using such a framework, complex post-translational modifications of the CTD are viewed as a means for the dynamic "programming" of Rpb1p by CTD effectors, and thus, for the modular transcriptional regulation of discrete regulatory networks in eukaryotes. Using this paradigm one would predict that the systematic manipulation of the symbolic structure of the CTD (i.e., the number of repeats and/or phosphorylation pattern) would result in distinct and discrete phenotypic effects. In other words, given that the regulation and biochemical function of CTD kinases, phosphatases and cis-trans isomerases is evolutionarily selectable, it should be possible—at least in theory—for the expression profile of a given cell type to be "programmed" as a function of the activity of the sum total of CTD effectors. In this short communication we provide evidence supporting such a point of view by analyzing the phenotypic effects of synthetically constructed *rpb1* alleles.

To begin, we first sought to determine whether the CTD was indeed essential in *S. pombe*. Using the methods described by Karagiannis and Balasubramanian[17] diploid *S. pombe* strains bearing one wild-type and one synthetically constructed mutant copy of the *rpb1* gene (marked with the *ura4*$^+$ selectable marker) were created (**Table S1**). The respective diploid strains were then sporulated and the resulting asci subject to tetrad analysis. Heterozygous diploids bearing *rpb1* alleles encoding the CTD "rump" (i.e., a region encoding 4 imperfect heptad repeats; YGL TSP SYS PSS PGY STS PAY MPS SPS) followed by only eight or ten perfect heptad repeats (*rpb1-8XCTD*, *rpb1-10XCTD*)—as opposed to the 29 perfect repeats that are present in wild-type strains—generated asci that displayed 2:2 segregation of phenotypically normal Ura$^+$:Ura$^-$ progeny (**Fig. 1A**, bottom two panels). In contrast, heterozygous diploids bearing *rpb1* alleles encoding three heptad repeats (*rpb1-3XCTD*), or no heptads whatsoever (*rpb1-0XCTD*), generated asci that segregated two viable Ura$^-$ progeny to two inviable progeny (**Fig. 1A**, top two panels). Microscopic inspection of the inviable segregants revealed that

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**Table 1.** Viability of progeny from tetrads derived from the indicated sporulated diploids

| Sporulated diploid | Number of Tetrads with 2/4 viable progeny | Number of Tetrads with 3/4 viable progeny | Number of Tetrads with 4/4 viable progeny |
|---|---|---|---|
| *rpb1*$^+$*/rpb1-0XCTD* | 33 | 0 | 0 |
| *rpbt*$^+$*/rpb1-3XCTD* | 36 | 0 | 0 |
| *rpb1*$^+$*/rpb1-5XCTD* | 9 | 19 | 14 |
| *rpb1*$^+$*/rpb1-8XCTD* | 0 | 2 | 32 |
| *rpb1*$^+$*/rpb1-10XCTD* | 0 | 0 | 33 |
| *rpb1*$^+$*/rpb1-12XS2ECTD* | 31 | 6 | 3 |
| *rpb1*$^+$*/rpb1-12XS5ACTD* | 4 | 15 | 19 |
| *rpb1*$^+$*/rpb1-12XS5ECTD* | 34 | 0 | 0 |
| *rpb1*$^+$*/rpb1-12XS7ASCTD* | 0 | 0 | 37 |
| *rpb1*$^+$*/rpb1-12XS7ECTD* | 30 | 8 | 2 |

the spores had indeed germinated, but then formed small microcolonies composed of cells displaying unusual morphological abnormalities (**Fig. 1B**).

Interestingly, heterozygous diploids expressing *rpb1* alleles encoding five heptad repeats (*rpb1-5XCTD*) generated asci that displayed more complex segregation patterns. In some cases tetrads segregated two normal Ura$^-$ progeny to two inviable progeny. In other instances two normal Ura$^-$ progeny segregated along with one, or two, viable Ura$^+$ progeny (**Table 1**). Invariably, the Ura$^+$ progeny grew poorly and displayed morphological defects (**Fig. 1B**). Viable Ura$^+$ progeny were confirmed to be *rpb1-5XCTD* segregants via colony PCR (data not shown).

To more closely examine the morphological phenotypes of the *rpb1-5XCTD* strain, cells were examined by fluorescence microscopy after being stained with DAPI and aniline blue (to visualize nuclear and cell wall/septal material, respectively). Interestingly, *rpb1-5XCTD* cells displayed many bizarre and pleiotropic morphological phenotypes that defied simple categorization. While many cells appeared phenotypically normal, other cells exhibited one or more of the following: a wee or semi-wee phenotype, multiple septa, e-nucleate compartments, "tea"-like branching, bent and curved "ban" phenotypes, and/or an "orb"-like depolarized appearance[18] (**Fig. 1C**).

Having demonstrated the essential nature of the CTD in *S. pombe*—together with the fact that truncation of the CTD leads to complex morphological defects—we next decided to examine the effects of mutations altering CTD phosphorylation. To standardize the analysis *rpb1* alleles bearing exactly 12 copies of the $Y_1S_2P_3T_4S_5P_6S_7$ heptad were examined. Please note at this point that *rpb1-12XS2ACTD* mutants (where all serine-2 residues have been exchanged with alanine in order to mimic a constitutively dephosphorylated state) have already been extensively characterized and shown to display defects related to cytokinesis and meiosis.[17,19-22] Furthermore, loss of function mutants in the Ser-2 CTD kinase, Lsk1p, have also independently been demonstrated to be defective in the activation of bipolar growth.[23] Thus, the morphogenetic consequences of impaired Ser-2 phosphorylation have already been clearly established and are not presented here.

Thus, we next examined *rpb1-12XS2ECT*D mutants (in which serine-2 residues have been exchanged with glutamate to mimic a constitutively phosphorylated state). In the majority of cases *rpb1*$^+$*/rpb1-12XS2ECT*D diploids generated tetrads that segregated two morphologically normal Ura$^-$ progeny to two inviable progeny. In other rare instances two normal Ura$^-$ progeny segregated along with one, or two viable Ura$^+$ progeny (**Table 1**). Again, the Ura$^+$ progeny (confirmed to be *rpb1-12XS2ECTD* segregants via colony PCR) were slow growing due to morphological defects. These cells possessed multiple septa and often displayed "tea"-like branching (**Fig. 2A–C**).

Intrigued by the consistent and somewhat unexpected appearance of morphological phenotypes, we continued by examining the effects of phosphomimetic mutations at the serine-5 position. Similar to *rpb1*$^+$*/rpb1-12XS2ECTD* strains, *rpb1*$^+$*/rpb1-12XS5ACTD* diploids also generated asci displaying complex segregation patterns (**Table 1**, **Fig. 3A**). In this case, however, the Ura$^+$ progeny—although clearly morphologically abnormal—displayed phenotypes that were far less severe and clearly distinct from the abnormalities displayed by *rpb1-12XS2ECTD* mutants. While *rpb1-12XS5ACTD* mutants were indeed elongated and possessed multiple septa, they were never branched and e-nucleate compartments were not observed. Furthermore, cells often displayed a tapered appearance at one cell tip (**Fig. 3B**). *rpb1*$^+$*/rpb1-12XS5ECTD* diploids were also examined, and in contrast to *rpb1*$^+$*/rpb1-12XS5ACTD* strains, clearly segregated two viable Ura$^-$ progeny to two inviable progeny in all examined tetrads (**Table 1**, **Fig. 3C**). Microscopic inspection of the inviable spores again revealed small microcolonies composed of cells displaying clear morphological abnormalities (**Fig. 3D**).

To complete our analysis we subsequently examined the effects of phosphomimetic mutations at the serine-7 position. In contrast to *rpb1*$^+$*/rpb1-12XS5ACTD* and *rpb1*$^+$*/rpb1-12XS5ECTD* strains, *rpb1*$^+$*/rpb1-12XS7ACTD* diploids gave rise to asci that displayed 2:2 segregation of viable, morphologically normal Ura$^-$:Ura$^+$ progeny (**Table 1**). Indeed the Ura$^+$ progeny (confirmed to be *rpb1-12XS7ACTD* mutants by colony PCR) appeared indistinguishable from wild-type cells when grown at 25°C. However, in contrast to *rpb1-12XCTD* control cells, *rpb1-12XS7ACTD* mutants displayed a striking curved appearance characteristic of "ban" mutants when cultured at 36°C (**Fig. 4A**). Lastly, an examination of *rpb1-12XS7ECTD* mutants revealed morphological phenotypes

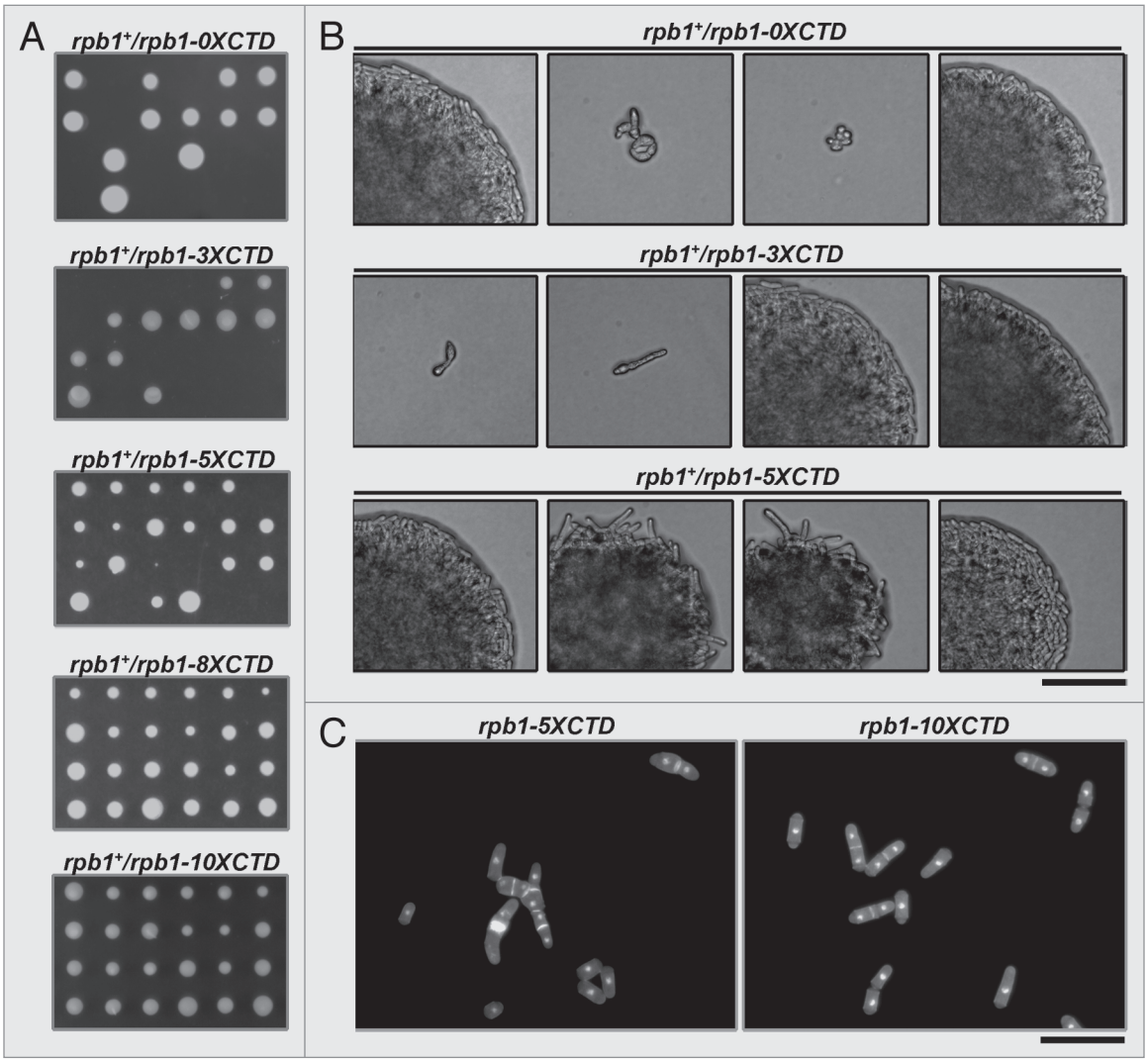


**Figure 1.** Partial truncation of the Rpb1p CTD leads to morphological abnormalities in *Schizosaccharomyces pombe*. (**A**) Diploids of the indicated genotype were sporulated on SPA media and the resulting asci examined via tetrad analysis. The four meiotic spores of individual dissected tetrads were place in vertical rows on YES plates an incubated at 30°C for 3 d. (**B**) Higher magnification micrographs of progeny from individual dissected tetrads of the indicated genotype. Scale bar equals 50 microns. (**C**) *rpb1-5XCTD* and *rpb1-10XCTD* mutants were grown to an OD of 0.4 in YES media at 30°C and then fixed and stained with DAPI and aniline blue to visualize nuclei and cell wall/septal material, respectively. Scale bar equals 20 microns.

characterized by the appearance of highly elongated cells with multiple septa and in some instances, "tea"-like branching. Thus, in the final analysis, modulation of Ser-7 phosphorylation could also clearly be shown to influence morphogenesis.

Taking all data together, we were somewhat surprised to see that altering the symbolic structure of the CTD would so clearly impact morphogenesis in fission yeast (especially considering the CTD's well-established roles in the transcription cycle and pre-mRNA processing). If phosphoregulation of the CTD were critical to the transcription cycle in any universal or general sense, then one would have expected such changes to be invariably lethal. In contrast, while the observed morphological abnormalities were severe in some instances (*rpb1-5XCTD*, *rpb1-12XS2ECTD*, *rpb1-12XS5ECTD*, *rpb1-12XS7ECTD*), in other cases the character of the abnormalities were clearly distinct and much more subtle in nature (*rpb1-12XS2ACTD*, *rpb1-12XS5ACTD*, *rpb1-12XS7ACTD*). While others have reported that *rpb1-14XS5ACTD*, *rpb1-14XS2ECTD* and *rpb1-8XCTD* mutants are inviable[11] we clearly show here that viable *rpb1-12XS5ACTD*, *rpb1-12XS2ECTD* and *rpb1-8XCTD* progeny can indeed be recovered from heterozygous diploids—albeit not in all tetrads due to the stochastic effects of the observed morphological abnormalities on colony formation. We suggest that these stochastic effects on colony formation, together with the slow growing nature of the colonies, are the root cause of these discrepancies. Thus, in our final analysis, our data make it abundantly clear that major modifications to the phosphoregulation of the CTD can indeed be tolerated. More importantly, these data also clearly demonstrate that such modifications are an important determinant in the control of morphogenetic properties in fission yeast.

Given these data, together with the unusual character of the CTD (and its conspicuous location as part of a complex required

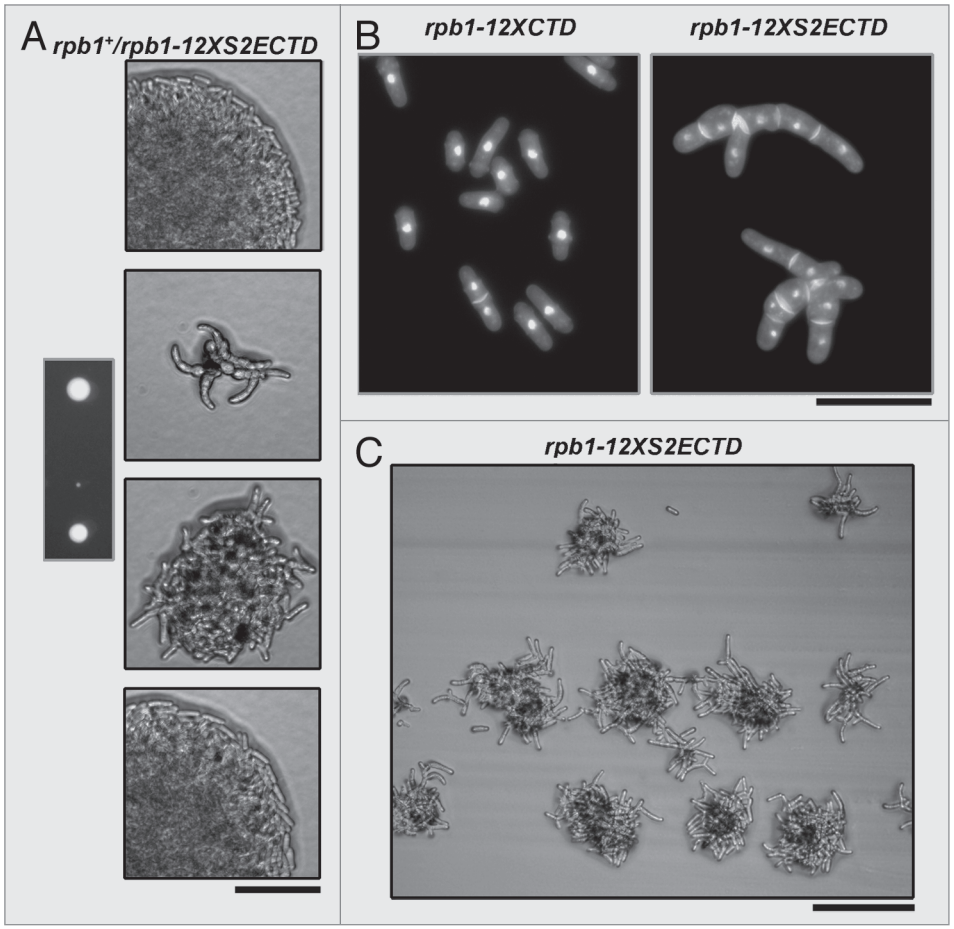


**Figure 2.** *rpb1-12XS2ECTD* mutants exhibit a "tea"-like branching phenotype. (**A**) *rpb1*$^{+}$*/rpb1-12XS2ECTD* diploids were sporulated on SPA media and the resulting asci examined via tetrad analysis. The four meiotic spores of an individual dissected tetrad are shown on the left after 3 d growth on YES media at 30°C. Higher magnification micrographs of the individual progeny are shown in the right-most four panels. Scale bar equals 50 microns. (**B**) *rpb1-12XCTD* and *rpb1-12XS2ECTD* mutants were grown to an OD of 0.4 in YES media at 30°C and then fixed and stained with DAPI and aniline blue to visualize nuclei and cell wall/septal material, respectively. Scale bar equals 20 microns. (**C**) One viable Ura$^{+}$ *rpb1-12S2ECTD* progeny colony from an individual tetrad was restreaked to a YES plate and incubated at 30°C for 24 h. Scale bar equals 100 microns.

for the transcriptional control of all protein coding genes in almost all developmentally complex eukaryotes)[7] we suggest a paradigm based upon the concept of "algorithmic transformation" as a basis for further investigation. This concept rests upon the foundations of information theory laid by Claude Shannon, Andrey Kolmogorov and in particular, by the more recent work of Gregory Chaitin.[24-26]

We define an algorithmic transformation to be a genetically controlled change in the symbolic structure of the CTD according to a simple rule (or "algorithm"). For example, a simple (i.e., non-algorithmic) point mutation in the *rpb1* sequence encoding the CTD would have the potential to alter the symbolic structure of just one heptad. In contrast, a loss of function mutation in, for example, a Ser-5 CTD kinase (or a regulatory change resulting in decreased kinase activity) would alter the symbolic structure of all heptads by setting all Ser-5 residues to the non-phosphorylated (or null) state. Thus, in the case of the algorithmic transformation described above, a single regulatory event could precipitate comprehensive changes to the algorithmic information content of the CTD.[15] More complex regulation—of multiple CTD effectors simultaneously—could thus, in theory, result in the sophisticated temporal control of CTD configuration.

Based on: (1) the immense informational entropy present within the CTD[15] (i.e., the incredible number of unique CTD configurations possible); and (2) the fact that the biochemical function and/or regulatory activity of CTD effectors (kinases, phosphatases, cis-trans isomerases) is evolutionarily selectable, we suggest a model in which this entropy is harnessed to code for transcriptional "programs" with the capability of outputing particular expression profiles as a function of developmental/metabolic/environmental signals. In other words, "algorithmic" transformations—such as the ones created artificially in this report—are viewed as having the potential to comprehensively affect transcriptional output by virtue of their ability to communicate with RNA pol II via altering the algorithmic information content of the CTD. Put more succinctly, in the same way that a waterfall possesses potential energy that can be harnessed for any number of useful purposes, it is envisioned that the CTD possesses an informational potential (i.e., entropy) that can also be harnessed; in this case to modulate the control of transcription.

What biological processes could be affected? In answering this question a key characteristic of algorithmic control systems are brought to the fore. Any biological process affected by Rpb1p and its interactors could in theory be targeted. This is to say, any individual cell type subject to a particular set of selective pressures, could in theory evolve distinct regulatory systems (based on CTD kinases/phosphatases/cis-trans isomerases and their upstream effectors) capable of harnessing the entropy—i.e., producing unique and distinct CTD configurations or "algorithms"—in order to modulate gene expression. In the empirical example presented here in fission yeast, it is clear that algorithmic modulation of the CTD affects morphogenesis. However, in other cell types (subject to distinct selective pressures) unique properties could be specified for algorithmic control. Thus, in the same sense that a Turing machine can be classified as "universal," algorithmic transformation of the CTD can also be thought of as a universal system.

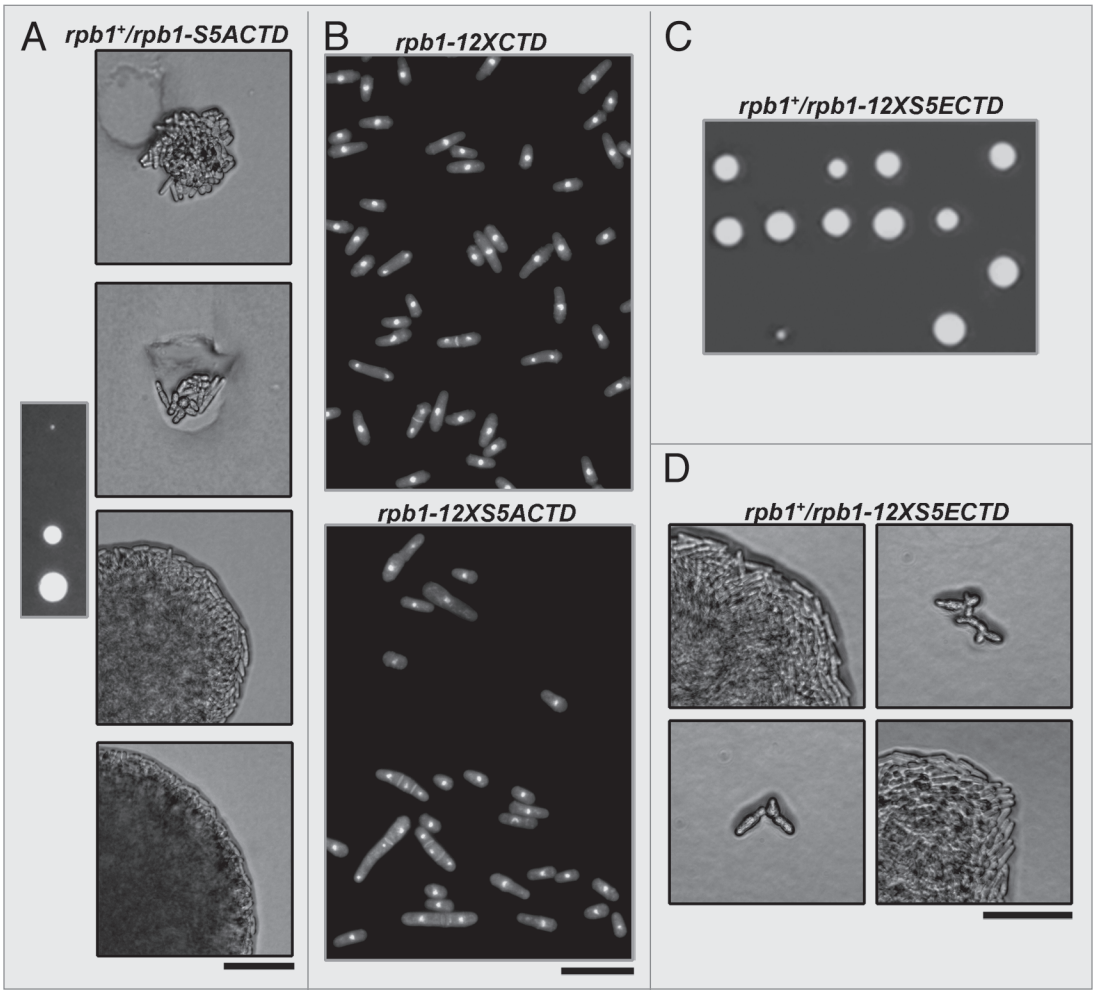


**Figure 3.** *rpb1-12XS5ACTD* mutants exhibit morphological abnormalities distinct from the other mutant *rpb1* alleles analyzed in this study. (**A**) *rpb1-12XS5ACTD* diploids were sporulated on SPA media and the resulting asci examined via tetrad analysis. The four meiotic spores of an individual dissected tetrad are shown on the left after 3 d growth on YES media at 30°C. Higher magnification micrographs of the individual progeny are shown in the right-most four panels. Scale bar equals 50 microns. (**B**) *rpb1-12XCTD* and *rpb1-12XS5ACTD* mutants were grown to an OD of 0.4 in YES media at 30°C and then fixed and stained with DAPI and aniline blue to visualize nuclei and cell wall/septal material, respectively. Scale bar equals 20 microns. (**C**) *rpb1-12XS5ECTD* diploids were sporulated on SPA media and the resulting asci examined via tetrad analysis. The four meiotic spores of individual dissected tetrads were place in vertical rows on YES plates an incubated at 30°C for 3 d. (**D**) Micrographs of progeny from an individual dissected tetrad derived from *rpb1+/rpb1-12XS5ECTD* diploids. Scale bar equals 50 microns.

In conclusion, we would like to briefly comment on the character of the morphological phenotypes observed here, and their similarity to those exhibited by fission yeast cells perturbed with respect to the microtubule cytoskeleton. Remarkably, mutations (or drug treatments) that affect microtubule function result in the same classic phenotypes (branched, curved, and/or bent cells) as displayed here by cells expressing mutant *rpb1* alleles.[27] Future work will thus focus on better delineating the unexpected relationship between algorithmic modulation of the CTD and fission yeast morphogenetic control.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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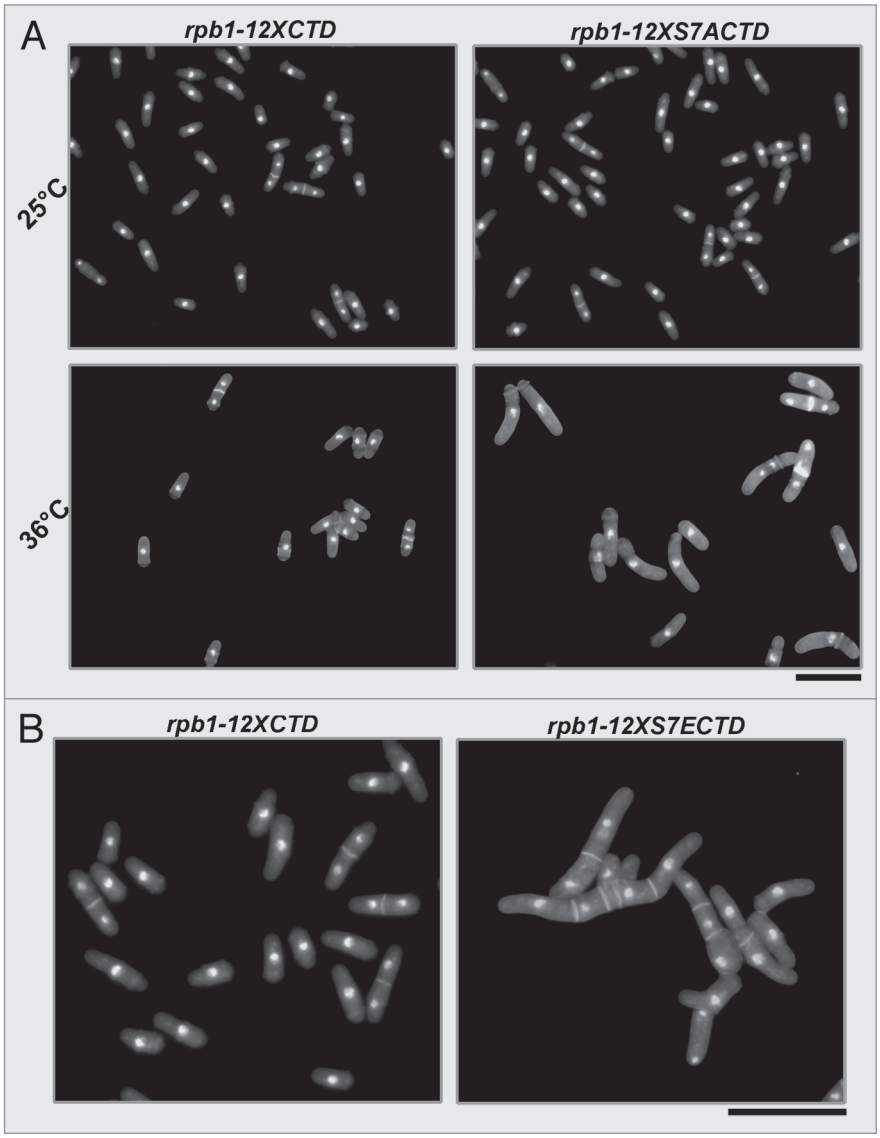


**Figure 4.** *rpb1-12XS7ACTD* mutants exhibit a temperature-sensitive "ban"-like phenotype. (**A**) *rpb1-12XCTD* and *rpb1-12XS7ACTD* mutants were grown to an OD of 0.4 in YES media at 25°C or 36°C and then fixed and stained with DAPI and aniline blue to visualize nuclei and cell wall/septal material, respectively. Scale bar equals 20 microns. (**B**) *rpb1-12XCTD* and *rpb1-12XS7ECTD* mutants were grown to an OD of 0.4 in YES media at 30°C and then fixed and stained with DAPI and aniline blue to visualize nuclei and cell wall/septal material, respectively. Scale bar equals 20 microns.


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