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MULTIFUNCTIONAL CYTOKINESIS GENES IN *SCHIZOSACCHAROMYCES POMBE**

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The proper division of cells is essential for the production of viable daughter cells. In plants and fungi, the dividing cell produces a cross-wall or septum that bisects the cytoplasm. For separation of the daughter cells, the septum has to be cleaved. To study the regulation of this process, we isolated mutants defective in septum cleavage. The mutants showed highly pleiotropic phenotypes and defined 17 novel genes. The deduced amino acid sequences of the products of the cloned genes exhibited homologies to various transcription regulators of other organisms. The homologies and the pleiotropic effects of the mutations on sexual development, stress response, mitotic stability, septum initiation and septum placement indicated that these genes affect cell separation indirectly, through multifunctional regulatory modules.

Keywords: cytokinesis, yeast, *Schizosaccharomyces*, transcription, sterility

INTRODUCTION

The process of cell division (cytokinesis), wich leads to the production of two daughter cells from one parent, is a fundamental feature of all living organisms. It is a highly regulated process which ensures the correct distribution of cell organelles necessary for the life of the successor cells. The mechanism and the regulation of division vary in different eukaryotic organisms [for a recent review, see 12]. In animal cells, an actomyosin contractile ring is formed perpendicularly to the axis of the spindle. The ring constricts and pinches off the membrane to form two daughter cells. In contrast, plant cells do not form an actomyosin ring and their cytokinesis is accomplished through a centrifugal process which involves an expanding cell plate that fuses with a predetermined zone of the plasma membrane to produce a new cell wall or septum between the daughters. Fungi appear to have features of both types of cytokinesis: they form contractile rings similar to those of animal cells, and they also produce septa composed of cell-wall-like material. Two fungal species, the budding yeast *Saccharomyces cerevisiae* and the fission yeast *Schizosaccharomyces pombe*,

*Dedicated to Professor Lajos Ferenczy on the occasion of his 70th birthday.

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are particularly well suited for the study of eukaryotic cytokinesis, because they have a number of favourable technical features. A great advantage of these organisms is that they have both haploid and diploid phases in their life cycles. The haploid phase provides a convenient possibility for the isolation of mutants defective in cytokinesis, whereas the diploid phase offers possibilities for genetic analysis of the mutants. Both yeasts are amenable to manipulation with recombinant DNA techniques and are convenient for cytological analysis. In this report, we summarise the results we have obtained in the analysis of a group of cytokinesis genes identified in the fission yeast *S. pombe.*

Cytokinesis in fission yeasts

The fission yeasts (organisms which are classified in the genus *Schizosaccharomyces*) are the extant representatives of an ancient phylogenetic branch of *Fungi,* which separated very early from the lineage of *Ascomycetes* [for a review, see 27]. It is hypothesised that, in consequence of this early separation, the fission yeasts retained features of the common ancestors of animals and fungi, which makes them somewhat more similar in certain features to the cells of present-day animals than to budding yeast cells. Cytokinesis is one of the processes which display this closer relationship to animals. *S. pombe* cells form a contractile actomyosin ring, usually halfway between their poles, during the early stages of mitosis [18] and this ring anticipates the site of cytokinesis. As in the case of animal cells, the position of the ring (division site) is determined by the spindle of the mitotic nucleus [31]. In contrast, in the budding yeast *Saccharomyces cerevisiae*, the site of the division is determined by the location of the bud, which is predetermined by the position of the previous bud sites [4]. When the actomyosin ring of the fission yeast cell constricts, an indentation forms around the plasmamembrane. With time, this deepens and forms a furrow. The furrow is filled with a centripetally growing three-layer structure, the septum [14, 28], composed of a beta-glucan-containing layer (primary septum) and two flanking layers (secondary septa), which contain galactomannan. The septum bisects the cell into two daughter cells, but holds them together. For their separation, the primary septum and the adjacent region of the mother cell wall have to be broken down by a process called septum cleavage. Cytological observations suggest that the cleavage process begins with (most probably enzymatic) degradation of the cell wall and continues with spontaneous dissolution of the primary septum 28. The secondary septa do not degrade, but bulge out and become the “new ends” of the daughter cells.

Fission yeast mutants defective in cell separation

A large number of genes and proteins involved in the initiation and the organisation of the actomyosin ring and the septum have been described and characterised [reviewed in 16]. These genes were identified through the analysis of conditionally

lethal mutants, which could not divide under the restrictive conditions. In contrast, very little is known about the genes of cell separation. Their identification is hampered by the fact that cell separation in fission yeasts is a post-M-phase event, which usually takes place after the exit from the cell cycle and overlaps with G1 and the early S phase of the new cell cycle [2]. Thus, the inactivation of the separation machinery is neither lethal nor inhibitory to cell proliferation. Consequently, the mutants which are defective in this process do not exhibit any selectable phenotype.

To overcome this technical difficulty, we isolated cell separation mutants by microscopic observation of the growth morphology (production of hyphae) and by indirect selection based on the pleiotropic effects of the mutations (e.g. resistance to cell wall lytic enzymes and reduced fertility) [8, 9, 29]. Besides their mycelial morphology, most *sep* mutants displayed pleiotropic phenotypes in diverse processes and functions such as conjugation, sporulation, pheromone production, stress response, septum positioning and structure [8, 9].

The family of sep *genes*

The complementation and recombination analysis of the mutants identified 17 (16 *sep* and one *spl*) novel genes (Table 1) [8, 9, 29]. None of them were allelic to the cell division mutants defective in actin ring formation or septum synthesis.

sep1 was the first cell separation gene to be identified [29]. Its mutant allele *sep1-1* confers mycelial morphology with a highly regular branching pattern and an increased mitotic instability in the diploid phase.

The mutants defective in genes *sep2*$^+$ to *sep5*$^+$ are resistant to cell-wall lytic enzymes [9]. Cells of *sep2-SA2* frequently form twin septa separated by anucleate minicells, if the cell length is extended. This suggests that a polar signal may operate in the division site selection and *sep2-SA2* is partially defective in its generation or activity. *sep2-SA2* synthetically interacts with *cex1-SA2*, a mutation that increases cell length: the cells of the double mutant *sep2-SA2 cex1-SA2* are mostly diploid [9].

The mutants *sep6*$^-$ to *sep16*$^-$ are either sterile or exert very poor mating activity [8]. All can produce M-factor (the pheromone of M cells), but *sep8-295, sep11-556* and *sep16-638* do not secrete detectable amounts of P-factor (the pheromone of P cells). Three of them, *sep8-295, sep13-572* and *sep16-638,* are also defective in meiosis and sporulation. Their defects are epistatic over *pat1-114*, suggesting that the wild-type alleles of these genes act downstream of *pat1*$^+$*,* the negative regulator of the transition from the vegetative cell cycle to the sexual programme in G1 [26]. With the exception of *sep10-412,* none of the mutants survived a 10-min heat shock, although 20% of the cells in the wild-type cultures remained viable even after being exposed to the shock for 20 min. Most mutants are also hypersensitive to the presence of Cl^- in the medium [8].

An interesting interaction was found between certain *sep* mutations and the mutations of the M-phase initiation genes *wee1*$^+$*, cdc2*$^+$ and *cdc25*$^+$. *sep1-1, sep9-307* and *sep15-598* evoked dikaryosis in cells that did not have functional *wee1*$^+$. The cells

Table 1
The *sep* and *spl* genes of *Schizosaccharomyces pombe*

Gene	Mutant phenotype	Deletion/disruption phenotype	Map position	Homology	Ref.
sep1	Highly filamentous; slightly increased sensitivity to $CaCl_2$ and $MgCl_2$; slightly increased resistance to benomyl; fertile; increased instability in diploid phase; genetic interactions with *cdc4-8, cdc2w, cdc25, wee1⁻, sep9-307 and spl1-1* mutations	Highly filamentous; fertile	Chr. 2	Forkhead-type transcription factors	7, 23, 28, 29, 34
sep2	Filamentous; resistant to cell-wall lytic enzymes; fertile; septa are frequently composed of multiple layers; formation of twin septa and anucleate minicells if the cell length is extended; genetic interaction with *cex1-SA2*	n.d.	n.d.	Sequence not available	9
sep3	Filamentous; resistant to cell-wall lytic enzymes; fertile	n.d.	n.d.	Sequence not available	9
sep4	Filamentous; resistant to cell-wall lytic enzymes; fertile	n.d.	n.d.	Sequence not available	9
sep5	Filamentous; resistant to cell-wall lytic enzymes; fertile	n.d.	n.d.	Sequence not available	9
sep6	ts lethal; filamentous at permissive temperatures; hypersensitive to Cl^- and heat-shock; sterile; poor sporulation; low spore viability; sporulation defect partially suppressed by *pat1-114*; genetic interaction with *cdc16-116*	n.d.	n.d.	Sequence not available	8
sep7	ts lethal; filamentous at permissive temperatures; hypersensitive to Cl^- and heat-shock; sterile; poor sporulation; low spore viability; sporulation defect partially suppressed by *pat1-114*	n.d.	n.d.	Sequence not available	8
sep8	ts lethal; highly filamentous at permissive temperatures; hypersensitive to Cl^- and heat-shock; sterile; no P-factor production; no sporulation; epistatic over *pat1-114*	n.d.	n.d.	Sequence not available	8

sep9	Poor growth at 36 °C; highly filamentous at all temperatures; hypersensitive to Cl^- and heat-shock; sterile; poor sporulation; low spore viability; genetic interactions with *sep1-1* and *wee1*$^-$ mutations; sporulation defect partially suppressed by *pat1-114*	Filamentous	Chr. 1	Spt8 subunit of *Saccharomyces cerevisiae* SAGA complex	8, 30
sep10	Poor growth at 36 °C; filamentous at all temperatures; hypersensitive to Cl^-; sterile; poor sporulation; low spore viability; sporulation defect is partially suppressed by *pat1-114*	n.d.	Chr. 2	Soh1 of *Saccharomyces cerevisiae;* subunit of transcription complex	8, 32
sep11	ts lethal; highly filamentous at all temperatures; hypersensitive to Cl^- and heat-shock; sterile; no P-factor production; poor sporulation; low spore viability; epistatic over *pat1-114*	n.d.	n.d.	No homology	8, unpublished
sep12	reduced growth rate at 36 °C; filamentous at all temperatures; hypersensitive to Cl^- and heat-shock; poor fertility; reduced sporulation; reduced spore viability; sporulation defect suppressed by *pat1-114*	n.d.	n.d.	Sequence not available	8
sep13	ts lethal; filamentous at permissive temperatures; hypersensitive to Cl^- and heat-shock; sterile; no sporulation; sporulation defect is partially suppressed by *pat1-114*	n.d.	n.d.	Sequence not available	8
sep14	Poor growth at 36 °C; filamentous at all temperatures; hypersensitive to Cl^- and heat-shock; reduced fertility; poor sporulation; low spore viability; sporulation defect partially suppressed by *pat1-114*; genetic interaction with *sep1-1*	n.d.	n.d.	Sequence not available	8
sep15	ts lethal; slightly filamentous; hypersensitive to Cl^- and heat-shock; fertile; genetic interactions with *cdc16-116* and *wee1-112*; synthetic lethality with *sep1-1*	lethal	Chr. 2	Med8 subunit of *Saccharomyces cerevisiae* mediator complex	8, 33
sep16	ts lethal; occasionally misplaced septa at restrictive temperatures; filamentous at permissive temperatures; hypersensitive to Cl^- and heat-shock; sterile; no P-factor production; no sporulation; epistatic over *pat1-114*; synthetically lethal with *cdc4-8*	n.d.	n.d.	Sequence not available	8
spl1	ts lethal; bent cells and short hyphae at restrictive temperatures; fertile	n.d.	Chr. 1	Only suppressors cloned	20, 29

ts: temperature-sensitive; Chr.: chromosome; n.d.: not determined

that had a mutation in any of these *sep* genes and an inactive *wee1*$^-$ allele frequently skipped septation and produced binucleate cells [7, 8]. The double mutant *sep1-1 cdc2-1w* also formed dikaryon cells at high frequency. The product of *cdc2*$^+$ (p34^{cdc2}) is a protein kinase whose activation is required for the onset of mitosis [24]. The protein encoded by *wee1*$^+$ is a negative regulator of p34^{cdc2} [25]. The synthetic dikaryosis observed in the double mutants is reversible and suppressible by *cdc25-22* [7]. *cdc25*$^+$ encodes a phosphatase, an activator of p34^{cdc2} [24]. This suppressible synthetic dikaryosis suggests that the *sep* genes also perform functions which are not specific for cell separation. These functions can provide a regulatory link between the M-phase initiation machinery and the initiation of cell division.

The *sep1-1* mutation also interacts with *cdc4-8* [29], a mutation of *cdc4*$^+$ which encodes an EF-hand protein involved in the formation of the contractile ring [19]. This interaction confirms that *sep1*$^+$ is not specific for cytokinesis; it may also be involved in earlier events of cell division.

This complexity of mutant phenotypes indicates that the *sep* genes affect cell separation indirectly rather than directly, probably through regulatory modules that control diverse processes and functions.

The sep *genes encode regulators of transcription*

sep1$^+$ has been cloned and found to encode a protein containing a DNA-binding domain characteristic of the HNF-3/forkhead family of transcription factors [23]. Forkhead-type transcription factors have been identified in a wide range of eukaryotes, where they act as tissue-specific and developmental gene regulators (for a review, see 13). The disruption of *sep1*$^+$ is not lethal, the *sep1*$^+$ mRNA level is constant during cell cycle and the Sep1p protein accumulates in the nucleus [34]. These observations suggest that Sep1p might be a non-essential transcription factor which is continuously present throughout the cell cycle. One of its roles is to influence the transcription of *cdc15*$^+$, a gene implicated in controlling medial ring formation [6]. The steady-state *cdc15*$^+$ mRNA level fluctuates in the wild-type cells, but remains constant if *sep1*$^+$ is disrupted [34]. This regulatory role might account for the above-mentioned frequent skip of septation in certain double mutants. It is possible that the Sep1p protein has additional targets which are involved in septum cleavage and cell separation.

sep15 encodes a homologue of the Med8 subunit of the *Saccharomyces cerevisiae* transcriptional mediator complex [33]. Disruption of *sep15*$^+$ is lethal, indicating that Sep15p exerts an essential function, its role in cell separation being indirect. The mediator complex is assumed to act as a coupling factor by linking activating and repressing transcription complexes to the RNA polymerase II holoenzyme transcriptional machinery [15, 22]. A number of human homologues of mediator proteins have been identified [e.g. 17], which points to the possible existence of a corresponding mechanism in higher eukaryotes. To the best of our knowledge, Sep15p is the first med protein described in fission yeasts.

The deduced amino acid sequence of Sep10p shows a high degree of amino acid sequence homology to Soh1 of *Saccharomyces cerevisiae* [32]. The Soh1 protein was described as a protein that probably couples transcription, repair and recombination [5]. It interacts with Hpr1, a subunit of a complex which also acts as a mediator between the transcription apparatus and the DNA-binding regulatory factors [3]. In *Saccharomyces cerevisiae*, RNA polymerase II can form a complex either with the mediator complex or with this Hpr1-containing complex. The two forms of the polymerase II holoenzyme coexist in the cells and are thought to ensure the transcription of overlapping subsets of genes [3]. The existence of *S. pombe* homologues of subunits of both complexes indicates that similar complexes also exist in this fission yeast.

The product of *sep9*$^+$ [10, 30] is homologous to Spt8, a subunit of the SAGA complex. SAGA is a large complex of proteins, which incorporates multiple transcription-related functions, displaying histone acetyltransferase activity and interactions with transcription activators and the TATA-binding protein of TFIID [for a review see 11]. SAGA recognises promoters, binds to their upstream activation sequences and acetylates the histone tails of the nucleosomes, destabilising them and making the TATA box available for binding by TBP. Spt8 participates in this binding as an inhibitor [1].

Cloning of *spl1*$^+$ has been attempted, but only a multicopy suppressor could be isolated. It encodes a novel proline tRNA [20]. It is not clear yet how the overproduction of a tRNA can suppress the temperature-sensitivity and cell-separation defect conferred by the *spl1-1* mutation. Nevertheless, it is pertinent to mention here that in *Saccharomyces cerevisiae* a glutamine tRNA was found to participate in the transduction of signals that regulate the transitions between the yeast growth and the pseudohyphal phase [21].

Conclusions and perspectives

The homology of four *sep* genes to transcription regulators is consistent with the hypothesis that in *S. pombe* multifunctional regulatory modules related to intracellular signalling co-ordinate cell separation with numerous other processes, such as nuclear division, sexual differentiation and stress response. These modules seem to be functionally interlinked and control distinct but overlapping subsets of genes. The genes involved in the process of cell separation can be in the overlapping parts of the subsets. Future analysis will address these possibilities through the use of DNA microarrays once the *S. pombe* genome sequence is completed, and will attempt to identify the cell separation genes whose expression is influenced by the *sep* genes.

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