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Genes affecting the extension of chronological lifespan in *Schizosaccharomyces pombe* (fission yeast)

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Abstract

So far, more than 70 genes involved in the chronological lifespan (CLS) of *Schizosaccharomyces pombe* (fission yeast) have been reported. In this mini-review, we arrange and summarize these genes based on the reported genetic interactions between them and the physical interactions between their products. We describe the signal transduction pathways that affect CLS in *S. pombe*: target of rapamycin complex 1, cAMP-dependent protein kinase, Sty1, and Pmk1 pathways have important functions in the regulation of CLS extension. Furthermore, the Php transcription complex, Ecl1 family proteins, cyclin Clg1, and the cyclin-dependent kinase Pef1 are important for the regulation of CLS extension in *S. pombe*. Most of the known genes involved in CLS extension are related to these pathways and genes. In this review, we focus on the individual genes regulating CLS extension in *S. pombe* and discuss the interactions among them.

KEYWORDS
chronological lifespan, fission yeast, longevity, *Schizosaccharomyces pombe*, signal transduction, stationary phase

1 | INTRODUCTION

The fission yeast *Schizosaccharomyces pombe* is a model organism of unicellular eukaryotes (Hayles and Nurse, 2018). This yeast is considered to have diverged from the budding yeast *Saccharomyces cerevisiae* hundreds of million years ago (Hayles and Nurse, 2018; Hedges, 2002; Sipiczki, 2000), and studies using these yeast species have contributed significantly to the understanding of various cellular processes. *S. pombe* has been actively used for research in multiple fields, including cell cycle studies, cellular morphology, sexual development, splicing, and chromosome structure. Furthermore, much information is accumulating regarding the stationary phase of cells, particularly chronological lifespan (CLS) (Hayles and Nurse, 2018; Lin and Austriaco, 2014; Ohtsuka and Aiba, 2017; Roux et al., 2010b).

There are two yeast lifespan fields of study: replicative lifespan (RLS) and CLS (Chen and Runge, 2012; Longo et al., 2012; Roux et al., 2010b). RLS is the number of divisions a cell can undergo, whereas CLS is the length of time a cell can survive. CLS of yeast corresponds with the survival period of cells that have entered the stationary phase. Both types of lifespans are relatively easy to measure in *S. cerevisiae*. In contrast, it is difficult to distinguish between mother and daughter cells in *S. pombe* and the number of RLS studies is significantly lower than that of CLS studies (Erjavec et al., 2008; Ohtsuka and Aiba, 2017). However, in *S. cerevisiae*, although several common factors are related to RLS and CLS, the exact relationship between these two lifespans has not been clarified yet (Longo et al., 2012).

Recently, microfluidic devices were established to study yeast lifespan, allowing the study of RLS in *S. pombe* (Nakaoka, 2017;

Nakaoka and Wakamoto, 2017; Spivey et al., 2017). However, using this technique, at least two independent laboratories have reported that *S. pombe* is not related to RLS, that is, this yeast does not age replicatively and cellular aging and RLS can be unrelated in this yeast. Moreover, studies of the CLS of *S. pombe* are being conducted as actively as those of budding yeast. As described in detail later, some nutrient signaling pathways, including target of rapamycin (TOR) and cAMP-dependent protein kinase (PKA) pathways, have been found to affect the CLS of *S. pombe* as well as the lifespans of other model organisms such as nematodes, flies, and mammals (Chen and Runge, 2009; Fontana et al., 2010; Lin and Austriaco, 2014; Rallis et al., 2013; Roux et al., 2009, 2010b).

Growth environment greatly influences the CLS of *S. pombe*. Both calorie restriction and restriction of specific nutrients, that is, dietary restriction, are established methods of delaying aging and prolonging lifespan, and their effects are conserved widely in many organisms including yeast, nematodes, flies, and mammals (Fontana and Partridge, 2015; Fontana et al., 2010; Lee and Longo, 2016; Ohtsuka and Aiba, 2017). In *S. pombe*, the limitation of nutrients such as nitrogen, sulfur, specific amino acids, and trace metals, as well as restriction of glucose as a carbon source, contributes to CLS extension (Lin and Austriaco, 2014; Ohtsuka and Aiba, 2017; Ohtsuka et al., 2017, 2019; Shimasaki et al., 2017; Su et al., 1996). CLS extension by calorie restriction is known to involve the PKA pathway and the stress-dependent mitogen-activated protein kinase (MAPK) Sty1 pathway in *S. pombe* (Roux et al., 2009; Zuin et al., 2010a, 2010b). Sty1 is a stress-dependent MAPK, but it is also involved in the PKA pathway and nutrient signaling (Caspari, 1997; Madrid et al., 2004; Sansó et al., 2011; Stiefel et al., 2004). CLS extension due to the restriction of nutrients, such as sulfur, leucine, and zinc, depends on Ecl1 family genes and CLS regulators found in *S. pombe*, and CLS extensions by some types of dietary restriction may be associated with reduced translation including reduced ribosome level (Ohtsuka and Aiba, 2017). The relationship between translational repression and lifespan extension has been reported in other organisms including budding yeast and nematodes (Hansen et al., 2007; MacInnes, 2016; Steffen et al., 2008). Nitrogen restriction causes G1 arrest and G0 phase entry, where heterochromatin formation and autophagy have been implicated in the survival of *S. pombe* (Oya et al., 2019; Roche et al., 2016).

Moreover, studies on the effects of drugs on CLS in *S. pombe* suggest that supplementation with drugs such as acivicin, 3,3′-diindolylmethane, mangosteen, monensin sodium, mycophenolic acid, nigericin sodium, prostaglandin J_2, wortmannin, ribozinoindole-1, diazaborine, actinomycin D, tschimganine, β-hibitakanine, and Torin 1 can extend the CLS of *S. pombe* (Hibi et al., 2018; Ohtsuka and Aiba, 2017; Ohtsuka et al., 2017; Rodríguez-López et al., 2020; Stephan et al., 2013). Ribozinoindole-1 and diazaborine suppress rRNA maturation, and actinomycin D suppresses rRNA translation by acting on RNA polymerase (Cooper and Braverman, 1977; Hayashi et al., 2014; Kawashima et al., 2016; Loibl et al., 2014; Scala et al., 2016). The ionophores monensin and nigericin extend CLS by affecting vacuolar acidification (Stephan et al., 2013). Prostaglandin J_2 reportedly exhibits antiaging properties by inhibiting mitochondrial mitosis (Stephan et al., 2013). Acivicin and mycophenolic acid inhibit guanosine monophosphate (GMP) synthesis, suggesting a relationship between GMP level and CLS (Stephan et al., 2013). Torin 1 inhibits TOR, which is related to the lifespan regulation (Rodríguez-López et al., 2020).

Many studies report the relationship between aging and oxidative stress (Berlett and Stadtman, 1997; Fabrizio and Longo, 2003; Lu and Finkel, 2008; Muller et al., 2007). The well-known free radical theory states that free radicals produced as a byproduct, mainly from mitochondria, oxidize cellular components such as DNA, proteins, and lipids, which cause aging. According to this theory, if free radicals cause aging, increased antioxidant activity should suppress aging and extend lifespan. However, in studies using model organisms, including *S. pombe*, increasing antioxidant activity has not always been shown to suppress aging and extend lifespan (Lam et al., 2010; Ohtsuka et al., 2012; Sadowska-Bartosz and Bartosz, 2014; Selman et al., 2013).

Here, we summarize the relationship between gene groups and pathways among over 70 reported genes, each of which causes the CLS extension when it is overexpressed or deleted in *S. pombe*. Because the interactions of more than 70 longevity genes are extremely complicated, this review focuses only on the genes that cause longevity. Therefore, genes known to be involved in the CLS extension pathway, but not reported to cause the CLS extension by their activation or suppression, are not described in detail.

2 | NOVEL CLS-AFFECTING GENES: *git5*$^+$, *SPBC26H8.13c*, *nop14*$^+$, AND *grx4*$^+$

We searched the DNA region of the *S. pombe* genome that causes the CLS extension by overexpression using a multicopy plasmid and found that overexpression of each DNA regions containing *git5*$^+$, SPBC26H8.13, *nop14*$^+$, or *grx4*$^+$ caused CLS extension (Figure 1a,b). Interestingly, the deletion of *git5*$^+$ also extended the CLS (Figure 1c). *git5*$^+$ encodes the G protein subunit, which acts on glucose response and forms a heterotrimer with Gpa2 and Git11. Overexpression of *git5*$^+$ alone in this heterotrimer may disrupt the precise regulation of this heterocomplex and, like Δ*git5*, suppress the glucose signaling pathway.

This review adds these four genes to the 77 previously reported genes involved in CLS extension and summarizes the function of a total of 81 genes involved in the regulation of CLS extension.

3 | INTERACTIONS AMONG FACTORS THAT REGULATE CLS IN *S. pombe*

First, we summarized the physical and genetic interactions of 81 factors that are involved in CLS extension in *S. pombe* (Figure 2). Then, the factors that interact with many other factors involved in CLS extension were extracted and summarized as CLS-regulated gene product groups and CLS-regulated signal pathways (Figure 3). Some CLS regulatory genes encoded enzymes that are directly involved in energy metabolism (Figure 4). Below, we focus on the major signaling pathways and gene groups involved in CLS extension in *S. pombe* and discuss the regulation of CLS extension.

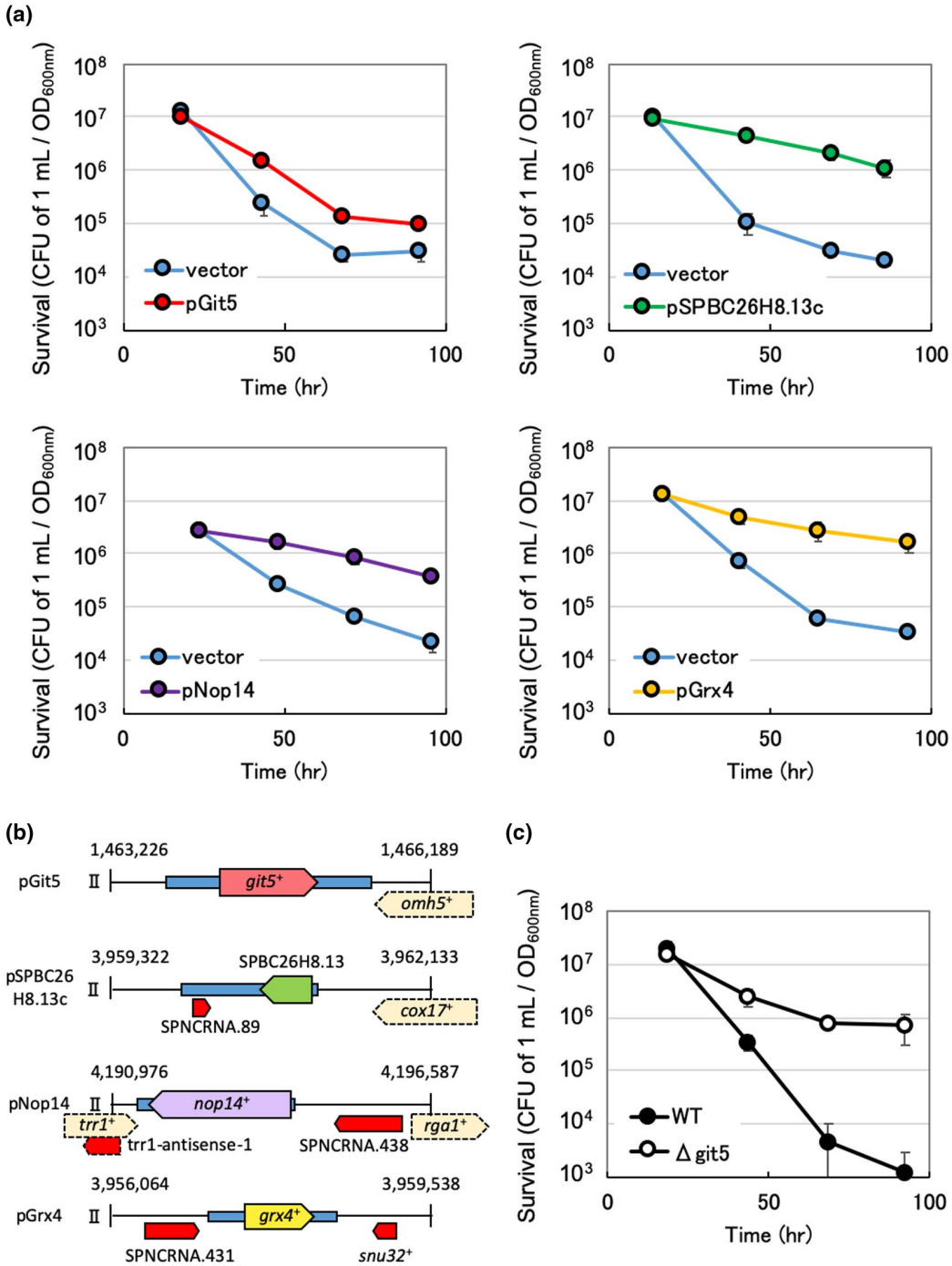

FIGURE 1 (a) The results of chronological lifespan (CLS) measurements. The strain of *Schizosaccharomyces pombe* used was JY333 and the plasmid vector was pLB-Dblet. To determine cell viability, the cells were grown in SD liquid medium, sampled at each growth phase, and then, plated on YE agar plates using suitable dilutions. After incubation for several days as 30°C, the number of colonies derived from 1 ml of culture was counted. This number was divided by the cell turbidity at the sampling time. (b) The DNA fragments that were inserted into the plasmids are carried by the cells whose CLS were measured. (c) The results of CLS measurement of wild-type JY333 and Δ*git5* are shown [Colour figure can be viewed at wileyonlinelibrary.com]

4 | TOR COMPLEX 1 PATHWAY

In many model organisms, suppression of the TOR complex 1 (TORC1) pathway extends lifespan (Fontana et al., 2010; Lees et al., 2016), and similar phenomena have occurred in *S. pombe* (Rodríguez-López et al., 2020). In *S. pombe*, *tor2*$^+$, which codes for a serine/threonine kinase of TORC1, is an essential gene. There is no analysis of the CLS of a *tor2*$^+$ deletion strain, but its temperature-sensitive (ts) mutant, *tor2-ts6*, has an extended CLS (Ohtsuka et al., 2019). Furthermore, the deletion of *tco89*$^+$, which encodes the TORC1 subunit, extends CLS (Rallis et al., 2013). The serine/threonine kinases in the AGC (protein kinase A/protein kinase G/protein kinase C) kinase family, Sck1 and Sck2, which are orthologs of *S. cerevisiae* Sch9, are phosphorylated by Tor2 as targets of TORC1 (Nakashima et al.,

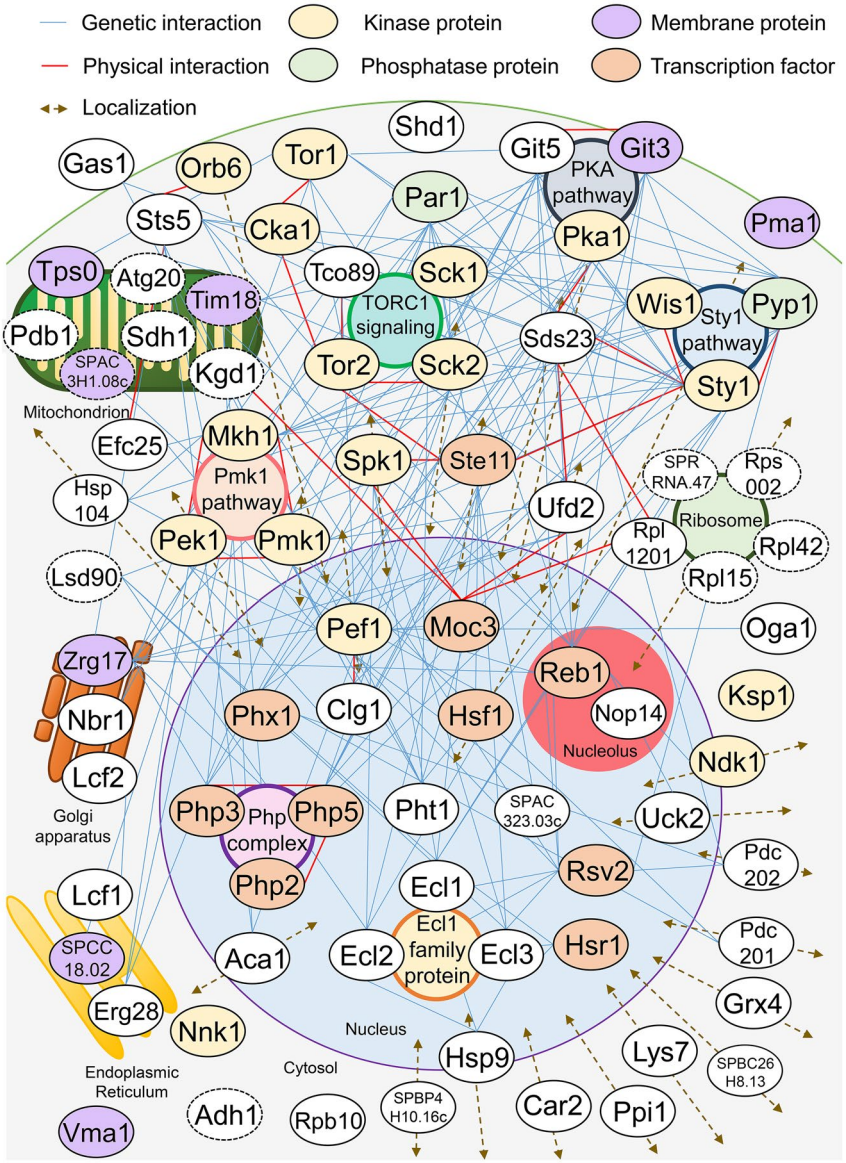

FIGURE 2 Factors that reportedly cause chronological lifespan extension in *Schizosaccharomyces pombe*. All the genetic and physical interactions reported so far are shown. Information on each factor's localization was based on the reports by Ding et al. (2000) and Matsuyama et al. (2006), in addition to those mentioned in the text. Dotted lines indicate factors with unknown localization. Studies in which two or more intracellular localization (e.g., nucleus and cytosol) were reported are indicated by double-headed arrows [Colour figure can be viewed at wileyonlinelibrary.com]

2012). The deletion of *S. cerevisiae SCH9* is known to extend the CLS (Madia et al., 2008) and, in *S. pombe*, the deletion of *sck2*$^+$ can lead to larger CLS extension than that of *sck1*$^+$ (Chen and Runge, 2009; Roux et al., 2006). CLS extension caused by Δ*sck2* occurs irrespective of the presence of Pka1, the loss of which also causes CLS extension, suggesting that the CLS extension mechanism by the TORC1 pathway and PKA pathway act in parallel (Roux et al., 2006). The regulation of CLS extension by the PKA pathway is described later.

Mass spectrometry analyses have identified Cka1 as a factor that interacts with the TOR complexes (Hayashi et al., 2007). The overexpression of *cka1*$^+$ extends CLS (Roux et al., 2010a). *cka1*$^+$ encodes a catalytic subunit of casein kinase 2 (CK2) (Nakazawa et al., 2019). Although it is unclear exactly how overexpression of *cka1*$^+$ affects the TORC1 pathway, it is considered that CLS extension is involved (Roux et al., 2010a). Because CK2 represses the transcription of ribosomal proteins (Moreira-Ramos et al., 2015), and the repression of ribosomes can extend CLS (Ohtsuka and Aiba, 2017), *cka1*$^+$ overexpression may repress ribosomes, leading to CLS extension.

Tor2 phosphorylates the transcription factor Ste11, which is essential for sexual differentiation, and phosphorylation suppresses its functions including nuclear localization (Otsubo et al., 2017). Although *ste11*$^+$ deletion does not affect CLS, its overexpression leads to CLS extension, albeit to a low extent (Ohtsuka et al., 2012). Therefore, Ste11 mainly regulates genes involved in sexual differentiation, but some Ste11-regulated genes may contribute to CLS extension.

The deletion of *zrg17*$^+$ extends CLS (Rallis et al., 2014). The cation diffusion facilitator (CDF) family protein Zrg17 forms a heteromer with Cis4, another CDF family protein, and is involved in Golgi membrane trafficking through the regulation of zinc homeostasis (Fang et al., 2008). Interestingly, synthetic genetic array analysis shows that *zrg17*$^+$ performs positive genetic interactions, wherein the double-mutant phenotype is weaker than anticipated, with *sck2*$^+$ (Rallis et al., 2014). This suggests that CLS extension by *zrg17*$^+$ deletion may be involved in the TORC1 pathway. Intriguingly, as mentioned above, it has also been reported that extracellular zinc concentration itself affects CLS (Shimasaki et al., 2017).

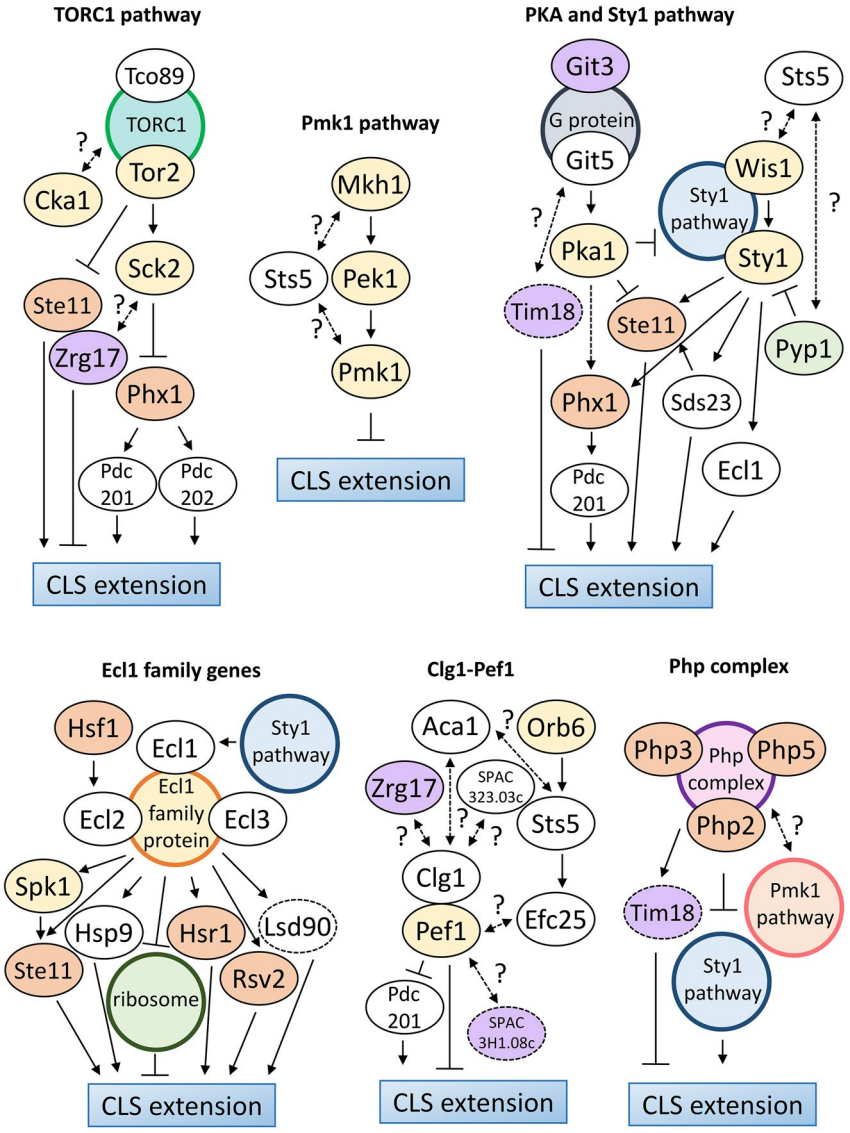

FIGURE 3 A hypothetical model summarizing the representative signal pathways and factors involved in chronological lifespan regulation in *Schizosaccharomyces pombe* [Colour figure can be viewed at wileyonlinelibrary.com]

Overexpression of the stationary phase-specific transcription factor Phx1 extends CLS and its deletion shortens CLS (Kim et al., 2012). Δ*sck2* longevity reportedly depends on *phx1*$^+$ (Kim et al., 2014), suggesting that Phx1 contributes to CLS extension downstream of the TORC1 pathway. Furthermore, Phx1 is required for the stationary phase-specific induction of *pdc201*$^+$ and *pdc202*$^+$, which encode pyruvate decarboxylases. The overexpression of both *pdc201*$^+$ and *pdc202*$^+$ extends CLS, whereas their deletion decreases CLS (Kim et al., 2014).

The CLS extension of Δ*sck2* reportedly depends on Sty1 (Zuin et al., 2010a, 2010b). However, it is unclear how much of the CLS extension induced by the deletion of *sck2*$^+$ depends on Sty1: under conditions wherein Δ*sck2* causes CLS extension, the comparison between survivals of *sty1*$^+$ single-deletion mutants and *sck2*$^+$ and *sty1*$^+$ double-deletion mutants during the early stationary phase has not been reported. A comprehensive analysis indicated that *tco89*$^+$, which encodes the TORC1 subunit, and *sty1*$^+$ have negative genetic interaction, wherein the double-mutant phenotype is stronger than expected from the phenotypes associated with the single mutants (Ryan et al., 2012). Therefore, the TORC1 pathway may be involved in CLS extension in parallel with Sty1.

Current findings indicate that in addition to the signal pathway cascading from TORC1 (including Tor2 and Tco89) to Sck2, the transcription factor Phx1 (as the downstream factor) and its regulated genes, (*pdc201*$^+$ and *pdc202*$^+$) contribute mainly to CLS extension by the TORC1 pathway in *S. pombe* (Figure 3). Furthermore, *zrg17*$^+$, which shows genetic interaction with *sck2*$^+$, may be involved in this pathway and affect CLS. Moreover, although its effect on CLS is not substantial, the transcription factor Ste11 can contribute to CLS extension in response to suppression of the TORC1 pathway. CK2 may also be involved in CLS regulation via this signaling pathway.

5 | PKA AND Sty1 PATHWAYS

Similar to the TORC1 pathway, inhibition of the PKA pathway is reportedly associated with CLS extension in *S. pombe* as well as in

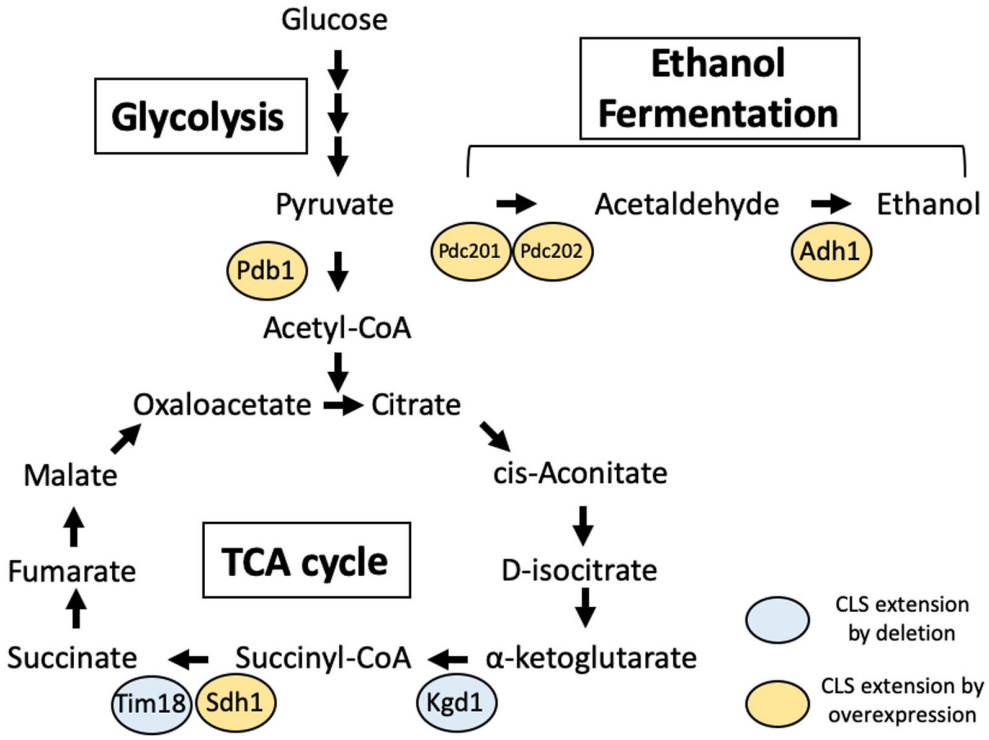

FIGURE 4 Model summarizing the chronological lifespan regulatory factors involved in energy metabolism [Colour figure can be viewed at wileyonlinelibrary.com]

other organisms, such as budding yeast and mice (Fabrizio et al., 2003; Fontana and Partridge, 2015; Fontana et al., 2010; Yan et al., 2007). In *S. pombe*, the deletion of the G protein-coupled glucose receptor Git3 located in the plasma membrane extends CLS (Roux et al., 2009; Stephan et al., 2013). Similarly, the deletion of Git5, which encodes a heterotrimeric G protein β-subunit that acts on this glucose receptor, also extends CLS (Figure 1). Signals from this glucose receptor are transmitted to PKA (Lin and Austriaco, 2014; Roux et al., 2010b). Besides, the deletion of *pka1*$^+$, which encodes the catalytic subunit of PKA (Gupta et al., 2011), also causes CLS extension (Roux et al., 2006). As described above, because Δ*pka1* and Δ*sck2* additively cause CLS extension (Roux et al., 2006), the TORC1 and PKA pathways are considered to contribute to CLS extension in parallel. This finding is consistent with the comprehensive analysis results that *git3*$^+$ and *git5*$^+$ indicate negative genetic interactions with *sck2*$^+$ (Rallis et al., 2014; Ryan et al., 2012). However, similar to the TORC1 pathway, the longevity of Δ*pka1* mutant cells reportedly requires *phx1*$^+$ (Kim et al., 2014). Therefore, although the upstream regions of the two signaling pathways differ, the downstream region may contain a common cell survival mechanism. However, *git5*$^+$ reportedly indicates negative genetic interaction with *pdc202*$^+$ (Ryan et al., 2012), which seems to act downstream of Phx1. Further analysis will clarify the relationship between these pathways in the regulation of CLS.

The PKA and Sty1 pathways have opposite effects on at least the regulation of CLS: inhibition of the PKA pathway extends CLS, whereas activation of the Sty1 pathway extends CLS (Roux et al., 2010b; Zuin et al., 2010a). Sty1 is a MAPK that responds to various stresses including heat, osmotic stress, oxidative stress, and nutritional stress in *S. pombe* (Vivancos et al., 2006). Deletion of *sty1*$^+$ shortens CLS, whereas its overexpression extends CLS (Hibi et al., 2018; Ohtsuka et al., 2008). Consistent with this, although *wis1*$^+$ encodes a MAPK kinase that phosphorylates Sty1, its activated mutation, *wis1-DD*, which promotes Sty1 phosphorylation, also has a long CLS (Zuin et al., 2010a). Furthermore, the deletion of *pyp1*$^+$, which encodes tyrosine phosphatase and the product dephosphorylates Sty1 (Sansó et al., 2011), leads to the activation of Sty1 and extension of CLS (Zuin et al., 2010a). Thus, the Sty1 pathway plays a crucial role in regulating CLS in *S. pombe*. Because CLS extension by Δ*pyp1* mutant cells does not occur when *phx1*$^+$ is absent (Kim et al., 2014), CLS extension by the activation of the Sty1 pathway may also depend on Phx1 (Figure 3).

As mentioned above, the PKA and Sty1 pathways (PKA–Sty1 pathway) are two pathways involved in CLS control, and there are many connections between them. Deletion of *pka1*$^+$ promotes Sty1 phosphorylation, and its longevity also requires *sty1*$^+$ (Zuin et al., 2010a; 2010b). This finding suggests that the longevity of Δ*pka1* mutant cells depends on *sty1*$^+$ and that the activation of the Sty1 pathway is important for CLS extension by suppressing the PKA pathway. This finding is consistent with the report that *pyp1*$^+$ overexpression suppresses the phenotypes that abnormally induce *fbp1*$^+$, encoding fructose-1,6-bisphosphatase, in *git3*$^+$, *git5*$^+$, and *pka1*$^+$ mutants each (Santo et al., 1996). It is also consistent with the comprehensive analysis demonstrating that both *git3*$^+$ and *git5*$^+$ indicate positive genetic interactions with *sty1*$^+$ (Ryan et al., 2012). However, *git5*$^+$ reportedly indicates negative genetic interaction with *pyp1*$^+$ and that deletion of both *pka1*$^+$ and *wis1*$^+$ causes synthetic growth defects (Jang et al., 2013; Ryan et al., 2012), suggesting that these pathways function in

parallel. This finding may not rule out the possibility of a CLS extension mechanism via the repression of the PKA pathway that does not depend on the Sty1 pathway.

Sds23, which encodes a PP2A-type phosphatase inhibitor, is thought to be involved in the PKA–Sty1 pathway and to regulate CLS in *S. pombe*. Sty1 reportedly interacts physically with Sds23 and directly phosphorylates it (Jang et al., 2013). Moreover, *sds23*$^+$ overexpression inhibits stress sensitivity in Δ*sty1* mutant cells (Yakura et al., 2006), suggesting that Sds23 acts downstream of Sty1. Overexpression of *sds23*$^+$ extends CLS, whereas its deletion reduces CLS (Roux et al., 2010a; Yakura et al., 2006). However, *sds23*$^+$ reportedly indicates negative genetic interaction with *pyp1*$^+$ (Ryan et al., 2012), suggesting that these factors may act in parallel. Meanwhile, another study, which used the yeast two-hybrid assay and pull-down assay, reports that Pka1 physically interacts with Sds23 (Jang et al., 2013). Although Jang et al. have shown that *pka1*$^+$ is required for Sds23 phosphorylation during the stationary phase and that the catalytic subunit of PKA can phosphorylate Sds23, further studies are needed to elucidate these detailed molecular mechanisms. This is because Pka1 is inactivated by Cgs1, a regulatory subunit of PKA, during the nutrient-poor stationary phase (Nishida et al., 2019). Additionally, since the deletion of *sds23*$^+$ reportedly increases CLS under nitrogen depletion (Sideri et al., 2014), further analysis is required to understand the CLS regulation of *sds23*$^+$ precisely.

Ecl1, which regulates CLS, is considered to contribute to CLS extension via the Sty1 pathway. Initially, *ecl1*$^+$ was identified as a factor that complements short CLS of Δ*sty1* mutant cells (Ohtsuka et al., 2008); subsequently, *ecl1*$^+$ is directly induced by Atf1, a transcription factor functioning downstream of Sty1 (Shimasaki et al., 2014).

Because the deletion of *pka1*$^+$ induces *ste11*$^+$ (Ohtsuka et al., 2008), *ste11*$^+$ also contributes to CLS extension by inhibiting the PKA pathway. While the suppression of the PKA pathway induces CLS extension and *ste11*$^+$, the activation of Sty1 pathway also induces CLS extension and *ste11*$^+$ (Shiozaki and Russell, 1996; Zuin et al., 2010a). Similarly, the overexpression of Sds23, the target of Sty1, induces *ste11*$^+$ (Paul et al., 2009). Furthermore, two-hybrid assay revealed that Sty1 physically interacts with Ste11 (Kjaerulff et al., 2005).

The deletion of *tim18*$^+$, which encodes the succinate dehydrogenase anchor subunit localized in the inner mitochondrial membrane, and may be involved in the tricarboxylic acid (TCA) cycle (Mercier et al., 2006), has been found to extend CLS (Rallis et al., 2014). *tim18*$^+$ reportedly has a negative genetic interaction with *sck2*$^+$ (involved in the TORC1 pathway) and positive genetic interaction with *git3*$^+$ (involved in the PKA pathway) (Rallis et al., 2014; Ryan et al., 2012). These findings suggest that CLS extension by the deletion of *tim18*$^+$ may occur in parallel with CLS extension via inhibition of the TORC1 pathway and may be involved in CLS extension via inhibition of the PKA pathway.

Thus, based on the findings obtained so far, it is likely that PKA and Sty1 pathways influence each other and contribute to CLS extension in *S. pombe* (Figure 3). Of note, CLS extension by glucose restriction is mediated through these pathways; low glucose levels inhibit the activity of Pka1 by suppressing signals from the receptor Git3 via G proteins, including Git5, and leads to the activation of MAPK Sty1 (Roux et al., 2006; Zuin et al., 2010a). When CLS extension occurs via the PKA–Sty1 pathway, the regulation of *ecl1*$^+$, *sds23*$^+$, *ste11*$^+$, and *tim18*$^+$ may also contribute to CLS extension.

Although the activation of the Sty1 pathway contributes to CLS extension in *S. pombe*, the deletion of *HOG1*, the homolog of *sty1*$^+$, reportedly extends CLS of budding yeast (Garay et al., 2014; Zuin et al., 2010b). Moreover, in the presence of Sch9, Hog1 is reportedly phosphorylated under amino acid starvation and can contribute to longevity (Santos et al., 2013, 2016). Thus, the involvement of *sty1*$^+$ and *HOG1* in CLS regulation may be partially conserved depending on growth conditions such as the nutritional state of the environment. However, there are various differences between the two MAPKs: Hog1 is strongly activated by osmotic stress, but other stresses do not lead the same level of activation like of Sty1 and, unlike *sty1*$^+$, *HOG1* does not appear to affect mating efficiency (Mutavchiev et al., 2016). Although the role of the PKA pathway in the conserved evolutionary regulation of lifespan is known, future studies should clarify whether the Sty1 pathway is conserved in longevity regulation.

6 | Pmk1 PATHWAY

Inhibition of the Pmk1 pathway, which plays an important role in maintaining cell wall integrity, extends CLS in *S. pombe* (Figure 3). The Pmk1 pathway is composed of MAPK Pmk1, MAPK kinase Pek1, and MAPK kinase kinase Mkh1, and their deletion extends CLS (Imai et al., 2020). Because both *pmk1*$^+$ and *mkh1*$^+$ have negative genetic interactions with *sck2*$^+$ (Rallis et al., 2014), the mechanisms of CLS extension by the Pmk1 and TORC1 pathways seem to function in parallel. Additionally, *pmk1*$^+$ has a negative genetic interaction with *git5*$^+$ (Ryan et al., 2012) and *mkh1*$^+$ has negative genetic interactions with the genes involved in the Sty1 pathway, including *wis1*$^+$, *pyp1*$^+$, and *sds23*$^+$ (Ryan et al., 2012; Sengar et al., 1997). Therefore, the mechanisms of CLS extension by the regulation of the Pmk1 and PKA–Sty1 pathways also seems to function in parallel. The transcription activity of the transcription factor Atf1, a target of Sty1, is reportedly regulated not only by Sty1 but also by Pmk1 (Zhou et al., 2012), suggesting that these pathways share common downstream factors, including Atf1 and factors regulated by Atf1. Moreover, although the overexpression of *wis1*$^+$ and *sty1*$^+$ does not complement all phenotypes of Δ*mkh1*, they restore this mutant's β-glucanase sensitivity (Sengar et al., 1997), indicating a connection between these pathways. Therefore, the mechanism of CLS extension regulated by the Pmk1 pathway may partially overlap with that of the PKA–Sty1 pathway. However, as described in detail later, in the absence of *sty1*$^+$ or *pmk1*$^+$, the point mutation of *gas1*$^+$ (*gas1–287*) does not extend CLS sufficiently, indicating that CLS extension by the *gas1*$^+$ mutation is partially dependent on both *sty1*$^+$ and *pmk1*$^+$ (Imai et al., 2020). However, when both *sty1*$^+$ and *pmk1*$^+$ are deleted, CLS extension of the *gas1* mutant disappears almost entirely (Imai et al.,

2020). This finding suggests that the mechanisms of CLS regulation via the Pmk1 or Sty1 pathway are not the same but that these pathways regulate the CLS in parallel, at least in part.

Meanwhile, the deletion of *SLT2*, a budding yeast ortholog of *pmk1*$^+$, reportedly shortens CLS (Marek and Korona, 2013); thus, the effect of this MAPK on longevity does not seem to be the same, at least among these yeasts.

7 | Ecl1 FAMILY GENES

The Ecl1 gene family is one of the most analyzed gene families in *S. pombe* CLS research (Ohtsuka and Aiba, 2017). *S. pombe* has three Ecl1 family genes, that is, *ecl1*$^+$, *ecl2*$^+$, and *ecl3*$^+$, whose overexpression extends CLS but triple deletion reduces CLS (Ohtsuka et al., 2008, 2009, 2011). Different signals induce these genes, but their gene products appear to have similar functions (Ohtsuka and Aiba, 2017). Ecl1 family gene-dependent CLS extension occurs under conditions that induce Ecl1 family genes such as sulfur or leucine depletion (Ohtsuka et al., 2017, 2019). Furthermore, nitrogen depletion slightly induces *ecl1*$^+$ (Miwa et al., 2011); oxidative stress induces *ecl1*$^+$ via Atf1 (Shimasaki et al., 2014); and heat stress induces *ecl2*$^+$ via Hsf1 (Ohtsuka et al., 2011), a heat shock transcription factor (Sakurai and Takemori, 2007). Overexpression of *hsf1*$^+$ induces CLS extension and the expression of *ste11*$^+$, both of which are dependent on Ecl1 family genes (Ohtsuka et al., 2011). Heat shock transcription factor is also known to affect the lifespan of the nematode *Caenorhabditis elegans*; decreased *hsf-1* promotes tissue senescence and overexpression of extend lifespan (Hsu et al., 2003). Meanwhile, although the induction of Ecl1 family genes has not been observed, these genes are also required for CLS extension due to zinc limitation (Ohtsuka et al., 2015; Shimasaki et al., 2017). These findings indicate that Ecl1 family genes respond to environments that are disadvantageous for growth, such as nutrient depletion and stress, and contribute to cell survival.

Ecl1 family genes induce various genes that affect CLS including *hsp9*$^+$, *hsr1*$^+$, *lsd90*$^+$, *spk1*$^+$, *ste11*$^+$, and *rsv2*$^+$, whose overexpression leads to CLS extension, and some inductions depend on the transcription factor Prr1 (Ohtsuka et al., 2012). *hsp9*$^+$ encodes a heat shock protein, and the involvement of heat shock proteins in lifespan and aging has been reported in other organisms, such as nematode and mammals (Fontana and Partridge, 2015; Fontana et al., 2010; Hsu et al., 2003; Walker and Lithgow, 2003). *hsr1*$^+$ encodes a transcription factor that has low homology to Msn2 and Msn4, which are known to be involved in CLS in budding yeast (Wei et al., 2009). Lsd90 has been suggested to be involved in phospholipid metabolism including very long-chain fatty acid metabolism (Yokoyama et al., 2008). Spk1, a MAPK involved in pheromone response, physically interacts with Ste11 and phosphorylates it in vitro (Kjaerulff et al., 2005). *rsv2*$^+$ encodes a zinc finger transcription factor that induces stress-related genes during spore formation (Mata et al., 2007). The mechanism of CLS extension regulated by *rsv2*$^+$ may be involved in that of Pef1, a cyclin-dependent kinase, because *rsv2*$^+$ has positive genetic interactions with *pef1*$^+$ (Roguev et al., 2008). *rsv2*$^+$ has a positive genetic interaction with *git5*$^+$ but causes synthetic growth defects with *pyp1*$^+$ (Dixon et al., 2008; Roguev et al., 2008; Ryan et al., 2012), suggesting that the mechanism of CLS extension by *rsv2*$^+$ may be related to that of the PKA pathway and not depend on the Sty1 pathway. Besides, *rsv2*$^+$ reportedly has negative genetic interactions with *mkh1*$^+$ and *pdc202*$^+$ (Roguev et al., 2008; Ryan et al., 2012). Thus, the CLS extension by *rsv2*$^+$ possibly occurs in parallel with the Pmk1 pathway and Pdc202. In *S. cerevisiae*, several studies of *RPN4*, a *rsv2*$^+$ homolog, indicates different CLS results: one reports that the deletion of *RPN4* increases RLS and another reports that its deletion decreases RLS (Kruegel et al., 2011; Longo et al., 2012; Schleit et al., 2013). Simultaneously, the loss of *UBR2*, which increases the Rpn4 level, extends RLS (Kruegel et al., 2011). Further research will be needed to clarify the precise CLS regulation of *rsv2*$^+$.

Ecl1 family genes also repress the expressions of many ribosomal proteins (Ohtsuka et al., 2012, 2017), some of which also depend on the transcription factor Prr1 (Ohtsuka et al., unpublished data). Furthermore, although many expressions of ribosomal proteins decrease during sulfur depletion, the repressions are dependent on Ecl1 family genes (Ohtsuka et al., 2017). CLS extension is also observed by the suppression of ribosomes by deletion of ribosomal proteins including *rpl1201*$^+$, *rpl15*$^+$, *rpl42*$^+$, and *rps002*$^+$ (which encode ribosomal proteins), by the deletion of *SPRRNA.47* (which encodes ribosomal RNA), and by drugs such as diazaborine or ribozinoindole-1 (Chen et al., 2013; Ohtsuka et al., 2017). Therefore, CLS extension by Ecl1 family genes may be due to the suppression of ribosomes (Ohtsuka and Aiba, 2017). Meanwhile, because yeast two-hybrid assay revealed that Rpl1201 physically interacts with Sds23 (Paul et al., 2009), CLS regulation by *sds23*$^+$ may also be involved in ribosome regulation. Regulation of lifespan via ribosomes has been documented in various organisms including *S. pombe* (Hansen et al., 2007; MacInnes, 2016; Ohtsuka and Aiba, 2017; Rodríguez-López et al., 2020; Steffen et al., 2008). In addition to Ecl1 family genes, the TORC1 pathway, including Sck2 ribosomal S6 kinase, and the PKA–Sty1 pathway, involved in Sds23, also affect ribosome regulation and control CLS. Ecl1 family genes, the TORC1 pathway, and the PKA–Sty1 pathway are closely related to response to dietary restriction of sulfur, nitrogen, and glucose, respectively, and all of these dietary restrictions lead to a significant reduction in ribosomes and extend CLS in *S. pombe* (Ohtsuka et al., 2017).

Consistent with the fact that Ecl1 family genes play an important role in CLS regulation in *S. pombe*, the *S. cerevisiae* ortholog *ECL1* also functions in CLS regulation in budding yeast. However, unlike *S. pombe*, which has three Ecl1 family genes, *S. cerevisiae* has only one, that is, *ECL1*, the overexpression of which extends CLS and deletion shortens CLS (Azuma et al., 2009). Recently, Ecl1 family genes were found to be involved in CLS regulation as downstream factors of the general amino acid control (amino acid response in mammals) (Ohtsuka et al., 2019). Nevertheless, the orthologs of this gene have not been found in higher organisms.

Although the molecular mechanisms of Ecl1 family proteins are currently unknown, these genes respond to various stresses,

particularly starvation, thereby contributing to the maintenance of cell survival and, consequently, CLS extension and sexual development, through the regulation of different other CLS-related genes.

8 | CYCLIN Clg1 AND CYCLIN-DEPENDENT KINASE Pef1

The deletion of *clg1*$^+$, which encodes a cyclin-like protein, extends CLS in *S. pombe* (Chen et al., 2013). Furthermore, the deletion of the cyclin-dependent kinase Pef1 that interacts with Clg1 extends CLS (Chen et al., 2013). CLS extension by Δ*clg1* depends on *cek1*$^+$, which encodes the homologous protein of budding yeast protein kinase Rim15, although the deletion of *cek1*$^+$ itself does not appear to have a significant effect on CLS in *S. pombe* (Chen et al., 2013).

CLS extension via Clg1 and Pef1 (Clg1–Pef1) suppression seems to function in parallel with the TORC1 pathway. *clg1*$^+$ has a negative genetic interaction with *sck2*$^+$, which is involved in the TORC1 pathway (Rallis et al., 2014). *pef1*$^+$ also has negative genetic interactions with *tco89*$^+$ and *sck2*$^+$ (Rallis et al., 2014; Ryan et al., 2012). Furthermore, CLS extension by Clg1–Pef1 suppression seems to function in parallel with the PKA–Sty1 pathway. *clg1*$^+$ has a negative genetic interaction with *pyp1*$^+$ (Ryan et al., 2012), and *pef1*$^+$ has negative genetic interactions with *git3*$^+$ and *pyp1*$^+$ (Dixon et al., 2008; Ryan et al., 2012). Furthermore, it seems that CLS extension by Clg1–Pef1 suppression occurs in parallel with the Pmk1 pathway because *clg1*$^+$ has negative genetic interactions with *mkh1*$^+$, *pek1*$^+$, and *pmk1*$^+$ (Ryan et al., 2012), and *pef1*$^+$ has negative genetic interactions with *pek1*$^+$ and *pmk1*$^+$ (Roguev et al., 2008; Ryan et al., 2012). Conversely, *pef1*$^+$ has positive genetic interactions with *pdc201*$^+$ and *zrg17*$^+$ (Ryan et al., 2012); therefore, the mechanism of CLS extension by Clg1–Pef1 suppression may partially overlap with that of other pathways including TORC1 and PKA–Sty1 pathways.

Three genes, *aca1*$^+$, *SPAC323.03c*, and *SPAC3H1.08c*, whose deletions extend CLS (Rallis et al., 2014), reportedly have a positive genetic interaction with *pef1*$^+$ (Roguev et al., 2008; Ryan et al., 2012). *aca1*$^+$ is a homolog of the budding yeast gene *MPR1* [which encodes an acetyltransferase of L-azetidine-2-carboxylic acid, which is a toxic L-proline analog (Nomura et al., 2003; Shichiri et al., 2001)] and acts to remove the intracellular oxidative stress (Du and Takagi, 2007). Based on sequence prediction, *SPAC323.03c* should encode a factor involved in peroxisome regulation, and *SPAC3H1.08c* encodes a mitochondrial calcium uniporter regulator. This indicates that the regulation of CLS extension by Clg1–Pef1 may be via the same pathway as that of *aca1*$^+$, *SPAC323.03c*, and *SPAC3H1.08c*. The negative interaction between *aca1*$^+$ and *tim18*$^+$ (Ryan et al., 2012) supports the hypothesis that *aca1*$^+$ and Clg1–Pef1 function in parallel with the PKA–Sty1 pathway.

Additionally, *pef1*$^+$ shows a synthetic growth defect with *efc25*$^+$, which encodes the Ras1 activator guanine nucleotide exchange factor (Dixon et al., 2008), and the deletion of *efc25*$^+$ extends CLS (Chen et al., 2019). The amount of Efc25 protein is upregulated by the conserved NDR/LATS kinase Orb6 through the phosphorylation of *efc25* mRNA-binding protein Sts5 (Chen et al., 2019). Similar to *efc25*$^+$, the non-phosphorylatable mutation at the Sts5 Ser-86 site, *sts5S86A*, as well as downregulation of Orb6 also extends CLS (Chen et al., 2019). Consistent with these relationships between Clg1–Pef1 and Orb6–Sts5–Efc25, *sts5*$^+$ shows a positive genetic interaction with *aca1*$^+$ (Ryan et al., 2012). Based on these findings, CLS regulation by Orb6–Sts5–Efc25, which regulates the Ras1 GTPase activity, may be involved in the regulation of Clg1–Pef1. Moreover, *sts5*$^+$ has positive genetic interactions with *mkh1*$^+$ and *pmk1*$^+$ (Ryan et al., 2012), and the cell morphology of *sts5* mutant is complemented by *wis1* deletion or *pyp1*$^+$ overexpression (Toda et al., 1996), suggesting that CLS extension mechanism by *sts5*$^+$ is also involved in the regulation of Pmk1 and Sty1 pathways. However, it has simultaneously been shown that *efc25*$^+$ has a negative genetic interaction with *mkh1*$^+$ (Ryan et al., 2012), but further studies will be needed to clarify the detailed mechanism. In addition, it has been reported that overexpression of *spk1*$^+$, a CLS regulator, complements the staurosporine sensitivity of *sts5* mutant (Toda et al., 1991). Furthermore, because *sts5*$^+$ has negative genetic interactions with *sck2*$^+$ and *zrg17*$^+$ (Rallis et al., 2014; Ryan et al., 2012), the CLS extension regulated by *sts5*$^+$ may act in parallel with the TORC1 pathway.

Although the mechanism of CLS extension by Clg1–Pef1 is unclear, except the involvement of *cek1*$^+$, it is possible that the mechanism is related to the functions of other CLS-regulated genes such as *aca1*$^+$, *zrg17*$^+$, *SPAC323.03c*, *SPAC3H1.08c*, *orb6*$^+$, *sts5*$^+$, and *efc25*$^+$.

9 | Php COMPLEX

CCAAT-binding factor (CBF) is a DNA-binding transcription complex that binds to promoter regions containing the CCAAT sequence (Janoo et al., 2001). *S. pombe* CBF acts as a Php complex and comprises Php2, Php3, Php5, and its repressor Php4, and it plays an important role in various cellular regulations including iron response, TCA cycle, and respiration (Mercier et al., 2008). Deletion of *php2*$^+$, *php3*$^+$, and *php5*$^+$, but not of *php4*$^+$, causes CLS extension (Takuma et al., 2013).

Since both *php3*$^+$ and *php5*$^+$ have negative interactions with *git3*$^+$ and *git5*$^+$ (Ryan et al., 2012), the Php complex appears to function in parallel with the PKA–Sty1 pathway. Reports of the negative genetic interactions between *php5*$^+$ and *pyp1*$^+$/*sds23*$^+$ support this idea (Ryan et al., 2012). Moreover, since *zrg17*$^+$, which has positive genetic interactions with factors involved in the TORC1 pathway and Clg1–Pef1, has negative genetic interactions with *php3*$^+$ and *php5*$^+$ (Ryan et al., 2012), the Php complex may function in parallel with these pathways. However, the deletion of *php2*$^+$ promotes Sty1 phosphorylation, and Sty1 is required for CLS extension by Δ*php2* (Takuma et al., 2013). Thus, the suppression of the Php complex activates the Sty1 pathway and leads to CLS extension, probably indirectly, depending on certain conditions, such as an increase in ROS level due to abnormal expressions of mitochondrial components. Consistent with this, *tim18*$^+$ expression, which has a positive genetic interaction with *git3*$^+$, is regulated by the Php complex (Mercier et al., 2006).

Meanwhile, since *php3*$^+$ has a positive genetic interaction with *mkh1*$^+$ (Ryan et al., 2012), CLS regulation via the Php complex may also be related to the Pmk1 pathway.

In *S. cerevisiae*, the CBF Hap complex affects CLS. In contrast with the Php complex of *S. pombe*, deletion of *HAP3*, which encodes a component of the Hap complex, shortens CLS (Laschober et al., 2010). Besides, *HAP4* overexpression extends CLS (Piper et al., 2006). The *S. pombe* Php complex, which carries Php4 as a repressor, may have a different regulatory system (Labbé et al., 2007), and the consistent effect to CLS by each CBF has not been observed, at least among budding yeast and *S. pombe*. Furthermore, although deletion of *tim18*$^+$ extends CLS in *S. pombe*, the deletion of *SDH4*, one of its homologs, shortens CLS in budding yeast (Chang et al., 2015). Based on the findings to date, the effects of these CBFs on longevity are not consistent, but many respiratory mutants including CBF affect the lifespan. Strong inhibition of respiration shortens lifespan of *C. elegans*, whereas mild inhibition extends lifespan (Rea et al., 2007). Considering this, the difference in the effect of each factor on lifespan may be due to the difference in their effect on respiration in these yeasts. Further studies of these factors will contribute to the understanding of conserved regulation of lifespan and respiration.

10 | OTHER GENES INVOLVED IN CLS

In addition to the TORC1 pathway, the PKA–Sty1 pathway, the Pmk1 pathway, Ecl1 family genes, Clg1–Pef1, and the Php complex, many genes are reportedly involved in CLS extension in *S. pombe*.

10.1 | *adh1*$^+$

Overexpression of *adh1*$^+$ extends CLS (Roux et al., 2010a). *adh1*$^+$ encodes alcohol dehydrogenase, which reduces the acetaldehyde level, the last step in alcohol fermentation, and promotes the ethanol production (Sakurai et al., 2004). Efficient conversion of toxic acetaldehyde to ethanol, which can be used as a carbon source (Sakurai et al., 2004), may make a significant contribution to cell survival, particularly in the nutrient-depleted stationary phase (Figure 4).

10.2 | *atg20*$^+$

Deletion of *atg20*$^+$, which functions in organelle autophagy in *S. pombe* (Zhao et al., 2016), extends CLS (Rallis et al., 2014). However, according to a report by Rallis et al., the survival of Δ*atg20* cells was lower during the early stationary phase than that of wild-type cells. Then, it increased after several days (Rallis et al., 2014), indicating the possibility of adaptive regrowth. Adaptive regrowth, which is often observed in short-lived mutants, has been discussed as a phenomenon in which individual cells adapt to the environment and undergo regrowth during the stationary phase, thereby interfering with accurate CLS measurement (Fabrizio et al., 2004; Ohtsuka et al., 2011; Zambrano and Kolter, 1996). Since autophagy is required for lifespan control in various organisms (Ellis et al., 2018; Fontana and Partridge, 2015; Kapahi et al., 2017), results indicating a lack of autophagy factor extends CLS may mean either the existence of an unknown mechanism between CLS regulation and autophagy or regrowth of the short-lived mutant due to autophagy deficiency. Further analysis will be needed for its determination. In the former case, because *atg20*$^+$ has a positive genetic interaction with *tim18*$^+$ (Ryan et al., 2012), CLS extension by Δ*atg20* may be involved in the PKA pathway or Php complex.

10.3 | *car2*$^+$

Deletion of *car2*$^+$, which encodes ornithine transaminase and acts on amino acid metabolism (Bicho et al., 2010), extends CLS (Rallis et al., 2014). Since Car2 is required for the conversion of arginine to proline, glutamic acid, glutamine, and lysine, CLS extension by Δ*car2* cells may be associated with the starvation of amino acids including lysine, which extends CLS (Ohtsuka et al., 2019).

10.4 | *erg28*$^+$

Overexpression of *erg28*$^+$ extends CLS (Ohtsuka et al., 2013). *erg28*$^+$ encodes a protein conserved from yeast to humans, and the product is involved in sterol synthesis (Gachotte et al., 2001). Since *erg28*$^+$ has negative genetic interactions with *mkh1*$^+$ and *pek1*$^+$ (Ryan et al., 2012), the mechanism of CLS extension may function in parallel with that of the Pmk1 pathway.

10.5 | *gas1*$^+$

gas1$^+$ encodes cell wall 1,3-β-glucanosyltransferase, and the point mutation *gas1-287* confer a long CLS (Imai et al., 2020). The CLS extension by *gas1-287* mutation depends on the Sty1 and Pmk1 pathways, both of which regulate CLS.

10.6 | *hsp104*$^+$

The deletion of the heat shock protein Hsp104 extends CLS (Rallis et al., 2014). *hsp104*$^+$ is induced by Hsf1 (Vjestica et al., 2013), whose overexpression causes CLS extension (Ohtsuka et al., 2011). Negative regulation of CLS by *hsp104*$^+$ seems inconsistent with previous reports of the positive contributions of heat shock proteins to longevity (Fontana et al., 2010; Walker and Lithgow, 2003). Meanwhile, some heat shock proteins, including Hsp90 and Hsp70–Hsp40 chaperons, are also known to be inhibitors of Hsf1 activity (Vjestica et al., 2013). Thus, the deletion of *hsp104*$^+$ might induce Hsf1 activation.

Because *hsp104*$^+$ reportedly has negative genetic interactions with *pyp1*$^+$ and *mkh1*$^+$ (Ryan et al., 2012), *hsp104*$^+$ in CLS may work in parallel with the Sty1 and Pmk1 pathways. In *S. cerevisiae*, the homolog

HSP104 is reportedly required for survival under nutrient deprivation (Werner-Washburne et al., 1993). Additionally, *HSP104* overexpression contributes to the suppression of short RLS in *SIR2* mutants and the deletion of *HSP104* itself both decreases and increases RLS (Erjavec et al., 2007; Kaeberlein et al., 2005). Further research will be needed to gain an accurate understanding of the longevity conferred by Hsp104.

10.7 | *nop14*$^+$

nop14$^+$ is an ortholog of the budding yeast *NOP14*, which is involved in the maturation of the 40S ribosomal subunit (Granneman and Baserga, 2004; Pérez-Fernández et al., 2007). As mentioned above, ribosome regulation has a significant influence on CLS, suggesting that the regulation of CLS via *nop14*$^+$ may be involved in ribosome regulation.

10.8 | *kgd1*$^+$

kgd1$^+$ is a homolog of the budding yeast *KGD1*, which encodes the mitochondrial α-ketoglutarate dehydrogenase complex subunit (Repetto and Tzagoloff, 1989). Its deletion reportedly causes CLS extension (Rallis et al., 2014). However, according to Rallis et al. (2014), the survival of *kgd1*$^+$ (*SPBC3h7.03c*)-deleted cells dropped sharply in the early stationary phase, stabilized, and was higher than that of wild-type cells after several days as well as that of Δ*atg20* cells, suggesting adaptive regrowth. In *S. cerevisiae*, deletion of *KGD1* decreases survival during stationary phase (Martinez et al., 2004). Further analysis will be needed to understand the role of Kgd1 in CLS regulation.

10.9 | *ksp1*$^+$

Deletion of *ksp1*$^+$, an ortholog of budding yeast *KSP1*, extends CLS (Rallis et al., 2014). Since *KSP1* is reported to be regulated by PKA and activates TORC1 (Umekawa and Klionsky, 2012), it may also be involved in these pathways and affect CLS.

10.10 | *lcf1*$^+$ and *lcf2*$^+$

Overexpression of *lcf1*$^+$, which encodes long-chain fatty acyl-CoA ligase, extends CLS (Oshiro et al., 2003), whereas its deletion shortens CLS (Fujita et al., 2007). *S. cerevisiae* has three homologs of *lcf1*$^+$: *FAA1*, *FAA3*, and *FAA4*. The deletion of *FAA1* also reduces survival during the stationary phase when cultured at 37°C, as does Δ*lcf1* (Martinez et al., 2004). Meanwhile, the deletion of *lcf2*$^+$, a paralog of *lcf1*$^+$, extends CLS (Fujita et al., 2007). Although both *lcf1*$^+$ and *lcf2*$^+$ are involved in CLS regulation, their effects on CLS are different, partly because the catalytic levels of these two enzymes for each fatty acid are slightly different, depending on their substrates. Analysis using deletion strains demonstrated that Lcf1 mainly contributes to the catalytic reactions of three substrates: myristic acid, palmitic acid, and oleic acid. However, the only contribution of Lcf2 is to the catalysis of myristic acid (Fujita et al., 2007). Although the short CLS of Δ*lcf1* and the long CLS of Δ*lcf2* were both observed under the same conditions, a slight reduction in the activity of fatty acyl-CoA ligase may be more advantageous than the intact condition for maintaining cell survival during the stationary phase under this condition.

10.11 | *lys7*$^+$

Deletion of *lys7*$^+$, involved in lysine biosynthesis, extends CLS (Rallis et al., 2014). It is known that the availability of amino acids including leucine, arginine, histidine, and lysine has a remarkable influence on CLS of *S. pombe* (Ohtsuka et al., 2019). In *S. pombe*, the CLS of auxotrophic cells requiring leucine, lysine, or arginine is extended when cultured in media without a corresponding amino acid. In contrast, the CLS of cells requiring histidine decreases dramatically under histidine-depleted conditions (Ohtsuka et al., 2019). Therefore, CLS extension by Δ*lys7* appears to be due to intracellular lysine restriction. The effects of amino acids on lifespan are reported in *S. pombe* and other organisms, such as budding yeast and animals. The restriction of specific amino acids, including asparagine, glutamate, and methionine, extends CLS in budding yeast, and a reduction of dietary amino acids, particularly tryptophan and methionine, extends lifespan in rodents (Dilova et al., 2007; Fontana and Partridge, 2015; Gallinetti et al., 2013; López-Otín et al., 2016). Genes involved in amino acid metabolism and the related signal transductions are thought to be commonly involved in lifespan regulation in both *S. pombe* and other organisms.

10.12 | *moc3*$^+$

The deletion of *moc3*$^+$ extends CLS (Rallis et al., 2014). *moc3*$^+$, which encodes a Zn finger-type protein localized in the nucleus, was identified as a factor that induces sexual differentiation even in the presence of cAMP, and is involved in stress response and sexual differentiation (Paul et al., 2009).

Since *moc3*$^+$ has a negative genetic interaction with *pef1*$^+$ (Ryan et al., 2012), its involvement in CLS may also be in parallel with that of Clg1–Pef1. Moreover, by yeast two-hybrid assay, it has been reported that Moc3 physically interacts with Kgd1 (Vo et al., 2016), although each reported intracellular localization of Moc3 and Kgd1 is not the same, namely, nucleus and mitochondria, respectively. Similarly, since Moc3 physically interacts with the ribosomal protein Rpl1201 and MAPK Spk1 (Paul et al., 2009; Vo et al., 2016), the mechanism of CLS extension related to Moc3 may be involved in these factors.

10.13 | *nbr1*$^+$

Deletion of *nbr1*$^+$ (*SPBP35G2.11c*) extends CLS (Rallis et al., 2014). Nbr1 is a homolog of the mammalian autophagy receptor NBR1 and

is distantly related to *S. cerevisiae* Atg19 (Zhao et al., 2016). Nbr1 mediates the transport of soluble hydrolases from the cytosol to the vacuole lumen (Liu et al., 2015).

10.14 | *ndk1*$^+$

The deletion of *ndk1*$^+$ extends CLS (Rallis et al., 2014). *ndk1*$^+$ encodes a subunit of nucleoside–diphosphate kinases (Izumiya and Yamamoto, 1995). However, its mechanism of CLS extension has not been analyzed yet.

10.15 | *nnk1*$^+$

Nonsense mutation of *nnk1*$^+$, a homolog of budding yeast *NNK1*, leads to CLS extension (Kurauchi et al., 2017). Since the budding yeast Nnk1 physically interacts with both Tor1 and Tor2 proteins (Breitkreutz et al., 2010), the mechanism of CLS regulation by *nnk1*$^+$ may be associated with TOR. Moreover, the deletion of budding yeast *NNK1* shortens CLS of *S. cerevisiae* (Garay et al., 2014). Since the deletion of *nnk1*$^+$ is lethal in *S. pombe*, accurate comparison among these yeasts is difficult. Thus, the possibility of Nnk1 as a factor regulating lifespan beyond the species has not been verified.

10.16 | *oga1*$^+$

Overexpression of *oga1*$^+$ extends CLS (Ohtsuka et al., 2013). Oga1 is a homolog of budding yeast Stm1, which binds guanine–quadruplex nucleic acids and is involved in the TOR pathway and ribosome control (Ohtsuka et al., 2013; Van Dyke et al., 2006). Stm1 is reportedly important for maintaining survival during nutrient depletion, insdicating that Stm1 may act as a ribosome preservation factor under these conditions (Van Dyke et al., 2006, 2013). The TOR pathway and ribosome regulation are known to be involved in a conserved lifespan extension pathway in response to nutrient limitation (MacInnes, 2016; Ohtsuka and Aiba, 2017; Ohtsuka et al., 2017; Steffen et al., 2008). Thus, the mechanism of CLS extension by *oga1*$^+$ may also be related to these processes. Since *oga1*$^+$ has a negative genetic interaction with *pef1*$^+$ (Ryan et al., 2012), CLS extension by *oga1*$^+$ may function in parallel with Clg1–Pef1.

10.17 | *par1*$^+$

The deletion of *par1*$^+$ slightly extends CLS (Rallis et al., 2014). *par1*$^+$ encodes a protein phosphatase 2A B′-regulatory subunit, and its deletion causes abnormal septum formation and increases the septation index (Le Goff et al., 2001). Because elongated multinucleate multiseptated cells also appear in Δ*par1* cells, this may also contribute to the high survival rate during the stationary phase. During colony formation, a connected cell population forms one colony regardless of the number of surviving cells among the population unless all cells in the population are dead. Cells with such a phenotype may not indicate accurate survival by CLS measurement using colony-forming units.

Since *par1*$^+$ has negative genetic interactions with *mkh1*$^+$, *pek1*$^+$, *pmk1*$^+$, *pyp1*$^+$, *sds23*$^+$, *erg28*$^+$, and *zrg17*$^+$ (Ryan et al., 2012), the CLS regulation mechanism may occur in parallel with that of the Pmk1 and PKA–Sty1 pathways, Erg28, and Zrg17. Conversely, since *par1*$^+$ has positive genetic interactions with *sck2*$^+$ and *nbr1*$^+$ (Rallis et al., 2014; Ryan et al., 2012), CLS extension by *par1*$^+$ may be involved in the TORC1 pathway and Nbr1, which is involved in autophagy. In *S. cerevisiae*, deletion of *RTS1*, a homolog of *par1*$^+$, shortens CLS (Marek and Korona, 2013).

10.18 | *pdb1*$^+$

Overexpression of *pdb1*$^+$, which encodes a subunit of pyruvate dehydrogenase, extends CLS (Ohtsuka et al., 2013). Although the CLS of *pdb1*$^+$-deleted cells has not been reported in *S. pombe*, deletion of *PDB1*, which is a homolog of *pdb1*$^+$ in *S. cerevisiae*, shortens CLS (Marek and Korona, 2013). Furthermore, in nematodes, dichloroacetate's activation of pyruvate dehydrogenase may lead to lifespan extension (Schaffer et al., 2011). Longevity regulation via pyruvate dehydrogenase may be conserved across species.

10.19 | *pdc201*$^+$ and *pdc202*$^+$

The transcription factor Phx1 may induce *pdc201*$^+$ and *pdc202*$^+$, both of which encode pyruvate decarboxylase, and their individual induction contributes to CLS extension (Kim et al., 2014). As homologs of *pdc201*$^+$ and *pdc202*$^+$, *S. cerevisiae* has three pyruvate decarboxylases: *PCD1*, *PDC5*, and *PDC6*. Unlike *S. pombe pdc201*$^+$ and *pdc202*$^+$, deletion of *PDC5* extends CLS (Garay et al., 2014). Therefore, at present, it is not easy to understand the regulation of CLS by pyruvate decarboxylase precisely across species.

10.20 | *pht1*$^+$

The deletion of *pht1*$^+$, which encodes the histone H2A variant H2A.Z, extends CLS (Carr et al., 1994). Since *pht1*$^+$ has negative genetic interactions with *pmk1*$^+$, *sty1*$^+$, *pef1*$^+$, *sts5*$^+$, *par1*$^+$, and *moc3*$^+$ (Roguev et al., 2008; Ryan et al., 2012), the mechanism of CLS extension by *pht1*$^+$ may be in parallel with the Pmk1 and Sty1 pathways, Clg–Pef1, Par1, and Moc3. In *S. cerevisiae*, deletion of *HTZ1*, a budding yeast homolog of *pht1*$^+$, also extends CLS (Garay et al., 2014). Furthermore, histone variants have been studied for their effects on aging in higher organisms (Contrepois et al., 2017; Re and Vinciguerra, 2017). CLS studies regulated by Pht1 may be useful in elucidating aging mechanisms across species.

10.21 | *pma1*$^+$

Two loss-of-function mutations (D138N and A270D) of Pma1 extend CLS (Ito et al., 2010; Naito et al., 2014). *pma1*$^+$ encodes P-type proton ATPase (Kashiwazaki et al., 2011; Naito et al., 2014; Ulaszewski et al., 1987), and Pma1 mutations reduce glucose intake in addition to CLS extension, so its relationship with calorie restriction has been discussed (Ito et al., 2010). In *S. cerevisiae*, the functional decline of Pma1 reportedly extends RLS; furthermore, differences in Pma1 distribution between mother and daughter cells and the effects on vacuolar acidity and RLS have also been discussed previously (Henderson et al., 2014).

10.22 | *ppi1*$^+$

Overexpression of *ppi1*$^+$ extends CLS (Ohtsuka et al., 2013). *ppi1*$^+$ encodes cyclophilin and has peptidyl-prolyl cis/trans isomerase activity similar to the rapamycin-acting protein FKBP (Siekierka et al., 1989; Skruzný et al., 2001; Van Dyke et al., 2013). The relationship between cyclophilin and aging is unclear (Nigro et al., 2013). Clarification of the regulatory mechanism of CLS extension by *ppi1*$^+$ will contribute to the understanding of the relationship between cyclophilin and aging.

10.23 | *reb1*$^+$

Deletion of *reb1*$^+$, which encodes RNA polymerase I transcription termination factor (Jaiswal et al., 2016), extends CLS (Rallis et al., 2014). However, Δ*reb1* cells have reportedly had lower survival during the early stationary phase than wild-type cells (Rallis et al., 2014), so the possibility of adaptive regrowth cannot be ruled out. Since *reb1*$^+$ has negative genetic interactions with *git3*$^+$, *tim18*$^+$, *sty1*$^+$, *sds23*$^+$, *pef1*$^+$, *sts5*$^+$, and *zrg17*$^+$ (Roguev et al., 2008; Ryan et al., 2012), the CLS extension mechanism by Reb1 may work in parallel with the PKA–Sty1 pathway and Clg1–Pef1. Additionally, *reb1*$^+$ has negative genetic interactions with *par1*$^+$ and *rsv2*$^+$ (Roguev et al., 2008; Ryan et al., 2012). Conversely, since *reb1*$^+$ has a positive genetic interaction with *ndk1*$^+$ (Ryan et al., 2012), these mechanisms of CLS regulation may work via the same pathways. Meanwhile, the deletions of the budding yeast *reb1*$^+$ homologs *REB1* and *NSI1* reportedly shorten RLS (Ha et al., 2012; Kamei et al., 2015).

10.24 | *rpb10*$^+$

Overexpression of *rpb10*$^+$, which encodes small subunits of RNA polymerase I, II, and III, extends CLS (Roux et al., 2010a). However, its interaction with other genes that cause CLS extension has not been reported; therefore, its mechanism of CLS extension is unknown.

10.25 | *sck1*$^+$

Overexpression of *sck1*$^+$ restores the phenotypes of *git3*, *git5*, and *pka1* mutants (Jin et al., 1995), and *sck1*$^+$ has positive genetic interactions with *sty1*$^+$ and *tim18*$^+$ (Ryan et al., 2012). Therefore, although the CLS extension by Δ*sck1* is weak, CLS regulation via *sck1*$^+$ may be involved in the TORC1 pathway and PKA–Sty1 pathway. However, in contrast to this hypothesis, a negative genetic interaction between *sck1*$^+$ and *pyp1*$^+$ has also been reported (Ryan et al., 2012).

10.26 | *sdh1*$^+$

Overexpression of *sdh1*$^+$, which encodes succinate dehydrogenase, extends CLS, and its deletion shortens CLS (Ohtsuka et al., 2013; Rallis et al., 2014). However, deletion of *SDH1* (a budding yeast homolog of *sdh1*$^+$) has been reported to extend RLS (McCormick et al., 2015). In *C. elegans*, addition of TCA cycle metabolites related to succinate dehydrogenase (e.g., malate, fumarate, and succinate) activates nuclear translocation of the DAF-16/FOXO transcription factor and suppresses oxidative stress (Edwards et al., 2013). Furthermore, the addition of malate or fumarate extends lifespan (Edwards et al., 2013). Similarly, in *C. elegans*, adding pyruvate and oxaloacetate also extends lifespan (Mouchiroud et al., 2011; Williams et al., 2009), similar to RNAi knockdown of aconitase or mitochondrial NAD^+-dependent isocitrate dehydrogenase (Hamilton et al., 2005; Rea et al., 2007). Thus, the knowledge regarding the TCA cycle and lifespan regulation is accumulating. It is unclear exactly how *sdh1*$^+$ affects CLS of *S. pombe*, but there may be a conserved mechanism of lifespan regulation related to the TCA cycle.

10.27 | *shd1*$^+$

The deletion of *shd1*$^+$, which encodes a cytoskeletal protein-binding protein, extends CLS (Rallis et al., 2014); however, the detailed mechanism for CLS regulation by *shd1*$^+$ remains unknown.

10.28 | *tor1*$^+$

The relationship between Tor2, a component of TORC1, and Tor1, the catalytic subunit of *S. pombe* TORC2, is complicated. While they have the opposite effect on response to sexual differentiation (Laboucarié et al., 2017; Otsubo et al., 2017), there are reports that they share the same function in cell survival in adverse environments (Uritani et al., 2006; Weisman and Choder, 2001). Similarly, regarding CLS, deletion of *tor1*$^+$ extends CLS in minimal (SD) medium, but shortens CLS in a complete (YE) medium (Ohtsuka et al., 2013; Rallis et al., 2013; Weisman and Choder, 2001). This indicates that the CLS of Δ*tor1* cells may be significantly affected by environmental and nutritional conditions. Since the deletion of *tor1*$^+$ causes hypersensitivities to various stresses induced by the environment

(Uritani et al., 2006; Weisman and Choder, 2001), the stresses caused by *tor1* deletion may lead to the activation of stress response pathways such as the Sty1 pathway and then, cause CLS extension. Consistent with this idea, Tor1 functions upstream of Sty1 (Schonbrun et al., 2009) and CLS extension by Δ*tor1* may be involved in the Sty1 pathway. However, *tor1*$^+$ reportedly has negative genetic interactions with *git3*$^+$ and *sds23*$^+$ (Ryan et al., 2012), making it difficult to understand exactly how Tor1 contributes to CLS regulation. Furthermore, since *tor1*$^+$ has a negative genetic interaction with *nbr1*$^+$ (Ryan et al., 2012), their involvement in CLS regulation may work in parallel.

10.29 | *tps0*$^+$

Overexpression of *tps0*$^+$, which encodes mitochondrial lipid translocator protein, extends CLS (Ohtsuka et al., 2013). Since *tps0*$^+$ has a negative genetic interaction with *tor1*$^+$ (Ryan et al., 2012), these mechanisms of CLS extension may work in parallel.

10.30 | *uck2*$^+$

The deletion of *uck2*$^+$, which encodes uracil phosphoribosyltransferase, extends CLS (Rallis et al., 2014). Since *uck2*$^+$ has a negative genetic interaction with *reb1*$^+$ (Ryan et al., 2012), CLS control of *uck2*$^+$ may work in parallel with *reb1*$^+$.

10.31 | *ufd2*$^+$

One study has reported that the deletion of *ufd2*$^+$ (*SPAC20H4.10*), which encodes ubiquitin–protein ligase E4, extends CLS (Jang et al., 2013), whereas another study stated that the CLS of Δ*ufd2* cells was almost the same as those of wild-type cells (Rallis et al., 2014). The effect of *ufd2*$^+$ on CLS may change depending on the culture conditions. Since *ufd2*$^+$ has positive genetic interactions with *git3*$^+$ and *git5*$^+$ (Ryan et al., 2012), CLS extension by *ufd2*$^+$ may be involved in the PKA pathway. This is consistent with the reports that Ufd2 physically interacts with Sds23 (Jang et al., 2013; Paul et al., 2009). Additionally, since *ufd2*$^+$ has a positive genetic interaction with *pmk1*$^+$ (Ryan et al., 2012), the CLS regulation mechanism by *ufd2*$^+$ may be involved in both the PKA–Sty1 and Pmk1 pathways. Although the CLS extension regulated by *ufd2*$^+$ may be environmentally dependent, *ufd2*$^+$ interacts with many other CLS regulators. *ufd2*$^+$ also has positive genetic interactions with *sck2*$^+$ and *par1*$^+$ (Rallis et al., 2014; Roguev et al., 2008), negative genetic interactions with *pef1*$^+$ and *zrg17*$^+$ (Roguev et al., 2008; Ryan et al., 2012), and the product Ufd2 physically interacts with Moc3 (Paul et al., 2009).

10.32 | *ure4*$^+$

The deletion of *ure4*$^+$, which encodes an urease accessory protein, extends CLS (Rallis et al., 2014); however, the mechanism of CLS extension has not yet been elucidated.

10.33 | *vma1*$^+$

Overexpression of *vma1*$^+$, which encodes the subunit A of vacuolar ATPase, extends CLS, and its deletion shortens CLS (Stephan et al., 2013). CLS regulation by *vma1*$^+$ may be due to vacuolar acidification (Stephan et al., 2013). In *S. cerevisiae*, the deletion of *VMA1*, the homolog of *vma1*$^+$, also shortens CLS (Marek and Korona, 2013). Because vacuolar acidification is important for RLS in budding yeast (Henderson et al., 2014), this may be one of the evolutionarily conserved mechanisms of lifespan regulation.

10.34 | SPAC323.03c

Deletion of *SPAC323.03c* extends CLS (Rallis et al., 2014). Since *SPAC323.03c* has a negative genetic interaction with *par1*$^+$ (Ryan et al., 2012), the CLS extension mechanism may be parallel with that of *par1*$^+$.

10.35 | SPBP4H10.16c

The deletion of *SPBP4H10.16c*, which may encode G-patch RNA-binding protein, extends CLS (Rallis et al., 2014). However, the deletion of *WHI2*, a budding yeast homolog of *SPBP4H10.16c*, decreases CLS (Burtner et al., 2011). An accurate understanding of this gene's role in CLS will require further study.

10.36 | SPCC18.02

Overexpression of *SPCC18.02*, which should encode a transmembrane transporter protein, extends CLS (Ohtsuka et al., 2013). Since *SPCC18.02* has a negative genetic interaction with *mkh1*$^+$ (Ryan et al., 2012), CLS extension by *SPCC18.02* is considered to be in parallel with the Pmk1 pathway.

11 | CONCLUSIONS

While many model organisms, such as budding yeasts, nematodes, flies, and rodents, contribute to aging research, many CLS studies using *S. pombe* have also been conducted. In this review, we have summarized about more than 80 genes involved in CLS extension revealed in studies using *S. pombe* and have organized them based on information not only from CLS studies but also from non-CLS studies including comprehensive interactome analysis. Many CLS regulatory genes have various interactions with many other CLS regulatory genes. Furthermore, among these CLS regulatory genes, we summarized the genes that have many interactions with each other and found that three pathways, namely, the TORC1, PKA–Sty1, and Pmk1 pathways, and three groups, namely, Ecl1 family genes, Clg1-Pef1, and the Php complex, play central roles in CLS regulation in *S. pombe*.

Among the large volume of current results, some interactions were difficult to interpret. This may be because some of the CLS

regulatory pathways function in parallel upstream, but have a common target downstream that regulates CLS extension. For example, in this review, the TORC1 and PKA–Sty1 pathways were described separately, but CLS extensions by both pathways are reportedly mediated by the common transcription factor Phx1 (Kim et al., 2014). Moreover, ribosome regulation may be important for CLS extension via the TORC1 pathway, Ecl1 family genes, and glucose restriction involved in the PKA–Sty1 pathway (Ohtsuka et al., 2017; Rodríguez-López et al., 2020).

Although *S. pombe* is a unicellular organism, its signaling pathways that respond to nutrition and starvation function to mediate lifespans similarly to those in multicellular organisms (Fontana and Partridge, 2015; Fontana et al., 2010; Kapahi et al., 2017), suggesting evolutionarily conserved mechanisms to regulate lifespan. Furthermore, evolutionarily conserved mechanisms of lifespan extension other than those that respond to nutrition or starvation may exist. CLS research in *S. pombe* will also make a significant contribution to the elucidation of the aging mechanism in the same way as that of other model organisms.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

HO has made major contributions to (i) this study and writing of the manuscript. TS and HA have contributed to (i) the factual and logical confirmation; and (ii) revision of this manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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