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REVIEW ARTICLE

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Extension of chronological lifespan in *Schizosaccharomyces pombe*

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Abstract

There are several examples in the nature wherein the mechanism of longevity control of unicellular organisms is evolutionarily conserved with that of higher multicellular organisms. The present microreview focuses on aging and longevity studies, particularly on chronological lifespan (CLS) concerning the unicellular eukaryotic fission yeast *Schizosaccharomyces pombe*. In *S. pombe*, >30 compounds, 8 types of nutrient restriction, and >80 genes that extend CLS have been reported. Several CLS control mechanisms are known to be involved in nutritional response, energy utilization, stress responses, translation, autophagy, and sexual differentiation. In unicellular organisms, the control of CLS is directly linked to the mechanism by which cells are maintained in limited-resource environments, and their genetic information is left to posterity. We believe that this important mechanism may have been preserved as a lifespan control mechanism for higher organisms.

KEYWORDS

aging, chronological lifespan, fission yeast, longevity, *Schizosaccharomyces pombe*, stationary phase

1 | INTRODUCTION

The ability to survive the depletion of certain resources contributes to an organism's ability to leave its genetic information to posterity. Under conditions of nutrient depletion, *Schizosaccharomyces pombe* cells generally initiate sexual differentiation to form spores with extremely strong stress tolerance, which thereby contribute to their survival maintenance (Plante & Labbé, 2019; Yang et al., 2017). However, in *S. pombe*, not all nutrient-depleted conditions promote a sexual differentiation response. For example, sulfur depletion halts the cells at G2 phase rather than at G1 phase, which is required for a proper mating reaction. Therefore, *S. pombe* cannot conjugate under sulfur depletion (Ohtsuka et al., 2017). Under such an environment, it is considered that selective pressure is applied depending on the length of chronological lifespan (CLS).

Yeasts possess two types of lifespan (Banerjee et al., 2020; Masumura et al., 2019; Mohammad et al., 2020; Roux et al., 2010): the replicative lifespan (RLS) and CLS. The RLS is represented by the number of divisions that a single

yeast cell undergoes, and it is a model for the aging process of dividing cells (such as stem cells) in higher eukaryotes. The CLS represents the time duration for which a population remains viable in the stationary phase, which is a model for the aging of nondividing cells (such as neurons) in higher eukaryotes. In *S. pombe*, CLS research is actively conducted, but RLS research is conducted less commonly (Legon & Rallis, 2021; Lin & Austriaco, 2014; Ohtsuka et al., 2021). In addition, analysis using a microfluidic device suggests that RLS in *S. pombe* is not involved in cellular aging (Nakaoka & Wakamoto, 2017; Spivey et al., 2017).

In this microreview, we have summarized and discussed CLS studies in *S. pombe*, particularly studies that investigate drugs, nutrient restrictions, and genes that cause CLS extension.

TABLE 1 Drugs that affect CLS extension

Drugs	Drug concentration extending CLS	Possible target factors or signals	References
Acivicin	20 μg/ml (≒100 μM)	GMP synthesis	Stephan et al. (2013)
Actinomycin D	2 μg/ml (≒ 2 μM)	RNA polymerase	Ohtsuka and Aiba (2017)
Auraptene	4 μg/ml (≒ 10 μM)	–	Stephan et al. (2013)
Caffeine	10 mM	DNA damage, cell wall damage, protein trafficking, cellular fitness, cell cycle arrest	Rallis et al. (2013) Calvo et al. (2009)
Calcofluor white	0.2 mg/ml (≒ 200 μM)	Chitin	Imai et al. (2020)
Diazaborine	5 μg/ml (≒ 20 μM)	Ribosome biogenesis	Ohtsuka et al. (2017)
3,3′-diindolylmethane (DIM)	20 μg/ml (≒ 80 μM)	–	Stephan et al. (2013)
Evodiamine	2 μg/ml (≒ 7 μM)	–	Stephan et al. (2013)
Galangin	4 μg/ml (≒ 10 μM)	–	Stephan et al. (2013)
Geranylgeranoic acid	4 μg/ml (≒ 10 μM)	–	Stephan et al. (2013)
α-hibitakanine	64 μg/ml (≒ 300 μM)	Sty1 pathway	Hibi et al. (2018)
β-hibitakanine	8 μg/ml (≒ 20 μM)	Sty1 pathway	Hibi et al. (2018)
Hypocrellin A	2 μg/ml (≒ 4 μM)	–	Stephan et al. (2013)
Mangosteen	50 μg/ml	–	Stephan et al. (2013)
Micafungin	0.04 μg/ml (≒ 30 nM)	β-glucan synthase	Imai et al. (2020)
Monensin	4 μg/ml (≒ 6 μM)	Vacuolar acidification	Stephan et al. (2013)
Mycophenolic acid (MPA)	20 μg/ml (≒ 60 μM)	GMP synthesis	Stephan et al. (2013)
Myriocin	150 nM	Sphingolipid biosynthesis	Huang et al. (2015)
(−)-nicotine	1 mg/ml (≒ 6 mM)	–	Stephan et al. (2013)
Nigericin	2 μg/ml (≒ 3 μM)	Vacuolar acidification	Stephan et al. (2013)
11αOH-KA	45 μg/ml (≒ 100 μM)	–	Batubara et al. (2020)
Plumbagin	4 μg/ml (≒ 20 μM)	–	Stephan et al. (2013)
Prostaglandin J_2 (PGJ_2)	20 μg/ml (≒ 60 μM)	Mitochondrial fission, PKA pathway	Stephan et al. (2013)
Rapamycin	100 μg/ml (≒ 100 μM) 50 nM	TORC1 pathway	Rallis et al. (2013) Huang et al. (2015)
Ribozinoindole-1 (Rbin-1)	0.8 μg/ml (≒ 3 μM)	Ribosome biogenesis	Ohtsuka et al. (2017)
Rotenone	4 μg/ml (≒ 10 μM)	Electron transport chain in mitochondria	Stephan et al. (2013)
Sclareol	4 μg/ml (≒ 10 μM)	–	Stephan et al. (2013)
Torin 1	8 μM	TORC1 and TORC2 pathways	Rodríguez-López et al. (2020)
Tschimganine	4 μg/ml (≒ 10 μM)	Sty1 pathway	Stephan et al. (2013)
Valinomycin	2 μg/ml (≒ 2 μM)	–	Stephan et al. (2013)
Vanadate	100 μM	P-type ATPases	Ito et al. (2010)
Wortmannin	2 μg/ml (≒ 5 μM)	Phosphoinositide 3-kinases	Stephan et al. (2013)

Abbreviations: ATP, adenosine triphosphate; GMP, guanosine monophosphate; PKA, protein kinase A; TORC1, target of rapamycin complex 1; TORC2, target of rapamycin complex 2.

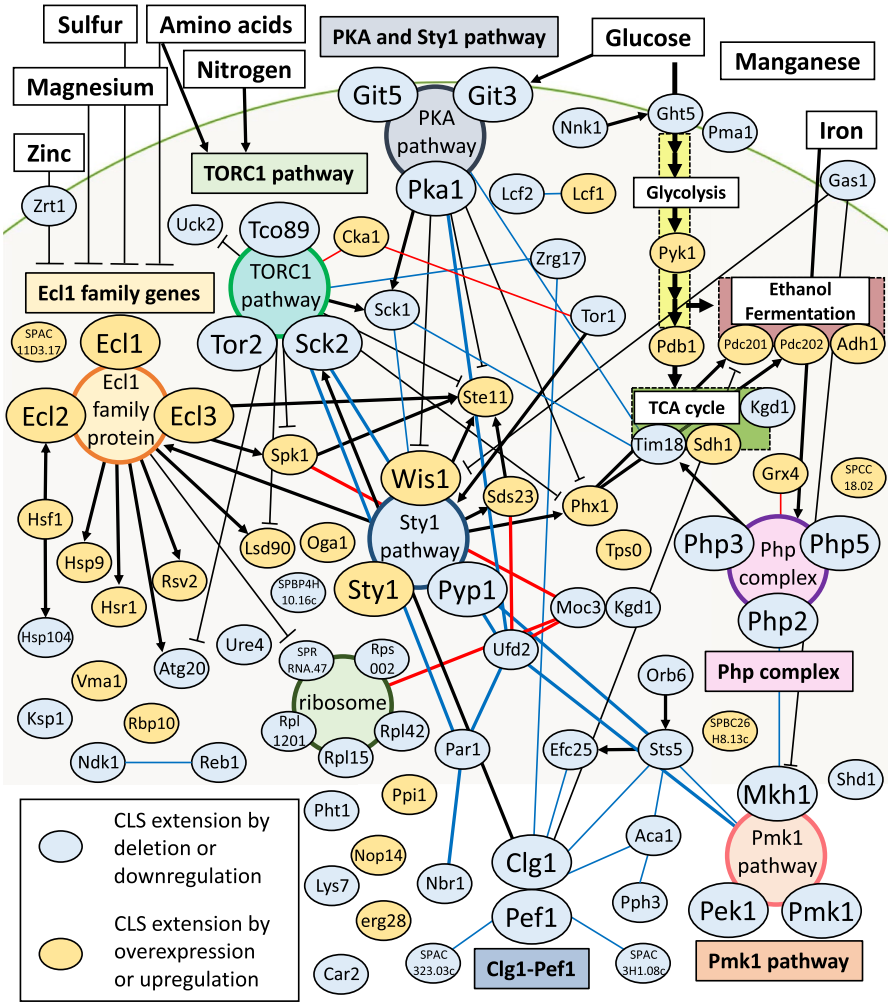

FIGURE 1 Hypothetical model summarizing the representative signaling pathways and factors involved in chronological lifespan (CLS) regulation in *Schizosaccharomyces pombe*. Genetic interactions with clear hierarchies are connected by black lines, and genetic interactions with unknown hierarchies are connected by blue lines. Physical interactions are connected by red lines

2 | CLS EXTENSION IN *SCHIZOSACCHAROMYCES POMBE* VIA DRUGS

Research into lifespan regulation using drugs such as rapamycin, metformin, and resveratrol has been conducted using various model organisms, including budding yeast, nematodes, flies, and mammals (Folch et al., 2018; Kaeberlein et al., 2016; López-Otín et al., 2016). Rapamycin has also been reported to extend CLS in *S. pombe* (Huang et al., 2015; Rallis et al., 2013), suggesting that the CLS extension mechanism of this yeast is evolutionarily conserved. In addition, although caffeine and myriocin themselves extend CLS in *S. pombe*, previous studies in which these drugs were used in combination with rapamycin and myriocin–rapamycin combination suggest presence of a strong synergistic CLS extension effect (Huang et al., 2015; Rallis et al., 2013).

Until date, >30 drugs have been demonstrated to contribute to CLS extension in *S. pombe* (Table 1). These drugs extend CLS in *S. pombe* by affecting several mechanisms: ribosomal regulation via rRNA maturation (e.g., diazaborine and Rbin-1); intracellular components, such as vacuoles (e.g., monensin and nigericin) and mitochondria (e.g., prostaglandin J_2); proton gradient across the plasma membrane (e.g., vanadate); and intracellular signal transductions involved in CLS regulation, such as the Pmk1 pathway (e.g., micafungin), Sty1 pathway (e.g., α-hibitakanine, β-hibitakanine, and tschimganine), and target of rapamycin complex 1 (TORC1) pathway (e.g., rapamycin and Torin 1; Hibi et al., 2018; Huang et al., 2015; Imai et al., 2020; Ito et al., 2010; Ohtsuka et al.,2017, 2021; Rallis et al., 2014; Rodríguez-López et al., 2020; Stephan et al., 2013; Zhou et al., 2013). In addition to rapamycin, caffeine, α-hibitakanine, myriocin, Torin 1, and wortmannin extend the lifespans of model organisms other than *S. pombe*, including those of budding yeast, nematode, and fly (Hibi et al., 2018; Huang et al., 2015; Li et al., 2019; Liu et al., 2013; Mason et al., 2018; Moskalev & Shaposhnikov, 2010).

3 | CLS EXTENSION BY NUTRITIONAL RESTRICTION IN *SCHIZOSACCHAROMYCES POMBE*

Dietary restriction, including calorie restriction, is known to extend the lifespan of various organisms (Fontana & Partridge, 2015; Kapahi et al., 2017; Ohtsuka et al., 2021),

TABLE 2 Genes that affect CLS extension

Genes	Functions of the product	How to extend CLS	Relationships with other CLS factors and pathways	Taxonomic conservation	References indicating CLS extension
aca1$^+$	L-azetidine-2-carboxylic acid acetyltransferase	Deletion	Clg1–Pef1, *pph3*$^+$, *sts5*$^+$, *tim18*$^+$	Fungi	Rallis et al. (2014)
adh1$^+$	Alcohol dehydrogenase	Overexpression		Bacteria Fungi	Roux et al. (2010)
atg20$^+$	Organelle autophagy	Deletion	TORC1 pathway, Ecl1 family genes, *tim18*$^+$	Fungi	Rallis et al. (2014)
car2$^+$	Ornithine transaminase	Deletion		Bacteria Fungi Metazoa Vertebrates	Rallis et al. (2014)
cka1$^+$	Catalytic subunit of casein kinase 2	Overexpression	TORC1 pathway, *tor1*$^+$	Fungi Metazoa Vertebrates	Roux, Arseneault, et al. (2010)
clg1$^+$	Cyclin-like protein involved in autophagy (predicted)	Deletion	PKA–Sty1 pathway, Pmk1 pathway, TORC1 pathway, Clg1–Pef1	Fungi	Chen et al. (2013)
ecl1$^+$	Extender of chronological lifespan	Overexpression	PKA–Sty1 pathway, Ecl1 family genes, *hsp9*$^+$, *hsr1*$^+$, *lsd90*$^+$, *rsv2*$^+$, *spk1*$^+$, *ste11*$^+$	Fungi	Ohtsuka et al. (2008) Ohtsuka et al. (2011) Ohtsuka et al. (2012)
ecl2$^+$	Extender of chronological lifespan	Overexpression	Ecl1 family genes, *hsp9*$^+$, *hsf1*$^+$, *hsr1*$^+$, *lsd90*$^+$, *rsv2*$^+$, *spk1*$^+$, *ste11*$^+$	Fungi	Ohtsuka et al. (2009) Ohtsuka et al. (2011) Ohtsuka et al. (2012)
ecl3$^+$	Extender of chronological lifespan	Overexpression	Ecl1 family genes, *hsp9*$^+$, *hsr1*$^+$, *lsd90*$^+$, *rsv2*$^+$, *spk1*$^+$, *ste11*$^+$	Fungi	Ohtsuka et al. (2009) Ohtsuka et al. (2011) Ohtsuka et al. (2012)
efc25$^+$	Ras1 activator guanine nucleotide exchange factor	Deletion	Pmk1 pathway, Clg1–Pef1, *sts5*$^+$	Fungi Metazoa Vertebrates	Chen et al. (2019)
erg28$^+$	Sterol synthesis	Overexpression	Pmk1 pathway, *par1*$^+$	Fungi Metazoa Vertebrates	Ohtsuka et al. (2013)
gas1$^+$	Cell wall 1,3-β-glucanosyltransferase	*gas1-287*	PKA–Sty1 pathway, Pmk1 pathway	Fungi	Imai et al. (2020)
ght5$^+$	Plasma membrane glucose/fructose:proton symporter	Deletion	*nnk1*$^+$, *sds23*$^+$, *tor1*$^+$	Fungi	Kurauchi et al. (2017)
git3$^+$	G protein-coupled receptor	Deletion	PKA–Sty1 pathway, TORC1 pathway, Clg1–Pef1, Php complex, *reb1*$^+$, *sck1*$^+$, *tim18*$^+$, *tor1*$^+$, *ufd2*$^+$	Fungi	Roux et al. (2009) Stephan et al. (2013)
git5$^+$	Heterotrimeric G protein beta subunit	Overexpression Deletion	PKA–Sty1 pathway, Pmk1 pathway, TORC1 pathway, Php complex, *sck1*$^+$, *pdc202*$^+$, *rsv2*$^+$, *ufd2*$^+$	Fungi Metazoa Vertebrates	Ohtsuka et al. (2021)
grx4$^+$	Monothiol glutaredoxin	Overexpression	Php complex	Bacteria Fungi Metazoa Vertebrates	Ohtsuka et al. (2021)

(Continues)

TABLE 2 (Continued)

Genes	Functions of the product	How to extend CLS	Relationships with other CLS factors and pathways	Taxonomic conservation	References indicating CLS extension
hsf1$^+$	Heat Shock Transcription Factor	Overexpression	Ecl1 family genes	Fungi Metazoa Vertebrates	Ohtsuka et al. (2011)
hsp9$^+$	Heat shock protein	Overexpression	Ecl1 family genes	Fungi	Ohtsuka et al. (2012)
hsr1$^+$	DNA-binding transcription factor	Overexpression	Ecl1 family genes	Fungi	Ohtsuka et al. (2012)
hsp104$^+$	Heat Shock Protein	Deletion	PKA–Sty1 pathway, Pmk1 pathway, *hsf1*$^+$	Bacteria Fungi Metazoa Vertebrates	Rallis et al. (2014)
kgd1$^+$	Mitochondrial α-ketoglutarate dehydrogenase complex subunit	Deletion	*moc3*$^+$	Bacteria Fungi Metazoa Vertebrates	Rallis et al. (2014)
ksp1$^+$	Serine/threonine protein kinase	Deletion		Fungi	Rallis et al. (2014)
lcf1$^+$	Long-chain fatty acyl-CoA ligase	Overexpression	*lcf2*$^+$	Bacteria Fungi Metazoa Vertebrates	Oshiro et al. (2003)
lcf2$^+$	Long-chain fatty acyl-CoA ligase	Deletion	*lcf1*$^+$	Fungi Metazoa Vertebrates	Fujita et al. (2007)
lsd90$^+$	Phospholipid metabolism (predicted)	Overexpression	PKA–Sty1 pathway, TORC1 pathway, Ecl1 family genes	–	Ohtsuka et al. (2012)
lys7$^+$	Lysine biosynthesis	Deletion		Bacteria Fungi Metazoa Vertebrates	Rallis et al. (2014)
mkh1$^+$	MAPKKK of cell wall integrity MAPK cascade	Deletion	PKA–Sty1 pathway, Pmk1 pathway, TORC1 pathway, Clg1–Pef1, Php complex, *efc25*$^+$, *erg28*$^+$, *par1*$^+$, *rsv2*$^+$, *sds23*$^+$, *sts5*$^+$, SPCC18.02	Fungi	Imai et al. (2020)
moc3$^+$	DNA-binding transcription factor	Deletion	Clg1–Pef1, *kgd1*$^+$, *pht1*$^+$, *rpl1201*$^+$, *spk1*$^+$, *ufd2*$^+$	Fungi	Rallis et al. (2014)
nbr1$^+$	Cargo receptor for selective autophagy	Deletion	*par1*$^+$, *tor1*$^+$	Fungi Metazoa Vertebrates	Rallis et al. (2014)
ndk1$^+$	Nucleoside-Diphosphate Kinase	Deletion	*reb1*$^+$	Bacteria Fungi Metazoa Vertebrates	Rallis et al. (2014)
nnk1$^+$	Serine/Threonine Protein Kinase	*nnk1-35*	*ght5*$^+$	Fungi	Kurauchi et al. (2017)
nop14$^+$	Maturation of 40S ribosomal subunit	Overexpression		Fungi Metazoa Vertebrates	Ohtsuka et al. (2021)

(Continues)

TABLE 2 (Continued)

Genes	Functions of the product	How to extend CLS	Relationships with other CLS factors and pathways	Taxonomic conservation	References indicating CLS extension
oga1$^+$	Homolog of budding yeast Stm1	Overexpression	Clg1–Pef1	Fungi	Ohtsuka et al. (2013)
orb6$^+$	NDR/LATS kinase	*orb6-as2*	*sts5*$^+$	Fungi Metazoa Vertebrates	Chen et al. (2019)
par1$^+$	Protein phosphatase PP2A regulatory subunit B-56	Deletion	PKA–Sty1 pathway, Pmk1 pathway, TORC1 pathway, Clg1–Pef1, *erg28*$^+$, *nbr1*$^+$, *pht1*$^+$, *reb1*$^+$, *sds23*$^+$, *spk1*$^+$, *ufd2*$^+$, *zrg17*$^+$, SPAC323.03c	Fungi Metazoa Vertebrates	Rallis et al. (2014)
pdb1$^+$	Pyruvate dehydrogenase	Overexpression		Bacteria Fungi Metazoa Vertebrates	Ohtsuka et al. (2013)
pdc201$^+$	Pyruvate decarboxylase (predicted)	Overexpression	Clg1–Pef1, *phx1*$^+$	Bacteria Fungi	Kim et al. (2014)
pdc202$^+$	Pyruvate decarboxylase (predicted)	Overexpression	PKA–Sty1 pathway, *phx1*$^+$, *rsv2*$^+$	Bacteria Fungi	Kim et al. (2014)
pef1$^+$	Pho85/PhoA-like cyclin-dependent kinase	Deletion	PKA–Sty1 pathway, Pmk1 pathway, TORC1 pathway, Clg1–Pef1, *aca1*$^+$, *efc25*$^+$, *moc3*$^+$, *oga1*$^+$, *pdc201*$^+$, *pht1*$^+$, *reb1*$^+$, *rsv2*$^+$, *ufd2*$^+$, *zrg17*$^+$, SPAC3H1.08c, SPAC323.03c	Fungi Metazoa Vertebrates	Chen et al. (2013)
pek1$^+$	MAPKK of cell wall integrity MAPK cascade	Deletion	Pmk1 pathway, Clg1–Pef1, *erg28*$^+$, *par1*$^+$	Fungi Metazoa Vertebrates	Imai et al. (2020)
php2$^+$	CCAAT-binding factor complex subunit	Deletion	PKA–Sty1 pathway, Php complex, *grx4*$^+$	Fungi Metazoa Vertebrates	Takuma et al. (2013)
php3$^+$	CCAAT-binding factor complex subunit	Deletion	PKA–Sty1 pathway, Pmk1 pathway, Php complex, *grx4*$^+$, *zrg17*$^+$	Fungi Metazoa Vertebrates	Takuma et al. (2013)
php5$^+$	CCAAT-binding factor complex subunit	Deletion	PKA–Sty1 pathway, Php complex, *grx4*$^+$, *sds23*$^+$, *zrg17*$^+$	Fungi Metazoa Vertebrates	Takuma et al. (2013)
pht1$^+$	Histone H2A variant H2A.Z	Deletion	PKA–Sty1 pathway, Pmk1 pathway, Clg1–Pef1, *moc3*$^+$, *par1*$^+$, *sts5*$^+$	Fungi Metazoa Vertebrates	Carr et al. (1994)
phx1$^+$	DNA-binding transcription factor	Overexpression	PKA–Sty1 pathway, TORC1 pathway, *pdc201*$^+$, *pdc202*$^+$	Fungi	Kim et al. (2012)
pka1$^+$	cAMP-dependent protein kinase catalytic subunit	Deletion	PKA–Sty1 pathway, TORC1 pathway, Php complex, *phx1*$^+$, *sck1*$^+$, *sds23*$^+$, *ste11*$^+$	Fungi Metazoa Vertebrates	Roux et al. (2006) Ohtsuka et al. (2008) Zuin, Carmona, et al. (2010) Rallis et al. (2021)

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TABLE 2 (Continued)

Genes	Functions of the product	How to extend CLS	Relationships with other CLS factors and pathways	Taxonomic conservation	References indicating CLS extension
pma1$^+$	Plasma membrane P-type proton exporting ATPase, P3-type	*pma1-L16, pma1-L18*		Fungi	Ito et al. (2010) Naito et al. (2014)
pmk1$^+$	MAPK of cell wall integrity MAPK cascade	Deletion	PKA–Sty1 pathway, Pmk1 pathway, TORC1 pathway, Clg1–Pef1, *par1*$^+$, *pht1*$^+$, *sts5*$^+$, *ufd2*$^+$	Fungi Metazoa Vertebrates	Imai et al. (2020)
pph3$^+$	Protein phosphatase PP4 complex	Deletion	*aca1*$^+$, *reb1*$^+$	Fungi Metazoa Vertebrates	Shetty et al. (2020)
ppi1$^+$	Cyclophilin	Overexpression		Fungi Metazoa Vertebrates	Ohtsuka et al. (2013)
pyk1$^+$	Pyruvate kinase	T343A aa		Bacteria Fungi Metazoa Vertebrates	Kamrad et al. (2020)
pyp1$^+$	Tyrosine phosphatase	Deletion	PKA–Sty1 pathway, Pmk1 pathway, Ecl1 family genes, Clg1–Pef1, Php complex, *hsp104*$^+$, *lsd90*$^+$, *par1*$^+$, *phx1*$^+$, *rsv2*$^+$, *sck1*$^+$, *sds23*$^+$, *sts5*$^+$	Fungi Metazoa Vertebrates	Zuin, Carmona, et al. (2010) Kim et al. (2014)
reb1$^+$	RNA polymerase I transcription termination factor	Deletion	PKA–Sty1 pathway, Clg1–Pef1, *ndk1*$^+$, *par1*$^+$, *pph3*$^+$, *rsv2*$^+$, *sds23*$^+$, *sts5*$^+$, *tim18*$^+$, *uck2*$^+$, *zrg17*$^+$	Fungi Metazoa Vertebrates	Rallis et al. (2014)
rpb10$^+$	Small subunits of RNA polymerase I, II, and III	Overexpression		Fungi Metazoa Vertebrates	Roux, Arseneault, et al. (2010)
rpl1201$^+$	60S ribosomal protein L12.1/L12A	Deletion	*moc3*$^+$, *sds23*$^+$	Bacteria Fungi Metazoa Vertebrates	Ohtsuka et al. (2017)
rpl15$^+$	60S ribosomal protein L15 (predicted)	Deletion		Fungi Metazoa Vertebrates	Ohtsuka et al. (2017)
rpl42$^+$	60S ribosomal protein L36/L42	Deletion		Fungi Metazoa Vertebrates	Ohtsuka et al. (2017)
rps002$^+$	40S ribosomal protein S0B	Deletion		Bacteria Fungi Metazoa Vertebrates	Ohtsuka et al. (2017)
rsv2$^+$	Zinc finger transcription factor	Overexpression	PKA–Sty1 pathway, Pmk1 pathway, Ecl1 family genes, Clg1–Pef1, *pdc202*$^+$, *reb1*$^+$	Fungi	Ohtsuka et al. (2012)
sck1$^+$	Serine/threonine protein kinase	Deletion	PKA–Sty1 pathway, TORC1 pathway, *tim18*$^+$	Fungi Metazoa Vertebrates	Chen and Runge (2009)

(Continues)

TABLE 2 (Continued)

Genes	Functions of the product	How to extend CLS	Relationships with other CLS factors and pathways	Taxonomic conservation	References indicating CLS extension
sck2^{+}	Serine/threonine protein kinase S6K	Deletion	PKA–Sty1 pathway, Pmk1 pathway, TORC1 pathway, Clg1–Pef1, *par1*$^{+}$, *phx1*$^{+}$, *sck1*$^{+}$, *sts5*$^{+}$, *tim18*$^{+}$, *ufd2*$^{+}$, *zrg17*$^{+}$	Fungi Metazoa Vertebrates	Roux et al. (2006) Ohtsuka et al. (2008) Chen and Runge (2009) Zuin, Carmona, et al. (2010)
sdh1^{+}	Succinate dehydrogenase	Overexpression		Bacteria Fungi Metazoa Vertebrates	Ohtsuka et al. (2013)
sds23^{+}	PP2A-type phosphatase inhibitor	Overexpression	PKA–Sty1 pathway, Pmk1 pathway, Php complex, *ght5*$^{+}$, *par1*$^{+}$, *reb1*$^{+}$, *rpl1201*$^{+}$, *ste11*$^{+}$, *tor1*$^{+}$, *ufd2*$^{+}$	Fungi	Roux, Arseneault, et al. (2010)
shd1^{+}	Cytoskeletal protein-binding protein	Deletion		Fungi	Rallis et al. (2014)
spk1^{+}	MAPK involved in pheromone response	Overexpression	TORC1 pathway, Ecl1 family genes, *moc3*$^{+}$, *par1*$^{+}$, *ste11*$^{+}$, *sts5*$^{+}$	Fungi Metazoa Vertebrates	Ohtsuka et al. (2012)
ste11^{+}	Transcription factor essential for sexual development	Overexpression	PKA–Sty1 pathway, TORC1 pathway, Ecl1 family genes, *hsf1*$^{+}$, *sds23*$^{+}$, *spk1*$^{+}$, *tor1*$^{+}$	Fungi	Ohtsuka et al. (2012)
sts5^{+}	Cytoplasmic P body 3′-5′-exoribonuclease, Dis3L2-related (predicted)	*sts5-S86A*	PKA–Sty1 pathway, Pmk1 pathway, TORC1 pathway, *aca1*$^{+}$, *efc25*$^{+}$, *orb6*$^{+}$, *pht1*$^{+}$, *reb1*$^{+}$, *spk1*$^{+}$, *zrg17*$^{+}$	Fungi Metazoa Vertebrates	Chen et al. (2019)
sty1^{+}	MAPK of stress-activated MAPK cascade	Overexpression	PKA–Sty1 pathway, Pmk1 pathway, TORC1 pathway, Ecl1 family genes, Php complex, *pht1*$^{+}$, *reb1*$^{+}$, *sck1*$^{+}$, *sds23*$^{+}$, *ste11*$^{+}$, *tor1*$^{+}$	Fungi Metazoa Vertebrates	Hibi et al. (2018)
tco89^{+}	TORC1 subunit	Deletion	PKA–Sty1 pathway, TORC1 pathway, Clg1–Pef1	Fungi	Rallis et al. (2013)
tim18^{+}	Succinate dehydrogenase anchor	Deletion	PKA–Sty1 pathway, TORC1 pathway, Php complex, *aca1*$^{+}$, *atg20*$^{+}$, *reb1*$^{+}$, *sck1*$^{+}$	Fungi Metazoa Vertebrates	Rallis et al. (2014)
tor1^{+}	Protein kinase of TORC2	Deletion	PKA–Sty1 pathway, TORC1 pathway, *cka1*$^{+}$, *ght5*$^{+}$, *nbr1*$^{+}$, *sds23*$^{+}$, *ste11*$^{+}$, *tps0*$^{+}$	Fungi Metazoa Vertebrates	Ohtsuka et al. (2013)
tor2^{+}	Protein kinase of TORC1	*tor2-ts6* *tor2-L2048S*	TORC1 pathway, PKA–Sty1 pathway, *cka1*$^{+}$, *lsd90*$^{+}$, *sck1*$^{+}$, *spk1*$^{+}$, *ste11*$^{+}$, *tor1*$^{+}$, *uck2*$^{+}$	Fungi Metazoa Vertebrates	Ohtsuka et al. (2019) Shetty et al. (2020)
tps0^{+}	Mitochondrial lipid translocator protein	Overexpression	*tor1*$^{+}$	Bacteria Fungi Metazoa Vertebrates	Ohtsuka et al. (2013)
uck2^{+}	Uracil phosphoribosyltransferase	Deletion	TORC1 pathway, *reb1*$^{+}$	Bacteria Fungi Metazoa Vertebrates	Rallis et al. (2014)

(Continues)

TABLE 2 (Continued)

Genes	Functions of the product	How to extend CLS	Relationships with other CLS factors and pathways	Taxonomic conservation	References indicating CLS extension
ufd2$^+$	Ubiquitin–protein ligase E4	Deletion	PKA–Sty1 pathway, Pmk1 pathway, TORC1 pathway, Clg1–Pef1, *moc3*$^+$, *par1*$^+$, *sds23*$^+$, *zrg17*$^+$	Fungi Metazoa Vertebrates	Jang et al. (2013)
ure4$^+$	Urease accessory protein	Deletion		Bacteria Fungi	Rallis et al. (2014)
vma1$^+$	Subunit A of vacuolar ATPase	Overexpression		Fungi Metazoa Vertebrates	Stephan et al. (2013)
wis1$^+$	MAPKK of stress-activated MAPK cascade	*wis1-DD*	PKA–Sty1 pathway, Pmk1 pathway, *sds23*$^+$, *ste11*$^+$, *sts5*$^+$	Fungi Metazoa Vertebrates	Zuin, Carmona, et al. (2010)
zrt1$^+$	Zinc plasma membrane transporter	Deletion		Bacteria Fungi Metazoa Vertebrates	Shimasaki et al. (2017)
zrg17$^+$	Golgi zinc importer, CDF family	Deletion	TORC1 pathway, Clg1–Pef1, Php complex, *par1*$^+$, *reb1*$^+$, *sts5*$^+$, *ufd2*$^+$	Bacteria Fungi	Rallis et al. (2014)
SPAC3H1.08c	Mitochondrial calcium uniporter regulator (predicted)	Deletion	Clg1–Pef1	Fungi Metazoa Vertebrates	Rallis et al. (2014)
SPAC11D3.17	DNA-binding transcription factor	Overexpression		Fungi	This study
SPAC323.03c	Peroxisome regulation (predicted)	Deletion	Clg1–Pef1, *par1*$^+$	–	Rallis et al. (2014)
SPBC26H8.13c	Siva family protein	Overexpression		Metazoa Vertebrates	Ohtsuka et al. (2021)
SPBP4H10.16c	G-patch RNA-binding protein	Deletion		Fungi Metazoa Vertebrates	Rallis et al. (2014)
SPCC18.02	Membrane transporter (predicted)	Overexpression	Pmk1 pathway	Fungi	Ohtsuka et al. (2013)
SPRRNA.47	28S ribosomal RNA	Deletion		rRNA	Chen et al. (2013)

Note: The PKA–Sty1 pathway includes *git3*$^+$, *git5*$^+$, *pka1*$^+$, *pyp1*$^+$, *sty1*$^+$, and *wis1*$^+$. The Pmk1 pathway includes *mkh1*$^+$, *pek1*$^+$, and *pmk1*$^+$. The TORC1 pathway includes *sck2*$^+$, *tco89*$^+$, and *tor2*$^+$. The Ecl1 family genes include *ecl1*$^+$, *ecl2*$^+$, and *ecl3*$^+$. Clg1–Pef1 includes *clg1*$^+$ and *pef1*$^+$. The Php complex includes *php2*$^+$, *php3*$^+$, and *php5*$^+$. See Ohtsuka et al. (2021) for details regarding "Relationships with other CLS factors and pathways."

Abbreviations: ATP, adenosine triphosphate; CDF, cation diffusion facilitator; CLS, chronological lifespan; CoA, Coenzyme A; GMP, guanosine monophosphate; MAPK, mitogen-activated protein kinase; MAPKKK, mitogen-activated protein kinase kinase kinase; NDR/LATS, nuclear Dbf2-related/large tumor suppressor; PKA, protein kinase A; TORC1, target of rapamycin complex 1; TORC2, target of rapamycin complex 2.

and the restriction of various types of nutrients has been demonstrated to extend CLS in *S. pombe*. Glucose restriction (i.e., calorie restriction) has been reported to extend CLS via the PKA and the stress-responsive mitogen-activated protein kinase (MAPK) Sty1 pathways (Figure 1; Ohtsuka et al., 2021; Roux, Chartrand, et al., 2010; Sjölander et al., 2020; Zuin, Carmona, et al., 2010). Similarly, limiting nitrogen sources has been reported to halt the cell cycle at G1 and extend CLS (Hayles & Nurse, 2018; Ohtsuka et al., 2017; Su et al., 1996). The depletion of nitrogen sources suppresses the activity of TORC1, while the inhibition of the TORC1 pathway extends CLS (Ohtsuka et al., 2021; Otsubo & Yamamoto, 2012; Rallis et al., 2014; Rodríguez-López et al., 2020). The depletion of sulfur sources strongly induces *ecl1*$^+$, an Ecl1 family gene, and extends CLS by inducing autophagy and suppressing ribosomes in an Ecl1 family gene-dependent manner (Ohtsuka et al., 2017; Shimasaki et al., 2020).

In addition, calorie restriction halts the cell cycle at the G1 and G2 phases, whereas sulfur depletion halts the cell cycle at the G2 phase (Chen & Runge, 2009; Ohtsuka et al., 2017; Pluskal et al., 2011). Further, it has been reported that glucose restriction induces G2 arrest at least transiently (Masuda et al., 2016). Amino acid restriction, such as leucine, lysine, or arginine restriction, also leads to G1 arrest and CLS extension in the corresponding amino acid-auxotrophic yeast cells (Ohtsuka et al., 2019). The Ecl1 family genes are also important for this CLS extension. Magnesium restriction also extends CLS partially depending on Ecl1 family genes (Ohtsuka et al., 2021). Interestingly, this restriction activates general amino acid control pathway as well as amino acid restriction and induces *ecl1*$^+$ expression (Ohtsuka et al., 2021). Restriction of zinc, iron, or manganese also extends CLS, and zinc-restricted CLS extension also depends on the Ecl1 family genes (Shimasaki et al., 2017). Furthermore, some of these nutritional restrictions, including glucose, nitrogen, and sulfur restriction, have been shown to reduce ribosome levels, suggesting an association between translational regulation and CLS control (Ohtsuka & Aiba, 2017). The relationship between translation regulation and longevity has also been reported for budding yeasts and nematodes (Hansen et al., 2007; MacInnes, 2016; Steffen et al., 2008).

The restriction of various nutrient sources affects CLS in *S. pombe*, and the relationship between longevity and nutritional restriction is evolutionarily conserved (Fontana & Partridge, 2015; López-Otín et al., 2016; Santos et al., 2016). Understanding the mechanism of CLS extension for each nutritional restriction in *S. pombe* is expected to contribute to the elucidation of the basic mechanism of lifespan regulation and antiaging.

4 | CLS EXTENSION VIA GENETIC ALTERATION IN *SCHIZOSACCHAROMYCES POMBE*

Over 80 genetic changes that extend CLS in *S. pombe* have been elucidated (Figure 1; Table 2). The genes addressed here are those that have been demonstrated to cause CLS extension, and they do not include those that have been reported to cause CLS reduction alone.

We searched the DNA region of the *S. pombe* genome that causes CLS extension by overexpression using a multicopy plasmid. We found that the overexpression of the DNA region containing SPAC11D3.17 caused CLS extension (Figure 2). SPAC11D3.17 encodes a DNA-binding zinc finger transcription factor. The detailed mechanism of CLS extension is unknown, but it is induced by amino acid depletion and sulfur depletion (Duncan et al., 2018; Ohtsuka et al., 2017). It is also induced by the suppression of Tor2 (Matsuo et al., 2007). Therefore, it is considered to be controlled by TORC1.

Three main gene pathways have been identified as being involved in CLS extension in *S. pombe*: the PKA–Sty1 pathway, Pmk1 pathway, and TORC1 pathway, and three main factors are involved in CLS extension, namely, Clg1–Pef1, Ecl1 family genes, and the Php complex (Ohtsuka et al., 2021). The suppression of the PKA pathway has been reported to be involved in the lifespan of not only fission yeast but also other organisms, including budding yeast and mice (Fontana & Partridge, 2015; Fontana et al., 2010; Yan et al., 2007). In *S. pombe*, the deletion strains of G protein-coupled glucose receptor Git3, G protein Git5, and PKA catalytic subunit Pka1 are known to extend CLS (Ohtsuka et al., 2021; Roux et al.,2006, 2009). The PKA pathway in *S. pombe* is closely related to the Sty1 pathway in terms of nutritional response and CLS regulation (Caspari, 1997; Zuin, Carmona, et al., 2010). The suppression of the PKA pathway activates the Sty1 pathway, which has an opposite effect on CLS (Ohtsuka et al., 2021; Roux, Chartrand, et al., 2010; Zuin, Carmona, et al., 2010; Zuin et al., 2010). The overexpression of Sty1 extends CLS (Hibi et al., 2018). The activated mutation of *wis1*$^+$, which encodes a MAPK kinase of Sty1, *wis1-DD*, and deletion of *pyp1*$^+$, which encodes a phosphatase of Sty1, constitutively activate Sty1 and confer an extended CLS (Zuin, Carmona, et al., 2010). It is considered that calorie restriction-induced CLS extension in *S. pombe* is controlled by the PKA and Sty1 pathways (Roux, Chartrand, et al., 2010; Zuin, Carmona, et al., 2010).

The Pmk1 pathway plays an important role in maintaining cell wall integrity in *S. pombe*. The Pmk1 MAPK pathway consists of MAPK Pmk1, MAPK kinase Pek1, and MAPK kinase kinase Mkh1; the deletion of any of these genes extends CLS (Imai et al., 2020). It has been reported that the Pmk1 pathway is associated with the Php complex, *gas1*$^+$, and *sts5*$^+$, which are involved in CLS extension (Figure 1; Table 2; Ohtsuka et al., 2021).

TOR is a serine–threonine kinase that regulates cell growth and metabolism in response to environmental changes (Otsubo et al., 2020). In several model organisms, including *S. pombe*, the suppression of the TORC1 pathway extends lifespan (Filer et al., 2017; Lees et al., 2016; Rodríguez-López et al., 2020; Shetty et al., 2020). TORC1-related genetic changes that extend CLS include the deletion of *tco89*$^+$, which encodes a component of TORC1, and the inhibitory mutation of *tor2*$^+$, which encodes a catalytic subunit of TORC1 (Ohtsuka et al., 2019; Rallis et al., 2013; Shetty et al., 2020). *sck2*$^+$, which encodes S6 kinase, is believed to be a target of TORC1, and the deletion of *sck2*$^+$ also extends CLS (Chen & Runge, 2009; Roux et al., 2006). In addition, an experiment using *tor2-ts6* mutants demonstrated that the suppression of Tor2 increases the expression of *lsd90*$^+$, *spk1*$^+$, *ste11*$^+$, and SPAC11D3.17, which are known to cause CLS extension by

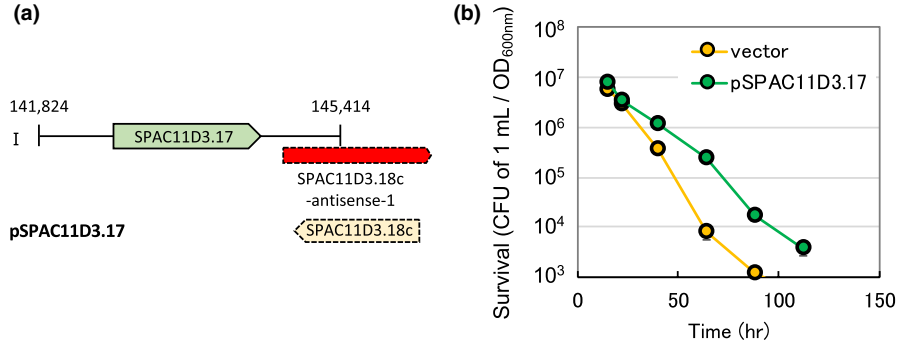

FIGURE 2 (a) The DNA fragment that was inserted into the plasmid was carried by the cells whose CLS was measured. (b) The results of the CLS measurements. The strain of *Schizosaccharomyces pombe* used was JY333, and the plasmid vector was pLB-Dblet. To determine cell viability, the cells were grown in SD liquid medium, sampled at each growth phase, and then plated onto yeast extract agar plates using suitable dilutions (Ohtsuka et al., 2008). After incubation for several days at 30°C, the number of colonies derived from 1 ml of the culture suspension was counted. This number was divided by the cell turbidity at the sampling time

their overexpression (Figure 1; Matsuo et al., 2007; Ohtsuka et al., 2012). Among these factors, *lsd90*$^+$, *spk1*$^+$, and *ste11*$^+$ are also upregulated by the overexpression of the Ecl1 family genes (Ohtsuka et al., 2012).

clg1$^+$ and *pef1*$^+$ encode a cyclin and a cyclin-dependent kinase 5 subfamily member that interacts with Clg1 (Matsuda et al., 2020). The deletion of *clg1*$^+$ and/or *pef1*$^+$ extends CLS (Chen et al., 2013). It was recently reported that Pef1 positively regulates TORC1 (Matsuda et al., 2020). Therefore, CLS extension by Clg1–Pef1 may also be closely associated with the TORC1 pathway. Although CLS extension by Δ*clg1* depends on *cek1*$^+$, which encodes the homologous protein of budding yeast kinase Rim15, the deletion of *cek1*$^+$ itself does not have a significant effect on CLS in *S. pombe* (Chen et al., 2013).

ecl1$^+$ was originally discovered as a gene that complements the short CLS in Δ*sty1* cells and was subsequently observed to extend CLS in *sty1*$^+$ cells (Ohtsuka et al., 2008). An Ecl1 family gene, *ECL1*, was detected in the budding yeast *Saccharomyces cerevisiae*, and three Ecl1 family genes were detected in *S. pombe*, each of which was found to extend CLS by its overexpression (Azuma et al., 2012; Ohtsuka & Aiba, 2017). In *S. pombe*, the Ecl1 family genes are induced by various environmental and starvation stresses. Oxidative stress induces *ecl1*$^+$ via the Sty1 pathway, and thermal stress induces *ecl2*$^+$ (Ohtsuka et al., 2011; Shimasaki et al., 2014). In addition, *ecl1*$^+$ is weakly induced by nitrogen starvation and strongly induced by sulfur, magnesium, or amino acid starvation (Miwa et al., 2011; Ohtsuka et al., 2017, 2019, 2021). Although the transcriptional inductions have not yet been clearly observed, the Ecl1 family genes are also required for the induction of sexual differentiation by zinc or iron starvation (Ohtsuka et al., 2015). Ecl1 family genes are induced in these unfavorable environments and are considered to play important roles in maintaining cell survival, including CLS extension.

The Php complex is a CCAAT-binding transcription factor complex of *S. pombe* that regulates the gene expression involved in various cellular processes, including iron responses, the TCA cycle, and respiration (Dlouhy et al., 2017; Mercier et al., 2008). The deletion of *php2*$^+$, *php3*$^+$, or *php5*$^+$, which encode subunits of the Php complex, has also been reported to extend CLS (Takuma et al., 2013).

Thus, the major pathways and genes that extend CLS in *S. pombe* appear to intricately interact with each other (Ohtsuka et al., 2021). We hope that future studies will clarify whether CLS extension by these pathways and factors results in one important basic process, such as the suppression of translational control, or multiple processes that additively cause CLS extension.

5 | CONCLUSIONS

Although several model organisms, including budding yeasts, nematodes, flies, and mammals, contribute to aging research, many CLS studies using *S. pombe* have also been conducted (Folch et al., 2018; Ohtsuka et al., 2021). In the present review, we summarized that 32 compounds, 8 types of nutrient restriction, and 87 genes revealed via studies using *S. pombe* were involved in CLS extension (Tables 1 and 2; Figure 1). The corresponding CLS-regulating genes have been found to induce some drugs and nutritional restrictions that extend CLS. Several genes that extend CLS are involved in energy metabolism, translational regulation, stress responses, autophagy induction, and sexual differentiation. In *S. pombe*, long CLS, i.e., the maintenance of survival in a long stationary phase, is likely to be closely related to the cellular response to survive starvation. It evidently makes sense that energy metabolism and translational regulation, which control cellular energy and resources, are closely related to CLS regulation. Increased stress responses also contribute to cell survival. Autophagy is induced by the inhibition of the TORC1 pathway or Pef1 and by the upregulation of the Ecl1 family genes (Matsuda et al., 2020; Otsubo et al., 2017;

Shimasaki et al., 2020). Although the overexpression of an autophagy gene leads to longevity in flies and mice (Hansen et al., 2018), it remains unclear whether autophagy induction itself is sufficient to extend CLS in *S. pombe*. However, it is predictable that autophagy is necessary for survival in the stationary phase in resource-poor environments, and some examples indicate that autophagy is required to maintain CLS (Kohda et al., 2007; Shimasaki et al., 2020). Moreover, the suppression of the PKA and TORC1 pathways as well as the activation of the Ecl1 family genes not only induce CLS extension but also induce the sexual differentiation response (Gupta et al., 2011; Ohtsuka et al., 2015; Otsubo et al., 2017). In a resource-depleted environment, a long CLS and the induction of spore-forming sexual differentiation can contribute to the maintenance of a yeast's genetic information by survival in that particular environment.

Chronological lifespan regulation, which is closely related to nutrient depletion and stationary phase response, is deeply involved in the maintenance of cell viability. We believe that the simple motive to survive nutrient starvation in unicellular organisms may be the basis for the maintenance of the cellular lifespan in multicellular organisms (and thus the antiaging mechanism) through evolutionary preservation.

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CONFLICT OF INTERESTS

None declared.

AUTHOR CONTRIBUTIONS

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

ETHICAL APPROVAL

Not applicable.

CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

CODE AVAILABILITY

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The manuscript has no associated data.

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