Demonstration of iodide-dependent UVA-triggered growth inhibition in *Saccharomyces cerevisiae* cells and identification of its suppressive molecules

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ABSTRACT

Upon white light illumination, the growth of the budding yeast *Saccharomyces cerevisiae* was extremely impaired only in the presence of iodide ions, but not fluoride, chloride and bromide ions. Action spectroscopy revealed that the maximum wavelength of the light is around at 373 nm, corresponding to the UVA region. Using a genetic approach, several genes, including OPY1, HEM1, and PAU11, were identified as suppressors of this growth inhibition. This iodide-dependent UVA-triggered growth inhibition method, along with its suppressive molecules, would be beneficial for understanding cell growth processes in eukaryotes and can be utilized for medium sterilization using UVA light.

1. Introduction

Organisms are composed of cells, which are fundamental units involved in various biological functions such as division, proliferation, and maintenance of homeostasis. When cells are exposed to significant environmental changes, their cellular membranes and nuclear structures can undergo collapse, resulting in growth defects [1]. These growth defects are categorized into several types, including apoptosis, autophagy and necrosis [1,2]. The dysregulation of these processes can lead to various diseases such as cancer and infection, indicating their biological significance [3].

In addition to the perspective of diseases, the artificial control of cell growth processes has implications not only for understanding their biological functions and mechanisms but also for sterilizing media containing infectious microorganisms. Various stimuli such as heat, pressure and light, have been used to impair cell growth. Among them, shorter wavelengths of light below 315 nm, including the γ-ray (10^{-12}-10^{-14} m) and UVB/C regions (280-315/200-280 nm), have been widely employed. However, they can also cause unexpected chemical reactions, generate radicals and fragment genomic DNA due to their high energy density [4]. On the other hand, longer wavelengths of light above 315 nm, including UVA (315-400 nm) and the visible region (400-700 nm), have relatively low energy density, resulting in lower cell damage compared to the γ-ray and UVB/C regions. In other words, a high intensity of longer wavelengths of light above 315 nm is required to inhibit cell growth. Additionally, chemical reagents have been widely utilized to facilitate or inhibit biological processes, including cell growth. Among them, iodine (I) widely exists in nature and forms the iodide ion (I^-) in solution due to its high polarity. When I^- is illuminated by UVA light around 385 nm, it leads to the formation of iodine molecules (I_2) [5,6]. It is known that I_2 exhibits toxicity to eukaryotes, including humans [7], although its molecular mechanism is still unclear.

Based on the background, we present a cell growth inhibition system that combines UVA and iodide in the yeast *Saccharomyces cerevisiae* as a model for eukaryotes. Additionally, we conduct overexpression profiling experiments to identify suppressive molecules for iodide-dependent UVA-triggered cell growth inhibition. As a result, several genes including OPY1, HEM1 and PAU11 were identified as suppressors. This protocontrollable method for inhibiting cell growth and the identification of its suppressive molecules can be beneficially utilized for understanding of the cell growth processes in eukaryotic cells and for sterilizing media using UVA light.

2. Materials and Methods

2.1. Strain, plasmid, culture media and growth conditions

The *S. cerevisiae* BY4741 strain (*MATa his3Δ1, leu2Δ0, met15Δ0* and *ura3Δ0*) [8] was used as

the wild-type strain in this study. The vector plasmid pTOWug2-836, containing the leucine synthesis gene LEU2 and the uracil synthesis gene URA3 as auxotrophic markers, was employed for transformation [9] and introduced into the BY4741 strain as described previously [10]. The cells were cultured in YPD medium or a synthetic complete (SC) medium. The YPD medium consisted of 10 g/L Bacto Yeast extract (BD, USA), 20 g/L Bacto Peptone (Gibco, USA), and 20 g/L D-glucose, while the SC medium contained 6.7 g/L Yeast Nitrogen Base with Ammonium Sulfate (MP, USA), 0.65 g/L DO supplement-HisLeuUra (Clontech, USA), 20 g/L D-glucose, 20 mg/L Histidine, 8 mg/L Uracil, and 100 mg/L Leucine. The SC-Ura medium refers to the SC medium without 8 mg/L Uracil. The optical density of the culture medium was monitored at 660 nm (OD_{660}) using a spectrophotometer (ADVANTEC TVS062CA). The opy1Δ strain was obtained from the yeast gene KO library (Funakoshi co. Ltd., Japan) as described previously [11].

2.2. Colony-formation assay and action spectroscopy

In this experiment, a 1 µl aliquot was taken from a 5 ml cell culture containing approximately 5×10^7 cells and diluted into 1 ml of pure water. This dilution process was repeated to obtain further diluted samples. Then, a 5 µl aliquot from each dilution was spotted onto a YPD plate containing 2 % agar with and without the respective salt (100 mM NaF, NaCl, NaBr, NaI) obtained from FUJIFILM Wako Pure Chemical Industries, Ltd., Japan. The plates were incubated at 30 ˚C for 24 hrs with and without white light, using the MAX-303 spectrometer (Asahi Spectra Co., Ltd., Japan) with a light intensity of 12 mW/cm^2 at 515 nm. After incubation, the number of colonies was counted, and if necessary, it was multiplied by the dilution factor. The survival rate and viability were determined by counting the number of cells capable of forming colonies on the plates.

For action spectroscopy, the wavelength was controlled by using specific cut-off filters (360 ± 10 nm, 400 ± 10 nm, 450 ± 10 nm, 500 ± 10 nm, 550 ± 10 nm, 600 ± 10 nm, provided by Asahi Spectra Co. Ltd., Tokyo, Japan). The growth inhibition rate, y, was measured at different wavelengths and plotted against the corresponding wavelength, denoted as x (nm). The data was fitted with a Gauss function using the following equation [eq. 1]:

$$y = y_0 + \frac{A}{w\sqrt{\pi/2}} e^{-2\frac{(x-x_c)^2}{w^2}} \quad \text{[eq. 1]}$$

where w represents the amplitude of the change in absorption differences, A is half width, x_c is the maximum wavelength, and y_0 is an offset value.

2.3. Identification of adaptive genes associated with iodide-dependent UVA-triggered cell growth inhibition

To identify adaptive genes associated with iodide-dependent UVA-triggered cell growth inhibition, we conducted overexpression profiling following the procedure described in the previous study [12]. The experimental steps were as follows: (1) *S. cerevisiae* cells containing the plasmid library gTOW6000, which covers all *S. cerevisiae* genes, were precultured in YPD medium at 30 ˚C for 24 hrs. (2) The precultured cells were then grown at 30 ˚C in SC-Ura medium containing 100 mM NaI under white light illumination with an intensity of 2 mW/cm^2 for 4 hrs. (3) The cultivated cell suspension was inoculated into flesh YPD medium containing 100 mM NaI. (4) Steps 2 and 3 were repeated 10 times to ensure sufficient exposure to iodide-dependent UVA-triggered growth inhibition. Next, plasmid DNA was extracted from the yeast cells and subjected to long-read sequencing to obtain the sequence information of the inserts, following the methodology described previously [12]. The sequencing of the library was performed according to the manufacturer's instructions [12]. The resulting sequence data was aligned to a reference genome sequence of *S. cerevisiae* to generate an alignment file. To analyze the data, the counts corresponding to each insert were converted into percentages (%) as occupancies. This profiling approach allowed us to identify the adaptive gene(s) potentially associated with iodide-dependent UVA-triggered growth inhibition of the *S. cerevisiae* cells.

3. Results

3.1. Iodide-dependent UVA-triggered growth inhibition in S. cerevisiae cells

We conducted a colony-formation assay on culture plate containing NaI with and without white light, including UVA and the visible region, to evaluate the effects of iondine on the growth and viability of the cells (Figures 1 and S1). As a control, we performed similar experiments on culture plates containing other salts, namely NaF, NaBr and NaCl (Figures 1). As observed, the cell culture without any additional salts (control) exhibited a similar colony-formation ability compared to cultures with concentrations ranging from 1 mM to 100 mM of NaCl, NaI, NaBr and NaF (Figures 1B (left panel), 1C (left panel) and S2). Similarly, the colony-formation ability of the cell culture without any additional salts (control) under white light irradiation was comparable to those with concentrations ranging from 1 mM to 100 mM of NaCl, NaBr and NaF (Figures 1B (right panel) and S2). Thus, the addition of salts and white light irradiation had minimal effects on the growth and viability of *S. cerevisiae* cells. However, when the cell culture was supplemented with 100 mM NaI and exposed to white light irradiation, the colony-formation ability was sifnificantly impaired (Figure 1C (right panel)). This clearly indicates that white light irradiation in the presence of NaI had a toxic effect on *S. cerevisiae* cells, leading to a decreased ability to form colonies.

The light source used in this study encompassed both the Visible (400-700 nm) and UVA (315-400 nm) regions (Figure S1). To determine the specific region responsible for the growth

inhibition, we performed action spectroscopy by measuring the viability of *S. cerevisiae* cells in the presence of 100 mM NaI under distinct wavelengths of light ranging from 360 nm to 600 nm (Figures 2A and 2B). The data were fitted with a Gauss function, and the peak was estimated to be around at 373 nm (Figure 2B). This indicates that UVA region (315-400 nm) is the effective range for inducing growth inhibition of *S. cerevisiae* cells.

3.2. Identification of suppressive molecules through overexpression profiling

To further investigate the mechanism of cell growth inhibition in *S. cerevisiae*, we conducted overexpression profiling experiments. Overexpression profiling is a recently developed method used to identity adaptive genes associated with stimulus-dependent growth defects, providing insights into biological activities such as cellular metabolism and signaling [12]. The overexpression profiling process involves four steps; 1) Construction of a library; 2) Competitive culture and passaging of the pooled library; 3) Long-read plasmid sequencing of plasmid inserts extracted from the cultured library pool; 4) Analysis of sequence data to calculate the frequencies of plasmid inserts and identify genes whose overexpression was functionally adaptive (GOFAs). Before conducting the overexpression profiling experiments in the culture solution, we first confirmed whether iodide-dependent UVA-triggered growth inhibition of *S. cerevisiae* cells could be observed not only in the colony-formation assay but also in the culture solution. The optical density of the SC culture medium showed similar changes between the samples with and without 100 mM NaI, whereas a dramatic decrease in optical density was observed only when the cells were exposed to white light irradiation at an intensity of 12 mW/cm^2 in the presence of 100 mM NaI (Figure 3A). This indicates that iodide-dependent UVA-triggered cell growth inhibition is observed not only on the solid agar plate, but also in the solution. Because light irradiation at an intensity of 12 mW/cm^2 is too strong to obtain the adaptive *S. cerevisiae* cells, we adjusted the light intensity to 2 mW/cm^2, which is a moderate intensity suitable for cell growth, as shown in Figure 3B.

Through repeated cultivation in the presence of both light irradiation (2 mW/cm^2) and NaI (100 mM), several genes, such as OPY1, HEM1 and PAU11, were enriched at higher levels ranging from 6.57 % to 28.91 % (Figure 3C), suggesting the presence of adaptive genes that suppressed iodide-dependent UVA-triggered cell growth inhibition. The identified adaptive genes are listed and summarized in Table 1. To further confirm the role of the adaptive genes, we focused on the highest occupied molecule. OPY1 (28.91 %), and prepared the *S. cerevisiae* cells lacking the natural OPY1 gene (opy1Δ). As a result, the opy1Δ strain became extremely sensitive to light irradiation in the presence of 100 mM NaI (Figure 3D), supporting the idea that an increase in OPY1 suppresses the toxic effect of iodide-dependent UVA-triggered growth inhibition in *S. cerevisiae* cells.

4. Discussion

In this study, we successfully developed a system for inhibiting cell growth in *S. cerevisiae* by combining UVA and iodide ions (Figures 1 and 2). Based on the results, we discuss the mechanism of this growth inhibition (Figure 3E). Iodide is an essential micronutrient that plays a crucial role in metabolism and is oxidized to produce iodine-containing thyroid hormones [13]. These hormones are necessary for controlling growth, metabolism, and many other body functions [13,14]. However, in addition to its beneficial aspects, it is known that iodide ion (I^-) can form toxic iodine molecules (I_2) upon UVA irradiation [5,6] (Figure 3E). Although the precise mechanism of the toxicity of the iodine molecule (I_2) is still unclear [7], it is likely that the intracellular signaling pathway involved in growth inhibition is activated by I_2. As shown in Figure 3 and Table 1, we have successfully identified molecules that suppress iodide-dependent UVA-triggered growth inhibition. Among them, we specifically focus on the top three molecules: OPY1 (Overproduction-induced pheromone-resistant yeast protein 1), HEM1 and PAU11 (Figure 3E). These molecules provide us with hints about the mechanism of iodide-dependent UVA-triggered cell growth inhibition in *S. cerevisiae*.

The highest adaptive gene, OPY1 (28.91 %), encodes a protein that binds to PtdIns(4,5)P_2, a phospholipid involved in cellular signaling and its regulation (Table 1) [15]. OPY1 negatively regulates the synthesis of PtdIns(4,5)P_2 and is present at a concentration of 1,560 molecules/cell during the logarithmic growth phase [15]. OPY1 has been reported to function as a sensor and modulator of PtdIns(4,5)P_2 synthesis through the conserved PtdIns(4)P 5-kinase, Mss4 [16]. PtdIns(4,5)P_2 is known to be an inhibitory molecule for MAP kinase and is involved in regulating key biological processes such as endocytosis and exocytosis. The increase in OPY1 expression may lead to the suppression of the iodide-dependent UVA-triggered growth defect through multiple mechanisms. First, since PtdIns(4,5)P_2 is essential signaling lipid, maintaining an appropriate level of PtdIns(4,5)P_2 is crucial for cell survival and growth [16]. By negatively regulating PtdIns(4,5)P_2 synthesis, OPY1 may prevent the excessive inhibition of MAP kinase activity, thus promoting cell growth. Additionally, OPY1 has been reported to specifically block the G1 arrest induced by mating pheromone [15]. This suggests that an increase in OPY1 expression may facilitate the cell division process, further contributing to the suppression of the growth defect triggered by UVA irradiation and iodide. Furthermore, OPY1 has been found to be associated with mitochondria, as indicated in the Saccharomyces Genome Data Base (SGD). Mitochondria are responsible for aerobic respiration and adenosine triphosphate (ATP) production, which are essential for cell energy metabolism. Overexpression of OPY1 may enhance ATP production by mitochondria, thereby supporting cell growth and suppressing the iodide-dependent UVA-trigged growth defect in *S. cerevisiae*. In future, it will be important to clarify

the specific roles of OPY1 in the suppression of growth inhibition induced by UVA irradiation and iodide. Further investigation can provide insights into the molecular mechanisms underlying the protective effect of OPY1 and its potential applications in understanding cellular responses to environmental stressors.

The second highest adaptive gene, HEM1 (7.80 %), encodes 5-aminolevulinate synthase, which is involved in heme synthesis (Table 1). HEM1 is a metalloprotein that contains a heme prosthetic group with an iron cation, similar to other heme-containing proteins like cytochrome c, myoglobin and hemoglobin. The heme proteins serve various biological processes such as oxygen delivery, oxygen reduction, and electron transfer [17,18]. Importantly, the chromophore heme absorbs light not only in the visible region (400 – 700 nm) but also in the UVA region (315-400 nm) due to its interaction with surrounding aromatic amino acid residues [17]. Based on this information, it is hypothesized that an increase in HEM1 expression may lead to a reduction in UVA absorption by iodide ions and inhibit the production of toxic iodine molecules (I_2) (Figure 3E). The presence of HEM1, with its heme prosthetic group, could potentially compete with iodide ions for UVA absorption, thus reducing the availability of UVA energy to drive the formation of I_2. This mechanism may contribute to the suppression of iodide-dependent UVA-triggered growth inhibition in *S. cerevisiae* cells.

On the other hand, the third highest adaptive gene, PAU11 (6.57 %), encodes a putative protein with an unknown function (Table 1). While the specific role of PAU11 is still unclear, it is suggested that PAU11 may be involved in cell division and/or its maintenance, as it suppresses the growth inhibition in *S. cerevisiae* cells (Figure 3C). Further investigation is required to elucidate the function of PAU11 and its contribution to the suppression of growth inhibition. In future studies, the inhibitory molecules identified in this research, including OPY1, HEM1 and PAU11, will be further investigated to understand their precise roles in the mechanism of cell growth inhibition and their potential applications in mitigating the toxic effects of iodide-dependent UVA exposure.

In conclusion, this study has successfully developed a system for inhibiting cell growth in *S. cerevisiae* by combining UVA irradiation and iodide ions. The induction of iodide-dependent UVA-triggered growth inhibition provides a valuable tool for studying cell growth processes in eukaryotic cells. Furthermore, the identification of suppressive molecules such as OPY1, HEM1 and PAU11 offers insights into the mechanism of growth inhibition and potential targets for further investigation. In addition, the photocontrolable growth inhibition method presented in this study can be utilized for sterilizing the medium by UVA light, which may be valuable in industrial settings or laboratory practices where contamination control is essential.

Author contributions

RO performed the experiments. RO, NS, KK and HM analyzed the data. YS made the figures. YS designed, conceptualized and supervised the research. YS wrote the manuscript.

Data availability statement

The data that support the findings of this study are available in the supplementary material of this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.xxxxxxx.

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Figure legends

Figure 1. **Colony-formation assay of *S. cerevisiae* cells with and without white light illumination in the presence and absence of salts**

(A) A schematic drawing of the experimental setup. *S. cerevisiae* cells were grown on YPD agar plates at 30 ˚C for 24 hrs, and a 10-fold dilution series was prepared. (B) Colony-formation assay for WT yeast stain (BY4741) carrying the vector plasmid (pTOWug2-836). The assay was conducted with and without light (*hν*) in the presence and absence of 100 mM NaF, NaCl, NaBr and NaI. The intensity of the white light source (MAX-303: Asahi Spectra Co., Ltd., Japan) was adjusted to 12 mW/cm^2 at 515 nm (0.1 mW/cm^2 at 373 nm) using an optical power meter (3664, Hioki E.E., Japan) with an optical sensor (9742, Hioki E.E., Japan). (C) The estimated survival rates, represented as bars, were determined by dividing the colony-formation ability without light by that with light in the presence of 100 mM NaF, NaCl, NaBr and NaI. The data were presented as mean ± standard error (n = 4, *p < 0.001; Dunnett's test).

Figure 2. Wavelength-dependency of iodide-dependent growth inhibition and the action spectroscopy

(A) Colony-formation assay of *S. cerevisiae* cells under various wavelengths of light in the presence of 100 mM NaI. The light intensity at each wavelength was adjusted to 2.5 mW/cm^2 using band path filters. (B) The plot showing the colony-formation ability of *S. cerevisiae* cells (defined as viability) as a function of the wavelengths of light. The data points were fitted with a Gauss function.

Figure 3. Identification of adaptive genes

(A) The time-dependent changes in OD_{660} of *S. cerevisiae* cells in the SC medium. The cells were incubated at 30 ˚C in the presence (NaI) and absence (control) of 100 mM NaI with white light (12 mW/cm^2 at 515 nm, 0.1 mW/cm^2 at 373 nm). The photographs represent the culture solution incubated for 72 hrs. (B) The OD_{660} of *S. cerevisiae* cells in the YPD medium after 24 hrs of incubation with and with white light (12 mW/cm^2 and 2 mW/cm^2 at 515 nm). Statistical analysis was performed, and the results were shown as mean ± standard error (n = 4, *p < 0.05, *p < 0.01; Dunnett's test). (C) Overexpression profiling. The experiments were repeatedly five (5) and ten (10) times. Molecules with high scores were represented in the profiling results. (D) Colony-formation assay for the yeast stain lacking the OPY1 gene (opy1Δ) with and without white light (h*ν*) in the presence of 100 mM NaI. The intensity of the white light source (MAX-303: Asahi Spectra Co., Ltd., Japan) was adjusted to 12 mW/cm^2 (at 515 nm) using an optical power meter (3664, Hioki E.E., Japan) equipped with an optical sensor (9742, Hioki E.E., Japan). A 10-fold dilution series of *S. cerevisiae* cells grown on YPD agar plates at 30 ˚C for 24 hrs was used for the assay. (E) A hypothetical model for iodide-dependent UVA-triggered cell growth inhibition in *S. cerevisiae*. Iodide ions (I^-) absorb UVA light and form iodine molecule (I_2) within the cells.

The top three suppressors, OPY1, HEM1 and PAU11, have been identified, and their putative roles in growth inhibition are illustrated in the model.

Table 1. The identified adaptive genes against iodide-dependent UVA-triggered growth inhibition in *S. cerevisiae* cells

Systematic name	Standard name	Occupancy (%)	Brief description
YBR129C	OPY1	28.91	PtdIns(4,5)P_2 binding protein that negatively regulates the synthesis of PtdIns(4,5)P_2
YDR232W	HEM1	7.80	5-aminolevulinate synthase
YGL261C	PAU11	6.57	Putative protein of unknown function
YGR267C	FOL2	3.27	GTP-cyclohydrolase I, catalyzes first step in folic acid biosynthesis
YLR445W	GMC2	2.20	Protein involved in meiotic crossing over
YKR071C	DRE2	1.92	Component of the cytosolic Fe-S protein assembly (CIA) machinery
YDL120W	YFH1	1.84	Mitochondrial matrix iron chaperone
YPR193C	HPA2	1.75	Tetrameric histone acetyltransferase
YEL066W	HPA3	1.41	D-Amino acid N-acetyltransferase that detoxifies D-amino acids
YEL067C	-	1.35	Putative protein of unknown function

Figure 1

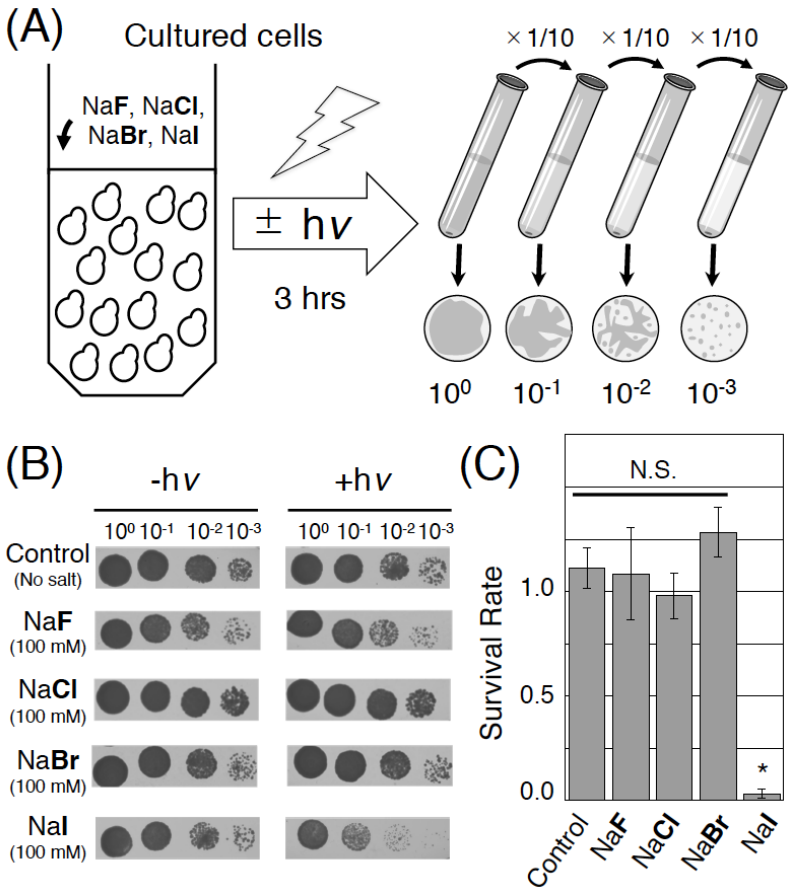

(A)
Cultured cells
NaF, NaCl,
NaBr, NaI
± hν
3 hrs
×1/10 ×1/10 ×1/10
10^0 10^-1 10^-2 10^-3
(B)
-hν
+hν
10^0 10^-1 10^-2 10^-3
Control
(No salt)
NaF
(100 mM)
NaCl
(100 mM)
NaBr
(100 mM)
NaI
(100 mM)
(C)
N.S.
Survival Rate
1.0
0.5
0.0
*
Control
NaF
NaCl
NaBr
NaI

Figure 2

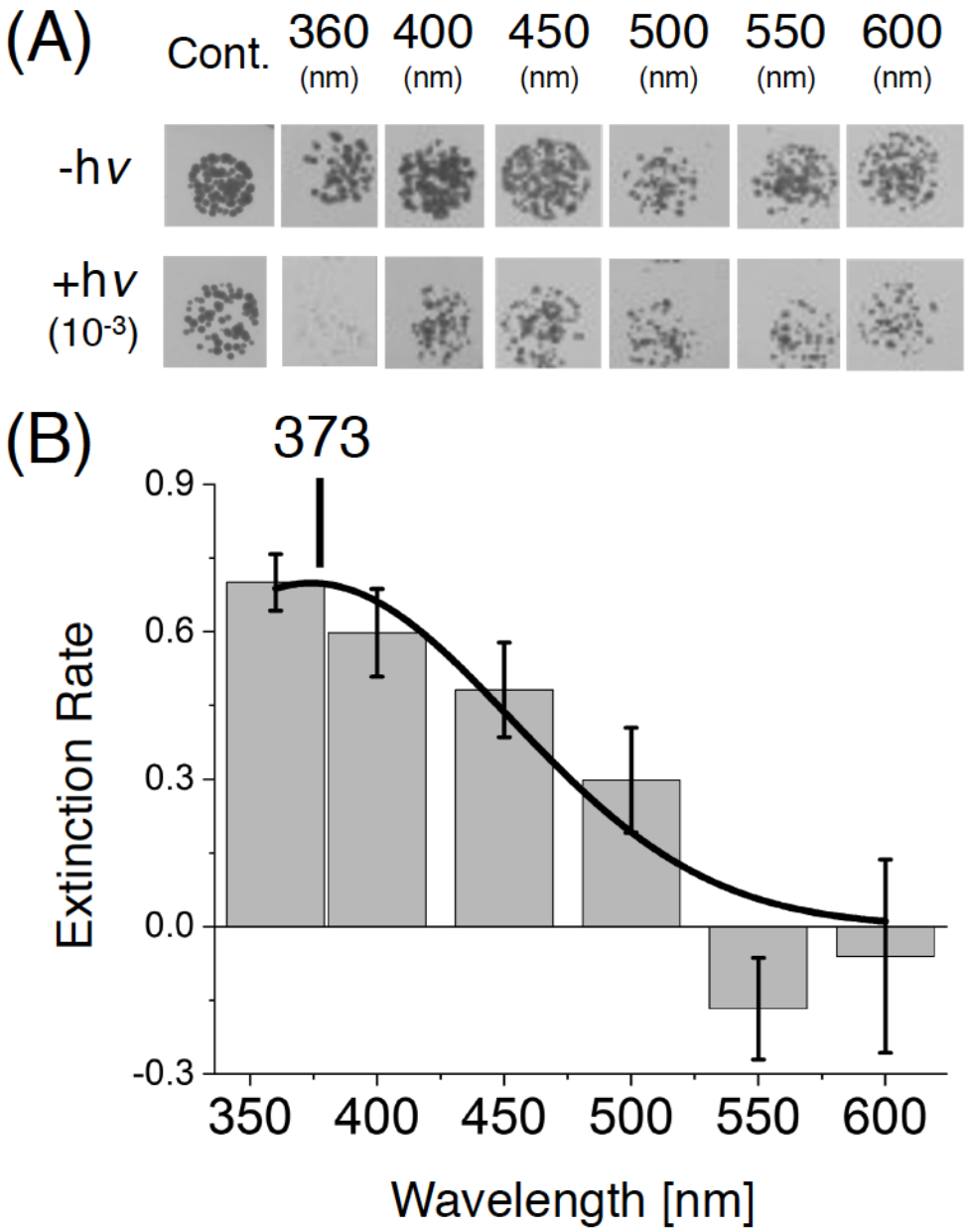
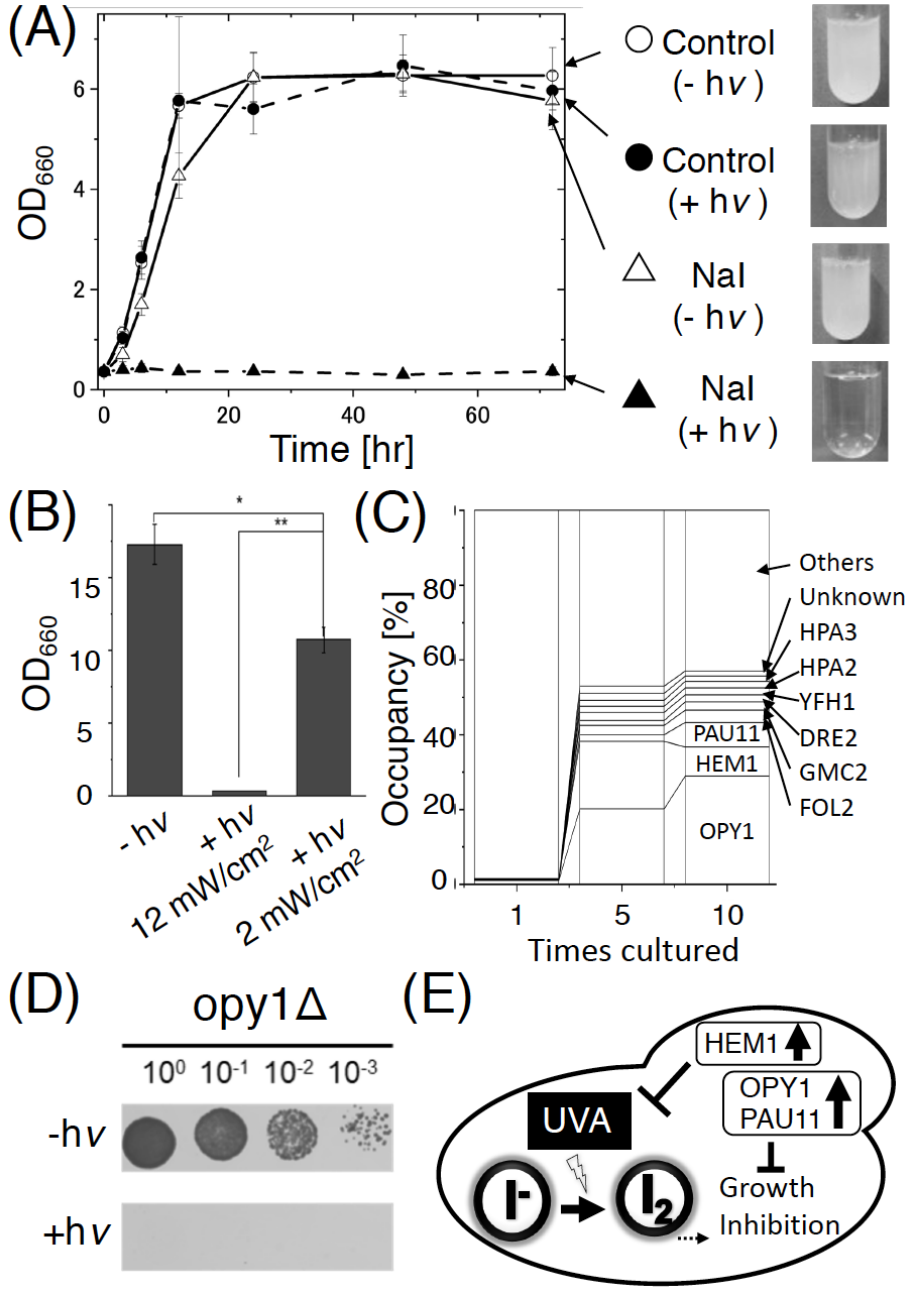

(A)
Cont.
360 (nm)
400 (nm)
450 (nm)
500 (nm)
550 (nm)
600 (nm)
-hν
+hν
(10-3)
(B)
373
Extinction Rate
0.9
0.6
0.3
0.0
-0.3
350
400
450
500
550
600
Wavelength [nm]

Figure 3


(A)
OD660
Time [hr]
Control (- hν)
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NaI (- hν)
NaI (+ hν)
(B)
OD660
- hν
+ hν 12 mW/cm2
+ hν 2 mW/cm2
(C)
Occupancy [%]
Times cultured
Others
Unknown
HPA3
HPA2
YFH1
DRE2
GMC2
FOL2
PAU11
HEM1
OPY1
(D)
opy1Δ
10^0 10^-1 10^-2 10^-3
-hν
+hν
(E)
HEM1
OPY1
PAU11
UVA
Growth Inhibition