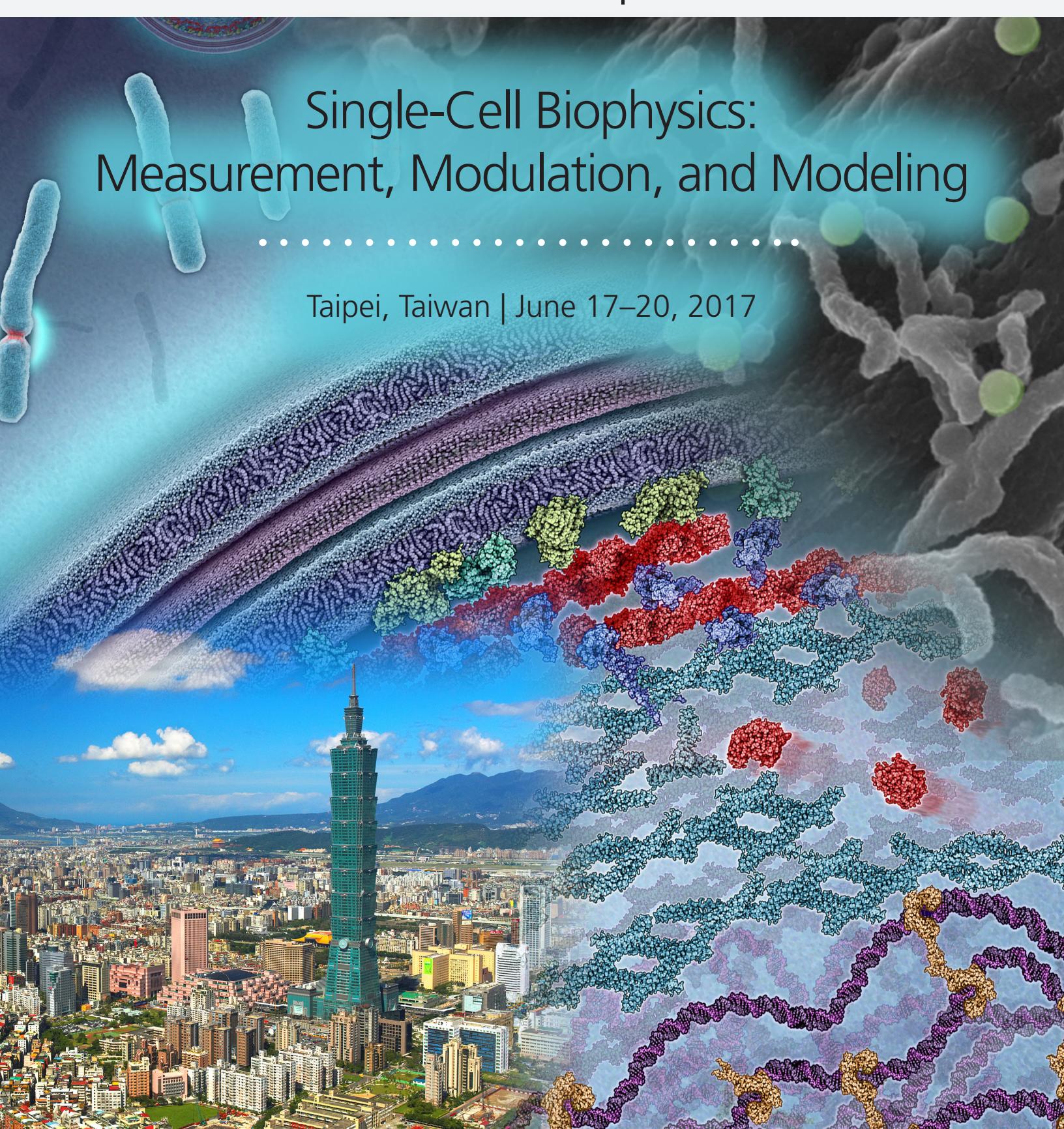


# Single-Cell Biophysics: Measurement, Modulation, and Modeling

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**15-POS      Board 8****Information Transduction Capacity of Mitochondrial Retrograde Signaling****Shao-Ting Chiu<sup>1</sup>, Jun-Yi Leu<sup>2</sup>, An-Chi Wei<sup>1</sup>.**<sup>1</sup>National Taiwan University, Taipei, Taiwan, <sup>2</sup>Academia Sinica, Taipei, Taiwan.

Mitochondrial retrograde signaling takes part in the communication between mitochondria and the nucleus, which is essential for mitochondrial quality control and maintaining energy production in eukaryotic cells. However, it is unclear how many different mitochondrial statuses can be distinguished via mitochondrial retrograde signaling under inevitable biochemical noise. To address this issue, we used the budding yeast *S.cerevisiae* as a model organism, and investigated the information transduction capacity of the retrograde pathway. Mitochondrial membrane potential ( $\Delta\Psi m$ ) and translocation of Rtg3p/Rtp1p are considered to be the input and output of this noisy communication channel. We further used the parallel Gaussian channel with a common power constraint, based on the information theory, to model the retrograde signaling and to optimize the information-transmission rate based on the Kuhn-Tucker conditions and the water-filling method. The result implies the optimized  $\Delta\Psi m$  probability distribution that maximizes the information-transmission rate under a power constraint contributed by the limited concentration of Rtg3p and Rtg1p. Therefore, the receiver located in the nucleus can distinguish maximum statuses of mitochondrial quality by the retrograde signaling pathway under the optimized  $\Delta\Psi m$  probability distribution. In this study, we have provided an informatics view of mitochondrial retrograde signaling.

# The Information Transduction Capacity of Mitochondrial Retrograde Signaling

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## Introduction

Mitochondrial retrograde signaling takes part in the communication between mitochondria and the nucleus, which is essential for mitochondrial quality control and maintaining energy production in eukaryotic cells (Fig 1.). However, it is unclear how many different mitochondrial statuses can be distinguished via mitochondrial retrograde signaling under inevitable biochemical noise. To address this issue, we proposed a noisy communication channel and used budding yeast to investigate the retrograde response to damaged mitochondria.

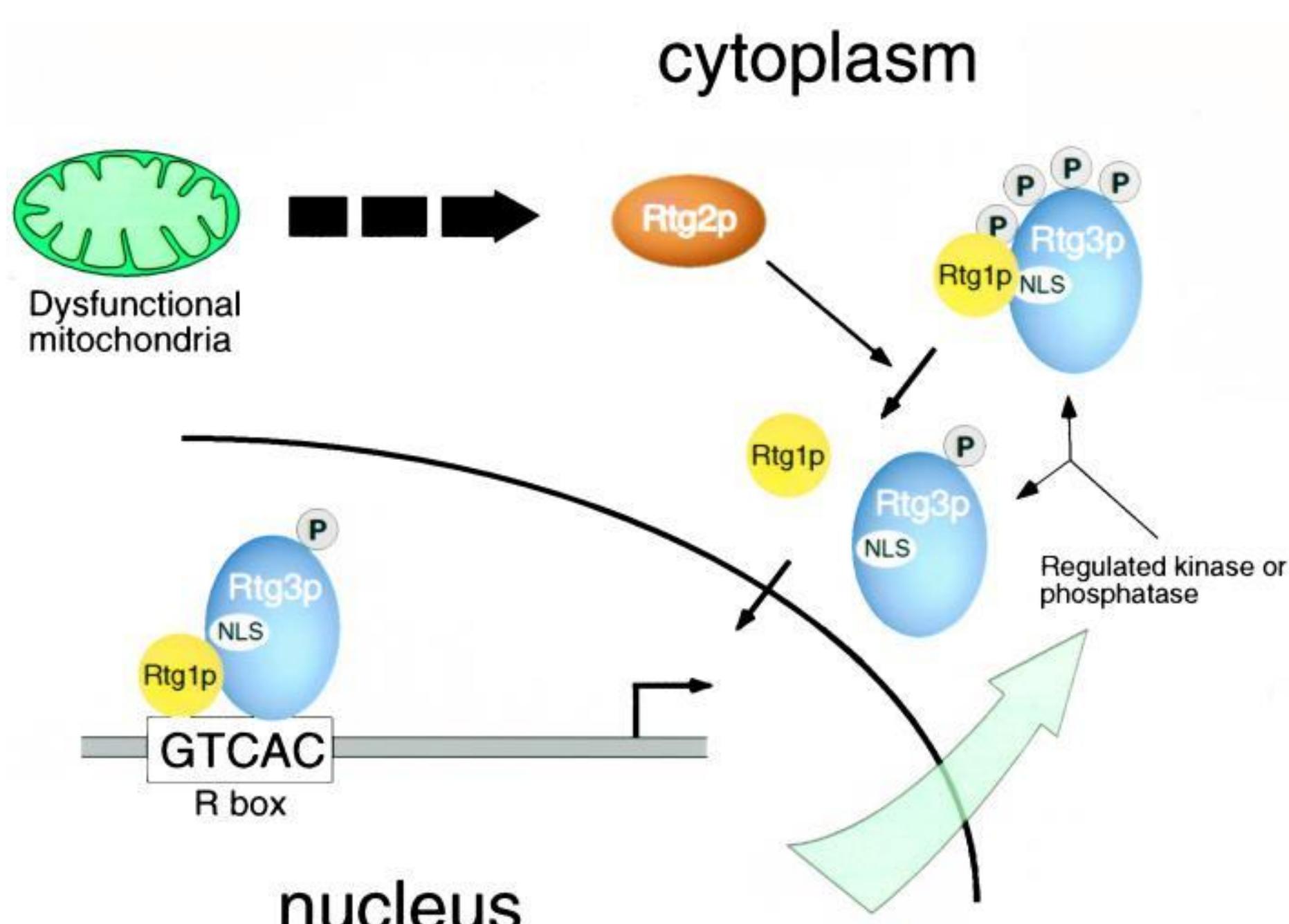


Fig 1. Mitochondrial retrograde signaling in budding yeast.  
(From Sekito T et al, 2000).

## Materials & Methods

### 1. Strains of *S. cerevisiae*

RTG1-GFP-his BY4741 X HTB1-mcherry-ura W303

RTG2-GFP-his BY4741 X HTB1-mcherry-ura W303

### 2. Image Acquisition

A DeltaVision microscope equipped with CoolSNAP HQ2 CCD. Image was acquired z stacks consisting of 30 slides in FITC and TRITC channels.

### 3. Chemical

Carbonyl cyanide 4-(trifluoromethoxy)phenylhydrazone (FCCP, uncoupler)  
MitoTracker Red (Mitochondrial dye)

### 4. Program and Image Processing

Python 2, Jython, Matlab and MitoGraph V 2.0,

## Model

Mitochondrial damage signal(s) and Rtg3p/Rtp1p translocation are considered to be input and output of the noisy communication channel (Fig 2.). We further used the parallel Gaussian channel with a common power constraint, based on information theory, to model the retrograde signaling from mitochondrial network to nucleus as well as to predict the information-transmission rate.

$$\begin{aligned} I(S; R) &= I(S_1, \dots, S_{N_{\text{mito}}}; R) \\ &= h(R) - h(R|S_1, \dots, S_{N_{\text{mito}}}) \\ &= h(R) - h(\sum_i S_i + Z_i | S_1, \dots, S_{N_{\text{mito}}}) \\ &\leq E[R^2] - h(\sum_i Z_i), \end{aligned}$$

where  $I$ , mutual information;  $S_i$ ,  $i^{\text{th}}$  mitochondrial damage signal;  
 $N_{\text{mito}}$ , number of mitochondria;  $R$ , retrograde response and  $R = \sum_i S_i + Z_i$  in parallel Gaussian channel;  $Z_i = \mathcal{N}(0, \alpha L_i)$ ;  $L_i$ , distance between  $i^{\text{th}}$  mitochondrion and nucleus;  $\alpha$ , noise coefficient.

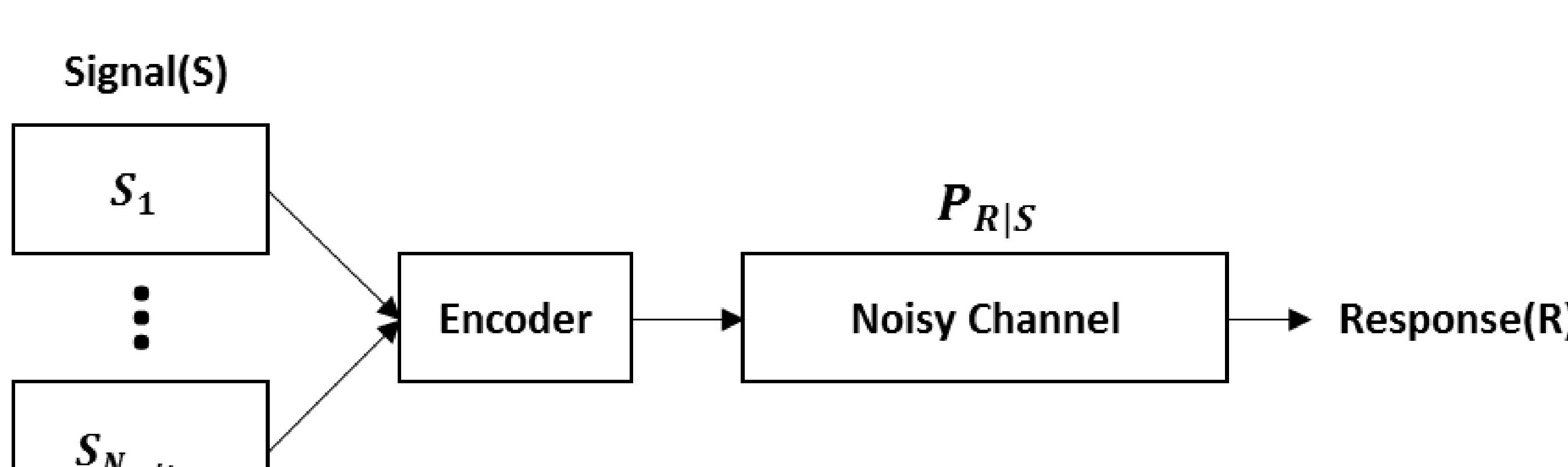


Fig 2. Diagram of the mitochondrial retrograde signal as a noisy communication channel.

## Results

1. Mitochondria in yeast form a three-dimensional network structure localized to the periphery of the cell (Fig 3.).

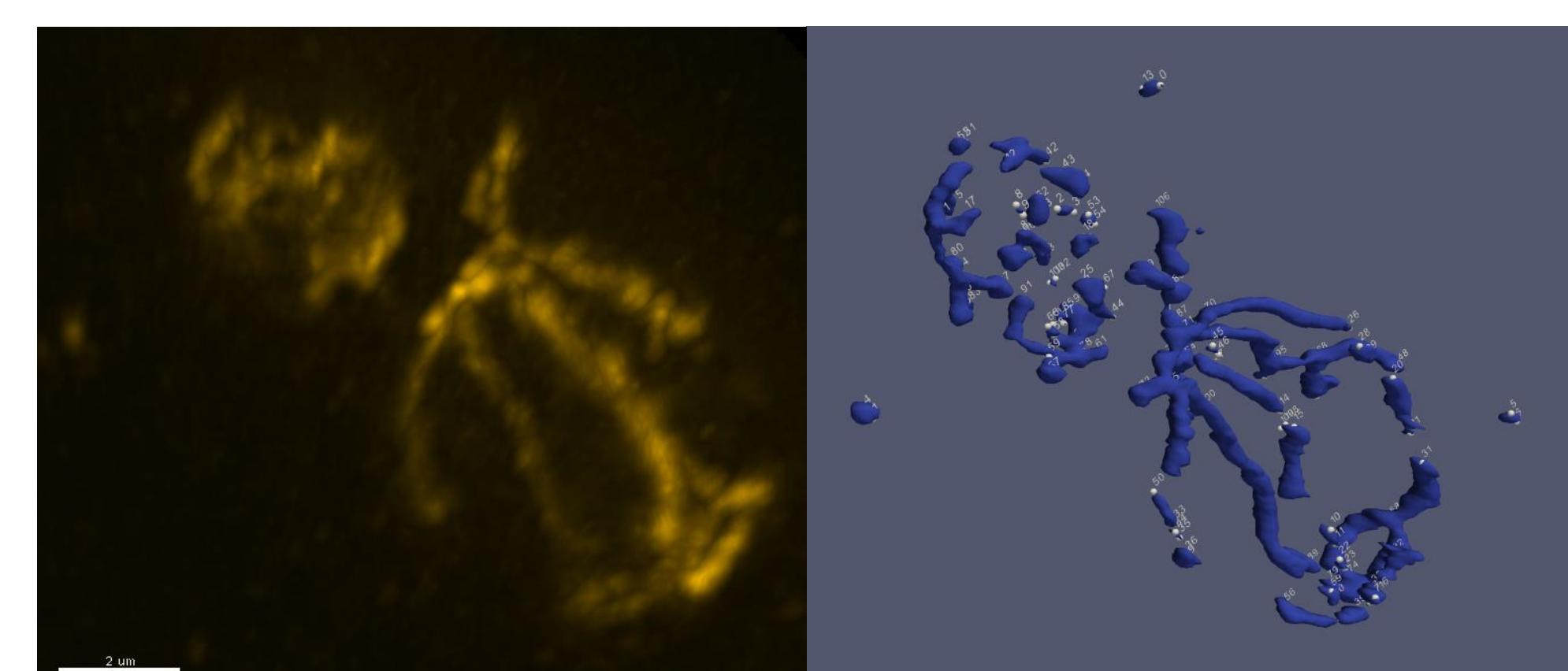


Fig 3. Mitochondrial network. (a) 3D mitochondrial structure labeled with MitoTracker Red (b) Mitochondrial network

2. FCCP, mitochondrial uncoupler, induces Rtg1p-GFP translocation from cytosol into nucleus, and Rtg2p is insensitive to the treatment (Fig 4.).

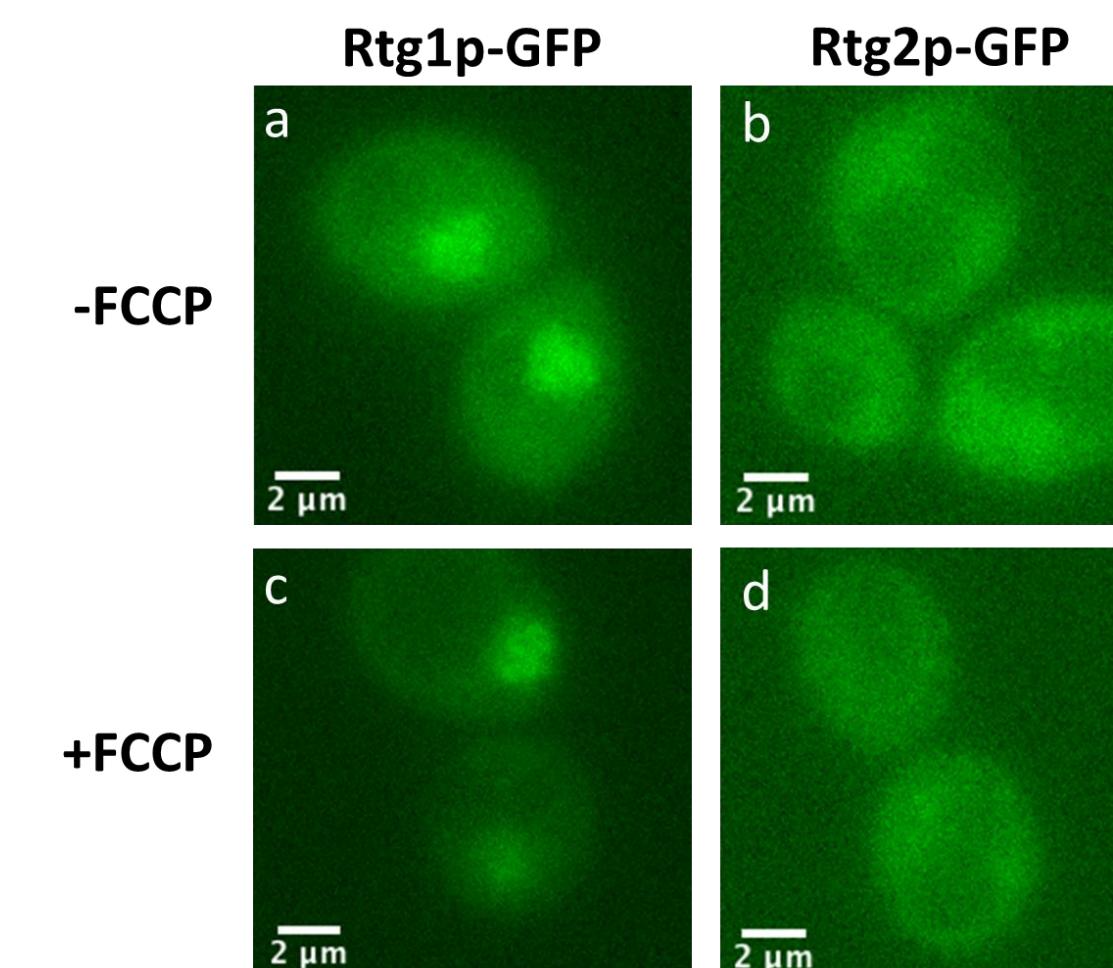


Fig 4. (a)(c) Subcellular localization Rtg1p which transfers to nucleus in FCCP treatment. (b)(d) Subcellular localization of Rtg2p which is insensitive to FCCP treatment (-FCCP: 0 μM FCCP; +FCCP: 15 μM FCCP)

3. Rtg1p is sensitive to FCCP treatment compared to Rtg2p (Fig 5.).

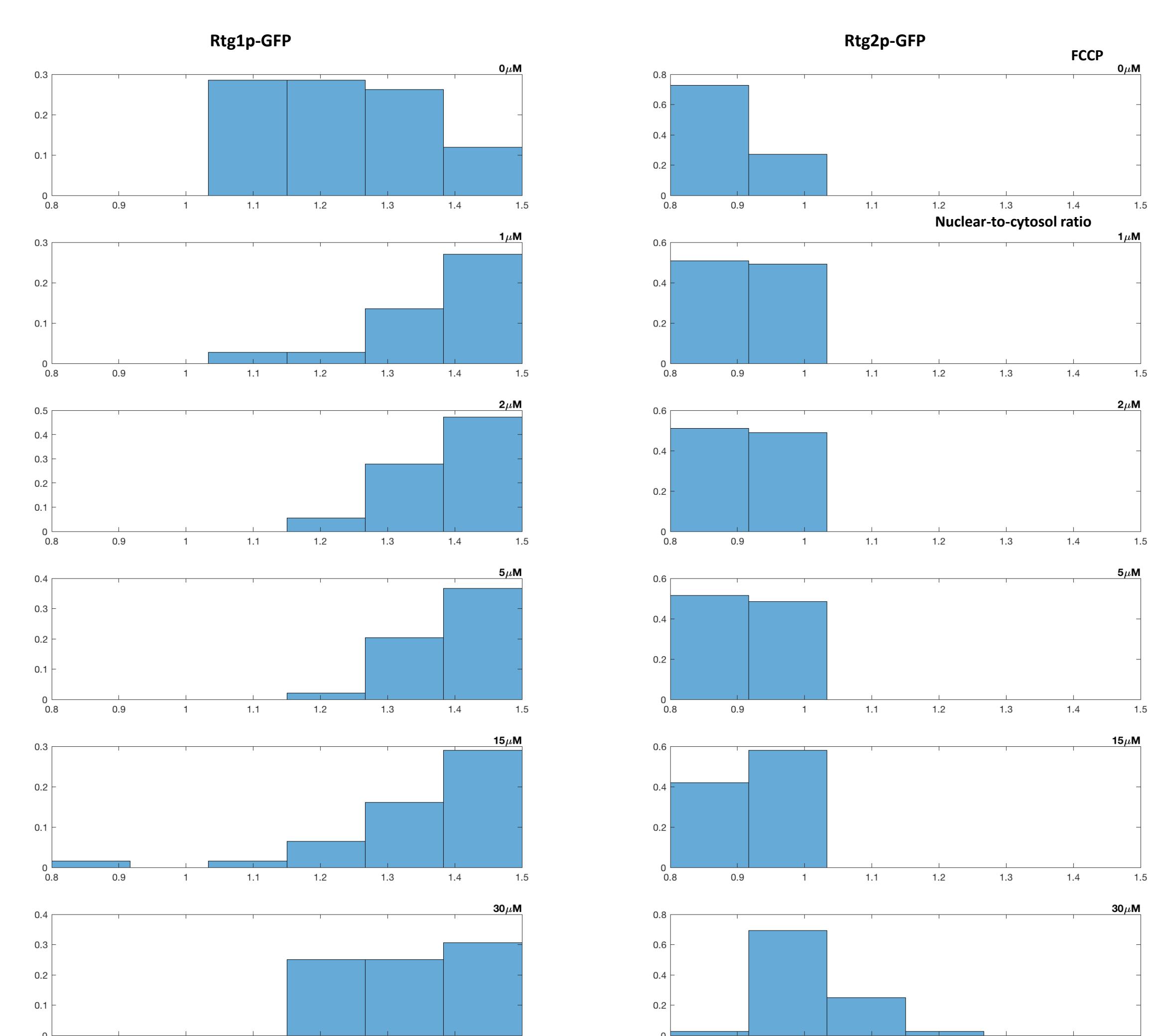


Fig 5. The histogram of FCCP dose response. The response is normalized by nuclear-to-cytosol ratio in GFP intensity at excitation of 488nm (number of samples  $\geq 25$ ). Besides, nucleus was labeled with Htb1-mCherry.

## Discussion & Conclusion

The spectral distribution of mitochondria indicate  $L_i$ , distance between  $i^{\text{th}}$  mitochondrion and nucleus, is not uniformly distributed. According to the model, the channel capacity is related to the 2<sup>nd</sup> moment of the retrograde response. To obtain the optimized information-transmission rate, different concentrations of FCCP, mitochondrial uncoupler, were used to induce retrograde response. The preliminary results imply that Rtg1-GFP is sensitive to FCCP within 30 μM, and the response of each cell is stochastic.

## References

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