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Article

A systematic study of the determinants of protein abundance memory in cell lineage

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ABSTRACT

Proteins are essential players of life activities. Intracellular protein levels directly affect cellular functions and cell fate. Upon cell division, the proteins in the mother cell are inherited by the daughters. However, what factors and by how much they affect this epigenetic inheritance of protein abundance remains unclear. Using both computational and experimental approaches, we systematically investigated this problem. We derived an analytical expression for the dependence of protein inheritance on various factors and showed that it agreed with numerical simulations of protein production and experimental results. Our work provides a framework for quantitative studies of protein inheritance and for the potential application of protein memory manipulation.

1. Introduction

Proteins are important functional players in cells, whose abundances directly affect physiological functions and the fate of the cells [1–4]. Since proteins are directly passed on from parent to progeny cells in each cell division, there are correlations in the abundance of each type of proteins within a cell lineage [5]. Such correlations may further lead to similar cell behavior within the lineage, thereby playing an important role in inheritance and environmental adaptation. The progeny cell inherits more than just the specific protein molecules from the parent cell; it also inherits a large number of cellular components, including the transcription and translation machineries, which complicates the protein abundance correlation in a cell lineage. Both the strength and the time scale of protein abundance memory in a cell lineage significantly depend on individual cases [6,7]: while the abundance memory of cyclins in budding yeast lasts less than one cell cycle [8], the memory of the expression of the lac gene in *E. coli* cell lineages lasts for many generations [1].

Recently, an increasing number of studies have suggested that the abundance memory of certain proteins in cell lineages was likely an active and flexible strategy for cells to adapt to changing environments, rather than a simple by-product of cell division [1,5,7,9]. For example, it was suggested that a long memory of protein abundance may help cell adapt to a fluctuating environment [1]. In addition, some proteins inherited from a parental cell can directly affect the apoptotic probability of the progeny cells [10,11].

Given the importance of protein inheritance in cell lineages, increasing theoretical and experimental efforts have been devoted to study the effects of different factors on protein inheritance and its potential impact on cellular behavior [1,5,12,13]. Such investigations undoubtedly contributed to our understanding of many issues related to protein inheritance. However, most studies thus far have focused on the inheritance of a particular protein or the contribution of one or a few specific factors to protein inheritance [1,10]. In reality, protein inheritance in the cell lineage is often affected by multiple factors at the same time. Do different factors have different effects on protein inheritance? Are the influences of these factors independent or synergetic? What is the quantitative relationship between the protein inheritance and the various influencing factors? The lack of answers to these questions has hindered our understanding of the general phenomenon of protein inheritance.

In this study, by combining theoretical approach and quantitative experiments, we systematically investigated the contributions of various factors to protein memory along the cell lineage. We constructed a simple model and, for the first time, gave an analytic formula for the dependence of protein memory on various factors: protein synthesis, protein degradation, volume ratio for uneven division, doubling time, intrinsic noise, extrinsic noise, partition

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noise during cell division, and the time scales of different noises. We validated the theory by performing both computer simulations and quantitative experiments.

2. Materials and methods

2.1. Stochastic simulations of the model

All simulations were performed using MATLAB (MathWorks). Stochastic simulation was performed using the Gillespie Algorithm [14–16]. To incorporate the extrinsic noise, the fluctuating production rate of protein was modeled as one "species". The system had two variables: the production rate number $K_p(t)$ and the protein number $S(t)$. The numbers of the protein and the production rate were updated according to the propensity based on Gillespie Algorithm.

The propensity was derived from the deterministic equations by incorporating a system size Ω through the conventional Van Kamppen expansion [17] and a rescaled constant for the protein production rate number. For the model simulation with the extrinsic noise incoporated into the production rate, the propensity function at time t was $[k_{pp}\Omega, 1/\tau, a_1K_p(t), S(t)k_d]$, where $k_{pp}\Omega$ and $1/\tau$ are the birth and death rates of protein production rate number $K_p(t)$, $a_1K_p(t)$ and k_d are the birth and death rates of protein number $S(t)$. In the steady-state, we had $\langle K_p(t)\rangle = k_{pp}\Omega\tau$ for average production rate number and $\langle S(t)\rangle = a_1k_{pp}\Omega\tau/k_d$ for the average protein copy number. We also had $k_p(t) = K_p(t)/\Omega$ for the protein production rate and $X(t) = S(t)/\Omega$ for protein concentration.

After sufficient time simulation, protein copy number reached a steady state, and the generated protein level data were recorded per cell doubling time T. The process was simulated 2000 times. Then, the Pearson correlation was calculated based on the recorded proteins.

2.2. Single-cell measurements using time-lapse microscopy

Standard methods were used throughout the study. To prepare the cells for time-lapse microscopy, we inoculated congenic W303 (*MATa his3-11,15 trp1-1 leu2-3 ura3-1 ade2-1*) cells from a colony into liquid SD, grew the cells for 12 h, and then diluted and cultured them for 12 h. Next, the cells that grew exponentially in SD liquid medium were seeded into a microfluidic chip in the same medium. For each experiment, stacks of 9 images were acquired every 5 min with 30 ms exposure for the bright-field channel, and 50 ms for the red channel and green channels. Microcolonies were tracked throughout the time series by identifying overlapping areas. Cell segmentation and tracing were performed based on bright field images and automatically obtained using the MATLAB customized software cellseg, which we previously developed [18,19]. Fluorescence quantification was performed using cellseg and ImageJ with Image5D plugin. The maximum intensity projection of z-stacks was reported for experiments to obtain the protein intensity.

2.3. Quantification of protein half-lives by FACS

W303 yeast strain with *Adh1Pr-GFP* (expressing GFP protein) or *Adh1Pr-GFP-PEST* (expressing GFP protein with a PEST tag) were grown in 5 mL of synthetic medium with 2% (w/v) glucose overnight at 30 °C and rotating. The overnight culture was diluted to an OD_{600} value of 0.1 in 20 mL of fresh medium and incubated until the cells reached the mid-logarithmic growth phase. Cycloheximide (translation inhibitor [20,21]) was added to a final concentration of 200 μg/mL, which is sufficiently high to inhibit protein synthesis without inducing a critical growth defect during the experiment. Next, 0.5 ml of yeast cells were quickly obtained from the culture every 10 min and 4.5 mL PBS buffer was added. FACS was performed to determine the protein fluorescence.

3. Results

3.1. Memory of protein abundance along the cell lineage with intrinsic noise

To investigate the memory of protein abundance along the cell lineage, we first constructed a simple model in which the rate of protein deposition is determined by the rates of protein synthesis (k_p) and degradation/dilution (k_d). The degradation/dilution rate k_d includes two parts (i.e., $k_d = k_{dil} + k_{deg}$): regulated degradation (k_{deg}) and dilution rate (k_{dil}) due to cell growth and division [22]. We considered both symmetrical and asymmetrical division by introducing the division size ratio α, which is defined as the ratio of corresponding volume to the total volume (i.e., $\frac{V_M}{V_M+V_D}$ for mother/lager cells, and $\frac{V_D}{V_M+V_D}$ for daughter/smaller cells). As a result, $k_{dil} = -\ln(\alpha)/T$, where T is the cell doubling time [5]. We assumed that the system was in steady state, and only the mother and daughter lineages were discussed for simplicity (Fig. 1).

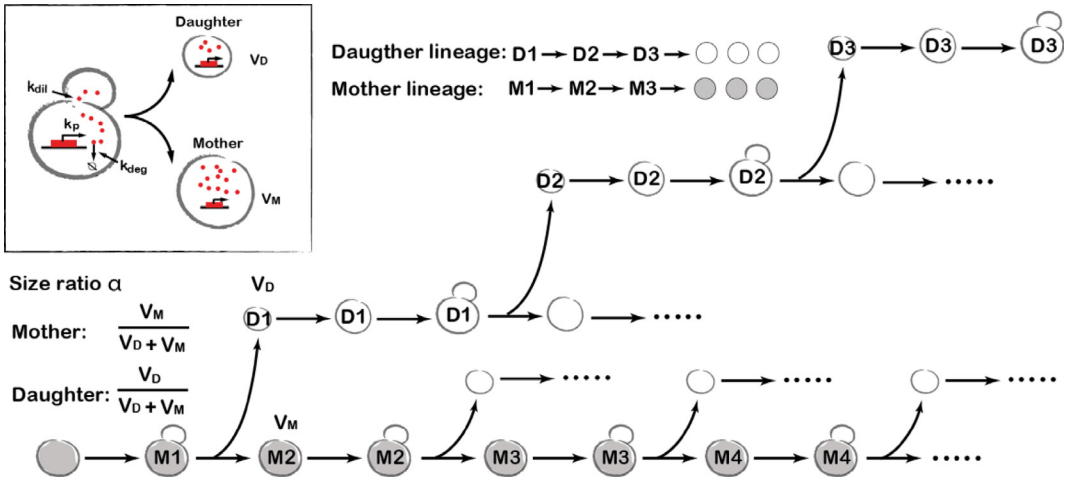

Fig. 1. Schematic view of the protein inheritance model in a cell lineage. The parameter k_p represents the protein production rate, while k_{deg} and k_{dil} represent the degradation rate and the dilution rate, respectively. The cell size ratio is the ratio of corresponding volume to the total volume (i.e. $\frac{V_M}{V_M+V_D}$ for mother cells, and $\frac{V_D}{V_M+V_D}$ for daughter cells).

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