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Dynamics of macroautophagy: Modeling and oscillatory behavior

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ABSTRACT

We propose a model for macroautophagy and study the resulting dynamics of autophagy in a system isolated from its extra-cellular environment. It is found that the intracellular concentrations of autophagosomes and autolysosomes display oscillations with their own natural frequencies. Such oscillatory behaviors, which are interrelated to the dynamics of intracellular ATP, amino acids, and proteins, are consistent with the very recent biological observations. Implications of this theoretical study of autophagy are discussed, with regard to the possibility of guiding molecular studies of autophagy.

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1. Introduction

Autophagy is evolutionarily conserved and strictly regulated mechanism for the sequestration of cytoplasmic materials into lysosomes. It is classified into several main classes depending on how cytoplasmic materials are delivered from cytosol to lysosomal lumens: (macro)autophagy, microautophagy, chaperone-mediated autophagy, crinophagy, and so on. Often autophagy stands for macroautophagy which is characterized by the double membranes, called phagophores, which engulf cytoplasmic materials before lysosomal sequestration [1]. Usually, autophagy is regarded as a means of protein recycling for the self-energy production during energy starvation [2–9]. In eukaryotic cells, however, it has achieved extra fundamental functions such as regulation of homeostasis and ultimately complex signaling pathways which are essential for life and death of cells [10].

Autophagy is an ongoing process at a steady pace. Nevertheless, it plays different roles, depending on the degree of its activation. Constitutive (basal-level) autophagy protects cells from stress, including starvation, oxidative stress, or other harmful conditions. In this way, it contributes to health and longevity via important housekeeping and quality control functions. On the other hand, excessive-level autophagy destroys important regulatory molecules and micro-organelles, and eventually induces spontaneous cell death [10]. Therefore, proper regulation of autophagy is essential for maintaining

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normal cellular functions and human health. Further, regulation and control of autophagy should have significance in the realization of drug development or treatment methods.

Even though physiological and molecular-level study of autophagy reveals basic mechanism for the regulation of autophagy and its biological roles, details of autophagy induction, multi-step maturation from autophagosomes to autolysosomes, and intralysosomal hydrolysis remain unexplored. Accordingly, dynamics of autophagosomes and autolysosomes *in vivo*, i.e., regulation and control of autophagy by various regulators in and out of cells is not fully understood. On the other hand, it is conceivable that the life phenomena at the fundamental level should be probed on the basis of complexity. In particular, cell-level phenomena may be properly understood in terms of emergent properties from nonlinear interactions among sub-cellular components, rather than linear summation of them [11]. In understanding the mechanism of autophagy, it is thus necessary to analyze the complex nature of intra- and extra-cellular signals and the roles of molecular components involving genes. Indeed it might have been noticed that the mechanism of autophagy and its role in the cell can be studied in terms of its organized complexity [12]. In other words, we need to understand the functions and inter-correlations of individual components and to comprehend the origin of complex behavior and emergent complexity, based on the research results from biochemistry, cell biology, molecular biology, and physiology.

This study attempts to examine the basic mechanism of autophagy from a biophysical viewpoint. For this purpose, we construct a mathematical model for autophagy and examine the dynamic behavior of the system. The obtained results lead us to understand the dynamics of autophagosomes and autolysosomes, which are morphologically detected in the autophagic process.

2. Dynamics of intracellular proteins, amino acids, and ATP

In this model a virtual cell is regarded as a closed system. It is therefore assumed that there is no material movement, namely, no influx or efflux of amino acids and ATP into and out of the cell. In addition, we do not consider any periodic variations of amino acid and ATP concentrations due to intracellular metabolism other than autophagy, thus disregarding external driving on the system.

For simplicity, we define resident proteins S_1 as the proteins and organelles which conduct normal functions in the cell. We further assume that they are made from normal folding intermediates transcribed normally into RNA from DNA and translated into the proteins, and denote their concentration by C_S^1. On the other hand, as abnormal proteins S_2, we refer to the proteins and organelles which conduct abnormal functions in the cell, and assume that they are made from two distinct sources: either from misfolded proteins and peptides, caused by genetic variants and mutations or intracellular conditions, or from resident proteins and organelles, damaged or aged by harmful conditions.

Although the portion and production rate of S_2 vary with species as well as the internal and external environments, in this model we regard both the abnormal protein production rate in the process of protein synthesis and the damaging rate from S_1 to S_2 as constants, specifically, taking the former to be $10^{-4}\,\mathrm{h}^{-1}$ (i.e., $0.01\%\,\mathrm{h}^{-1}$) of the total protein synthesis and the latter to be $0.0015\,\mathrm{h}^{-1}$. Incorporating these, we describe the dynamics of S_1 by

$$\frac{\mathrm{d}C_S^1}{\mathrm{d}t} = (1-\alpha)S - D_1 - \beta C_S^1 - P_1 C_S^1, \tag{1}$$

and that of S_2, with C_S^2 denoting the concentration of the abnormal proteins, by

$$\frac{\mathrm{d}C_S^2}{\mathrm{d}t} = \alpha S - D_2 + \beta C_S^1 - P_2 C_S^2, \tag{2}$$

where S represents the protein synthesis rate and α is the fraction of S_2 in the total protein synthesis from DNA. Accordingly, S_1 and S_2 are produced at the rates of $(1-\alpha)S$ and αS, respectively. Further, D_i (for $i = 1, 2$) represents the non-autophagic degradation rate of S_i, β the rate constant of transformation from S_1 to S_2, and P_i (for $i = 1, 2$) the specific rate for autophagosome formation from S_i. Base run parameter values are taken to be $\alpha = 1.00 \times 10^{-4}$ and $\beta = 1.50 \times 10^{-3}\,\mathrm{s}^{-1}$.

In addition, we note that the amino acid concentration may increase due to autophagic intralysosomal hydrolysis or non-autophagic processes such as de novo synthesis of amino acids and non-autophagic protein degradation. On the other hand, it is assumed to reduce only via protein synthesis. For simplicity, we suppose that an average hepatocyte protein molecule is composed of 500 amino acid residues, implying that 500 amino acids are consumed for the synthesis of a protein molecule. However, since the efficacy of protein recycling is presumably less than 100%, the increased amount of amino acids by intralysosomal hydrolysis or non-autophagic protein degradation should be less than 500 molecules in the degradation of one protein molecule. The dynamics of intracellular amino acids, the concentration of which is denoted by C_a, is thus described by

$$\frac{\mathrm{d}C_a}{\mathrm{d}t} = M_e + \mu_a H \sum_{i=1}^{2} C_L^i + \mu_d \sum_{i=1}^{2} D_i - \mu_s S, \tag{3}$$

where M_e represents the net intracellular amino acid generation rate due to various kinds of intracellular metabolism, μ_a and μ_d measure the mean numbers of amino acids produced from autophagic degradation and from non-autophagic degradation

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