Journal of Theoretical Biology 365 (2015) 190–196

Contents lists available at ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

Modeling of sensing potency of cytoskeletal systems decorated with metabolic enzymes

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HIGHLIGHTS

- The dynamic cytoskeleton interacts with proteins that are involved in metabolic or signaling pathways.
- Mathematical models for the interactions of metabolic pathways and microtubule assembly are evaluated.
- Functional consequences of these interactions are predicted in distinct situations.
- A kinetic model with relevant parameters reproduces altered tubulin assembly caused by a glycolytic enzyme.
- A mechanistic description allows the quantification of how cells sense the state of pathways.

ARTICLE INFO

Article history:
Received 2 July 2014
Received in revised form
11 September 2014
Accepted 15 October 2014
Available online 24 October 2014

Keywords:
Mathematical model
Metabolism
Microtubule
Sensing

ABSTRACT

The highly dynamic cytoskeleton interacts with enzymes and other proteins that are involved in metabolic or signaling pathways. These interactions can influence the structural and functional characteristics of the partners at the microscopic level of individual proteins and polymers. In this work the functional consequences of such interactions have been studied at the macroscopic level in order to evaluate the integrative and regulatory roles of the metabolic pathways associated with the microtubule cytoskeleton. Here we present mathematical models of the interactions between a hypothetical metabolic pathway and microtubule assembly, and explore for the first time the functional consequences of these interactions in distinct situations. The models include kinetic constants of the individual steps and testable, relevant parameters which allow the quantification of the coupled processes at the microscopic and macroscopic levels. For example our kinetic model for the self-assembly of microtubules reproduces the alteration of the time-dependent turbidity caused by pyruvate kinase binding. Our data reveal the power of a mechanistic description of a filamentous system to explain how cells sense the state of metabolic and other pathways.

1. Introduction

Metabolism in cells can be controlled according to the concept of cytoskeleton-driven modulation of enzymatic fluxes (Aon and Cortassa, 1997; Aon et al., 2000; and references therein) and/or metabolic channeling, which facilitates the intermediate transfer between the associated enzymes (stable or transient enzymatic complexes) (Ovádi and Srere, 2000, and references therein). There has been extensive theoretical and experimental analysis of the idea that the binding of metabolic enzymes to the cytoskeletal filaments affects their catalytic activity to cause significant alterations at microscopic and macroscopic levels; in addition, the sensitivity of these hetero-associations is modulated by factors such as the activity of the enzyme, its phosphorylation state, and interactions with other proteins (Aon and Cortassa, 2002, and references therein).

During the past decades an advanced level in the mathematical modeling of the main metabolic pathways has been achieved for different cell types (http://www.jjj.bio.vu.nl/cgi-bin/processModelSelection.py). One of these well-characterized pathways is glycolysis where the enzymes, in addition to their glycolytic activities, have structural functions that depend on their direct associations with the cytoskeletal networks (Aon and Cortassa, 2002; Cassimeris et al., 2012; Knull and Walsh, 1992; Ovádi et al., 2004; Sola-Penna et al., 2010). Although these models successfully characterize stationary and time-dependent metabolic states, many of them disregard the influence of an enzyme binding to

Abbreviations: PEP, phosphoenolpyruvate; PK, pyruvate kinase

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http://dx.doi.org/10.1016/j.jtbi.2014.10.018
0022-5193/

the cytoskeleton. Relevant papers have been published in this field in the last decade by the Aon group (Aon et al., 1996, 2000; Aon and Cortassa, 1997, 2002; Cortassa et al., 1994). A mathematical model was formulated for the coupling of microtubular proteins to the glycolytic pathway and its branches: the Krebs cycle, ethanolic fermentation, and the pentose phosphate pathway in yeast (Aon and Cortassa, 2002). It was suggested that tubulin partitioning between dimer and polymer pools might regulate multiple steps in metabolism (Cassimeris et al., 2012), and that the rates of individual enzymatic steps and metabolite concentrations change with the polymeric status of microtubules throughout the metabolic network (Aon and Cortassa, 2002).

The multifunctional microtubule network, an integral part of the eukaryotic cytoskeleton along with actin and intermediate filaments, plays crucial roles in cell division, motility, intracellular trafficking and the maintenance of cell shape and polarization (Conde and Caceres, 2009; de Forges et al., 2012). Cytoskeletal tubulin is also involved in the regulation of the voltage-dependent anion channel at the mitochondria–cytosol interface which ensures normal metabolite and energy exchange between mitochondria and cytoplasm through the permeability of the mitochondrial outer membrane (Rostovtseva and Bezrukov, 2012). The functionally important, reversible blockage of voltage-dependent anion channel by nanomolar to micromolar dimeric tubulin makes the mitochondrial outer membrane impermeable to ATP and other multi-charged anions (Rostovtseva et al., 2008).

Microtubules are known to interact with various glycolytic enzymes (Aon and Cortassa, 2002; Knull and Walsh, 1992; Sola-Penna et al., 2010). These transient interactions influence the structural and functional characteristics of both partners resulting in alterations in microtubule ultrastructure and enzyme activities (Ovádi et al., 2004). The binding of phosphofructokinase to microtubules results in the periodic cross-linking of microtubules and decreased enzyme activity due to the dissociation of the active tetrameric enzyme. The interaction between hexokinase and microtubules increases the activity of the enzyme without affecting the microtubule network, while the binding of pyruvate kinase impedes microtubule assembly without influencing the enzyme activity (Ovádi et al., 2004). While the interactions between glycolytic enzymes and cytoskeletal proteins have been intensively studied, much less is known about the consequences of the mutual interactions on the metabolic fluxes or the dynamics of the filamentous systems; one exception being the cardiomyocyte where microtubule stability was found to affect glycolysis during the early stages of hypoxia (Teng et al., 2010).

In the course of the microtubule assembly the head-to-tail association of tubulin heterodimers (composed of α and β tubulin monomers) into microtubules is coupled with multiple associations and various posttranslational modifications (Conde and Caceres, 2009; de Forges et al., 2012). Dynamic instability is a characteristic behavior of microtubules: an individual microtubule alternates between distinct phases of growth, pause and shrinkage, separated by rescue and catastrophe events, while the total amount of microtubules remains almost constant (Mitchison and Kirschner, 1984). This dynamic instability is central to the function of microtubules allowing them to reorganize rapidly, and to differentiate spatially and temporally in accordance with environmental signals and factors.

Reversible and irreversible nucleation–growth models, however, have been developed for tubulin polymerization based on Oosawa's classical model (Oosawa and Kasai, 1962; Morris et al., 2009; Flyvbjerg et al., 1996). The mathematical model for the one-dimensional polymerization dynamics of rod-like polymers such as actin or tubulin proposed by Edelstein-Keshet and Ermentrout (1998, 2000) can explain satisfactorily the length distribution of polymers when, following the initial nucleation, the reversible polymerization of subunits and the depolymerization of polymers are taken into account.

All these data led us to propose an integrative and regulatory role for microtubules in the metabolism of cells (Norris et al., 2013). In this hypothesis, the cytoskeleton senses and integrates the metabolic activity of the cells so as to meet the challenge of generating a single phenotype that must be coherent with various internal and external conditions (Ovádi and Norris, 2014). In the work presented here, we use mathematical models to predict the dynamics of tubulin polymerization coupled with kinetics of metabolite concentrations as a function of time in conditions in which metabolic enzymes bind to distinct polymers of the tubulin units. The result of this modeling is a quantitative description of the relationship between microtubule dynamics and kinetics of metabolite concentrations as a function of time which validates the hypothesis that the enzyme-decorated cytoskeletal microtubular network possesses a powerful sensing potency to transduce the information about the metabolic state of the cell into cytoskeletal dynamics.

2. Materials and methods

All the numerical simulations were performed with Mathematica for Students (version 4.1.1.0) software package (Wolfram Research; http://www.wolfram.com).

3. Results

A mathematical model has been developed that couples the self-assembly of tubulin subunits into polymers of different lengths (leading to the formation of microtubules) with the association with these polymers of an enzyme involved in a metabolic pathway. This model, $\mathrm{MODEL}_{\mathrm{coupled}}$, includes kinetic parameters characteristic of the assembly/disassembly of polymers and the enzyme binding to tubulin species; the model can predict the consequences of the hetero-association of the tubulin species and the enzyme on microtubule dynamics and kinetics of metabolite concentrations as a function of time. In addition, this model is extended to quantify the possible effect of a modulator on the coupled processes at the macroscopic level.

3.1. Tubulin polymerization at microscopic and macroscopic levels

The initial premises for the modeling of microtubule assembly/disassembly ($\mathrm{MODEL}_{\mathrm{assembly}}$) are the following: (i) microtubule assembly starts with nucleation that originates from the association of two subunits; (ii) nucleation is followed by the reversible polymerization/depolymerization of tubulin species by association/dissociation of subunits to/from the polymers; (iii) the length of polymers considered as microtubules is restricted; (iv) the rate constants of the assembly/disassembly, k_{on} and k_{off}, are independent of the length of the polymer except that of the nucleation (k_{init}) as well as that of the depolymerization of the maximum length polymer (k_c); (v) the 3D tube structure of microtubules is disregarded and they are considered as rod-like polymers. Accordingly, the time-dependent concentrations of the tubulin species can be calculated as described by Eq. (1) (Edelstein-Keshet and Ermentrout, 1998):

$$\frac{d[T_j]}{dt} = k_{off}[T_{j+1}] - k_{off}[T_j] - k_{on}[T_j][T_1] + k_{on}[T_{j-1}][T_1] \quad (1)$$

where $[T_j]$ represents the actual concentration of a given polymer consisting of j subunits which is produced by the depolymerization of $[T_{j+1}]$ as well as the polymerization of $[T_{j-1}]$, and