Journal of Theoretical Biology 429 (2017) 18–34

Contents lists available at ScienceDirect

Journal of Theoretical Biology

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

Exploring the effect of end-binding proteins and microtubule targeting chemotherapy drugs on microtubule dynamic instability

Diana White [a,*], Stéphane Honoré [b], Florence Hubert [c]

[a] Department of Mathematics, Clarkson University, New York, USA
[b] Aix-Marseille Université, INSERM UMR S 911, CRO2, Marseille, France
[c] Aix-Marseille Université, Institut de Mathématiques de Marseille (I2M), UMR 7373, France

ARTICLE INFO

Article history:
Received 11 December 2016
Revised 17 May 2017
Accepted 13 June 2017
Available online 20 June 2017

Keywords:
Microtubules
Dynamic instability
EBs
MTAs

ABSTRACT

Microtubules (MTs) play a key role in normal cell development and are a primary target for many cancer chemotherapy MT targeting agents (MTAs). As such, understanding MT dynamics in the presence of such agents, as well as other proteins that alter MT dynamics, is extremely important.

In general, MTs grow relatively slowly and shorten very fast (almost instantaneously), an event referred to as a catastrophe. These dynamics, referred to as *dynamic instability*, have been studied in both experimental and theoretical settings. In the presence of MTAs, it is well known that such agents work by suppressing MT dynamics, either by promoting MT polymerization or promoting MT depolymerization. However, recent in vitro experiments show that in the presence of end-binding proteins (EBs), low doses of MTAs can increase MT dynamic instability, rather than suppress it.

Here, we develop a novel mathematical model, to describe MT and EB dynamics, something which has not been done in a theoretical setting. Our MT model is based on previous modeling efforts, and consists of a pair of partial differential equations to describe length distributions for growing and shortening MT populations, and an ordinary differential equation (ODE) system to describe the time evolution for concentrations of GTP- and GDP-bound tubulin. A new extension of our approach is the use of an integral term, rather than an advection term, to describe very fast MT shortening events. Further, we introduce an ODE system to describe the binding and unbinding of EBs with MTs.

To compare simulation results with experiment, we define novel mathematical expressions for time- and distance-based catastrophe frequencies. These quantities help to define MT dynamics in in vivo and in vitro settings. Simulation results show that increasing concentrations of EBs work to increase time-based catastrophe while distance-based catastrophe is less affected by changes in EB concentration, a result that is consistent with experiment.

We further describe how EBs and MTAs alter MT dynamics. In the context of this modeling framework, we show that it is likely that MTAs and EBs do not work independently from one another. Thus, we propose a mechanism for how EBs can work synergistically with MTAs to promote MT dynamic instability at low MTA dose.

Published by Elsevier Ltd.

1. Introduction

Microtubules (MTs) are dynamic protein polymers found in all eukaryotic cells. They are crucial for normal cell development, playing key roles in many cellular processes including cell division, cell polarization, cell motility (Wade, 2009), and cell differentiation (Lacroix and Maddox, 2014). During cell division, MTs help provide the force required to pull two daughter cells apart, and help to properly segregate a cells genetic material (Wollman et al., 2005). During cell movement, MT network polarity helps to control the spatial and temporal coordination of migration events, contributing to persistent directed cell migration (Etienne-Manneville, 2013).

MTs are polarized polymers composed of α/β-tubulin heterodimers (Wade, 2009). In most animal cells, MTs grow from the centrosome of the cell, where they are nucleated and capped at their minus end (the end where the majority of α-tubulin is exposed). While their minus end is static, their plus end (the end where the majority of the β-tubulin is exposed), is very dynamic and grows through the addition of guanosine triphosphate (GTP)-bound tubulin dimers. GTP hydrolysis and phosphate release at the growing plus end of the MT lead to the formation of a distinct

* Corresponding author.
E-mail address: dtwhite@clarkson.edu (D. White).

http://dx.doi.org/10.1016/j.jtbi.2017.06.014
0022-5193/Published by Elsevier Ltd.

guanosine diphosphate (GDP) region at the back of a growing MT (Desai and Mitchison, 1997) and a stabilizing GTP region at the growing front.

If hydrolysis catches up with the growing front, the stabilizing GTP region is lost and the MT quickly depolymerizes, an event referred to as *catastrophe* (Desai and Mitchison, 1997). As a MT shortens, it is possible for the MT to switch back into a state of growing, an event referred to as *rescue*. The combined dynamics of slow growth and extremely fast depolymerization are referred to as *dynamic instability*, and is unique to MTs.

MTs are one of the primary targets for a large number of cancer chemotherapy drugs (Zhou and Giannakakou, 2005). The reason for this is because they play a key role in cell division and cell motility, and are large structures. Chemotherapy drugs that target MTs belong to a class of MT targeting agents (MTAs) whose primary role is to disrupt cell division and/or proliferation by altering MT dynamics. MTAs can be natural or synthetic, and alter the dynamics of MTs by preventing (MT stabilizing drugs) or promoting (MT destabilizing drugs) (Mukhtar et al., 2014) MT disassembly. The most common MTAs used in the treatment of cancers are those that bind to the vinca, colchicine, and taxane sites along MTs (Mukhtar et al., 2014). Drugs that bind to the vinca and colchicine sites (examples include vinblastine and vincristine) promote MT disassembly, while those that bind to the taxane site (examples include paclitaxel and patupilone) prevent disassembly. At clinically relevant doses, many of these drugs have been found to alter MT dynamics without significantly altering the total MT polymer mass (Zhou and Giannakakou, 2005).

Recent experiments have shown that a certain class of plus-end binding proteins may alter the effect of MTAs on MT dynamics. These proteins, referred to as end-binding proteins (EBs), are part of the +TIP family of proteins that have been found to interact with the growing plus ends of MTs through recognition of the nucleotide state of tubulin at the front end of a growing MT (Jiang and Akhmanova, 2011; Maurer et al., 2012; Zanic et al., 2009). In the presence of EBs, the action of high doses of MTAs on MT dynamics remains relatively unchanged. In particular, MTs polymerize in the presence of stabilizing drugs and depolymerize in the presence of destabilizing drugs. However, at low MTA doses, the dynamics of MTs vary depending on whether or not EBs are present, and the extent to which they are present. In particular, it has recently been discovered that EBs sensitize MTs to the action of MTAs at low MTA doses (Mohan et al., 2013), by promoting rather than suppressing MT dynamic instability.

Over the past few decades, since the discovery of MT dynamic instability (Mitchison and Kirschner, 1984), many mathematical and computational studies have been developed to better understand this dynamical process (Chen and Hill, 1985; Dogterom and Leibler, 1993; Flyvbjerg et al., 1994, 1996; Hinow et al., 2009; Martin et al., 1993; Mishra et al., 2005). Most computational models are designed to study MTs at the microscopic level, taking into consideration the addition and subtraction of individual tubulin dimers (Chen and Hill, 1985; Flyvbjerg et al., 1994, 1996; Martin et al., 1993). Deterministic models have been developed to understand this process at a macroscopic level (Dogterom and Leibler, 1993; Hinow et al., 2009; Mishra et al., 2005). Such models are used to describe the time evolution of length distributions for growing and shortening MT populations. A recent stochastic model has been developed to study the effects of certain MT associated proteins (MAPs) and MTAs on MT dynamics (Hinow et al., 2011). However, to our knowledge, no other theoretical model has been developed to study how EBs alter MT dynamics. In order to understand the possible synergistic effects that MTAs might have on EBs, we first require a detailed understanding of EB/MT dynamics.

We first present a model for MT dynamic instability. This model is an extension of the work by Hinow et al. (2009). Similar to the approach of Hinow et al. (2009), we use a system of partial differential equations (PDEs) to describe the evolution of growing and shortening MT populations, as well as a coupled system of ordinary differential equations (ODEs) to describe the time evolution of free GTP- and GDP-tubulin. This modeling approach is unique from other models since it describes both variations in total MT length and MT GTP-cap length. Describing the GTP-cap region of a MT is crucial to our approach, since it is at this location that EBs interact with MTs (Jiang and Akhmanova, 2011; Maurer et al., 2012; Zanic et al., 2009). Unlike the model of Hinow et al., we choose a piece-wise continuous growth function, based on experimental evidence, to describe the MT growth rate. Further we choose not to use an advection-type process to describe MT shortening. Instead, we describe MT shortening using an integral term to account for "instantaneous" shortening events of a given size. This is an important consideration, since MTs shorten extremely fast (relative to growth), where their shortening distances can vary according to experimental conditions. To highlight the difference between our new extension and the model of Hinow et al. (2009), we include a number of comparative simulations in the supplementary material.

Next, we develop a modeling framework to describe how EBs work to regulate MT dynamics. To describe the dynamics of EBs, we use a binding/unbinding ODE model, and assume that the primary effect of EBs on MTs is to increase the MT hydrolysis rate, as well as the rescue rate. We assume this since recent experimental studies have shown that the addition of EBs works to increase the time-based frequencies of catastrophe and rescue *in vitro* (Gardner et al., 2011; Vitre et al., 2008). A possible mechanism for the increase in catastrophe frequency is related to the EBs effect on the hydrolysis rate. In particular, some experiments show that the increase in catastrophe rate is correlated to an increase in the hydrolysis rate *in vitro*. Gardner et al. (2011); Maurer et al. (2014). In this study, we restrict ourselves to the study of EBs *in vitro* and leave the study of *in vivo* EB dynamics to our future work.

Finally, we explore the action of MTAs on MTs in the presence and absence of EBs. In the absence of EBs, we assume that the addition of MTAs works through alteration of model parameters directly linked to MT polymerization or depolymerization. By incorporating EB dynamics, we determine that EBs and MTAs do not work independently from one another at low MTA dose, in the context of our modeling framework. As such, we propose a mechanism for how MTAs and EBs can work in a synergistic fashion to promote MT dynamics at low MTA dose.

2. The model

We separate our modeling efforts into three portions. First, in Section 2.1, we describe a new model for MT dynamic instability, which is an extension of the model by Hinow et al. (2009). Here, we introduce a new non-local term to describe MT shortening, as well as a more realistic description for MT growth. Next, in Section 2.2, we describe a method for introducing EBs into the model. Finally, in Section 2.3, we describe a novel method for defining time- and distance-based catastrophe frequencies.

2.1. Modeling MT dynamic instability

Many theoretical models that have been developed to describe the densities of growing and shortening MT populations describe only the time evolution of MT length. In our model, we also take into account the length of the MT cap, which represents the binding region for EBs. In particular, we keep track of the length of the GTP-tubulin zone located at the front end of a growing MT. A similar modeling approach has been used by Hinow et al. (2009). However, unlike the model of Hinow et al., we take into account the action of EBs on MT dynamics. Further, we introduce a novel