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Review

Toward a systems-level view of mitotic checkpoints

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ABSTRACT

Reproduction and natural selection are the key elements of life. In order to reproduce, the genetic material must be doubled, separated and placed into two new daughter cells, each containing a complete set of chromosomes and organelles. In mitosis, transition from one process to the next is guided by intricate surveillance mechanisms, known as the mitotic checkpoints. Dis-regulation of cell division through checkpoint malfunction can lead to developmental defects and contribute to the development or progression of tumors.

This review approaches two important mitotic checkpoints, the spindle assembly checkpoint (SAC) and the spindle position checkpoint (SPOC). The highly conserved spindle assembly checkpoint (SAC) controls the onset of anaphase by preventing premature segregation of the sister chromatids of the duplicated genome, to the spindle poles. In contrast, the spindle position checkpoint (SPOC), in the budding yeast *Saccharomyces cerevisiae*, ensures that during asymmetric cell division mitotic exit does not occur until the spindle is properly aligned with the cell polarity axis. Although there are no known homologs, there is indication that functionally similar checkpoints exist also in animal cells. This review can be regarded as an "executable model", which could be easily translated into various quantitative concrete models like Petri nets, ODEs, PDEs, or stochastic particle simulations. It can also function as a base for developing quantitative models explaining the interplay of the various components and proteins controlling mitosis.

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1. Introduction

Correct DNA segregation during mitosis is a fundamental process that ensures the faithful inheritance of genomic information for the propagation of cell life. Segregation (Fig. 1) failures underlie many human health problems, most notably aneuploidy and cancer (Bargiela-Iparraguirre et al., 2014; Holland and Cleveland, 2009; Ling et al., 2014; London and Biggins, 2014; Suijkerbuijk and Kops, 2008; Teixeira et al., 2014). In order to avoid this catastrophe, cells contain active segregation machineries that grant proper DNA distribution into the daughter cells. This requires binding of proteins ("kinetochore proteins") to DNA sites ("centromeres") and actively transporting the DNA through the cellular space to the new location. When the genome is distributed over several or many chromosomes, each daughter cell must obtain the complete set of chromosomes. This requires a concerted action of combined transport requiring precise regulation ("mitotic checkpoints"). Hence, DNA segregation is an essential, highly ordered process that depends on the assembly and multi-functionality of numerous protein complexes that are regulated both in time and space.

Experimentalists have provided a wealth of information about the components of DNA segregation. However, DNA segregation is inherently complex and highly cross linked. It cannot be understood from reactions on the individual components (proteins, complexes etc) alone, but should be understood through considerations involving many components at the same time. The current experimental techniques are not sufficient to make quantitative predictions. Hence, the integration of experimental and computational approaches is employed for the understanding of biological systems. This approach recently received mainstream attention by scientists following the so called "Systems Biology" approach (see Fig. S1 and S2).

2. DNA segregation

Faithful DNA segregation can be understood in terms of three interacting sub-systems.

- Kinetochore assembly: the inner and outer kinetochore
- Kinetochore attachment, the spindle assembly checkpoint
- Placing the correct DNA into the right cell, the spindle position checkpoint

2.1. Kinetochore assembly: the inner and outer kinetochore

The kinetochore is a multi-protein complex that assembles solely at the centromere of each sister chromatid and contains over 100 proteins (Perpelescu and Fukagawa, 2011). These proteins can be classified into two functional groups: the inner-kinetochore, which is tightly associated with the centromere DNA, and the outer-kinetochore, which interacts with microtubules.

The inner kinetochore is composed of a centromeric CenpA and 16 CCAN (constitutive centromere-associated network) proteins (CenpC, CenpH, CenpI, CenpK to CenpU, CenpW, CenpX) (Okada et al., 2006). The inner kinetochore is relatively stable and present during most of the cell cycle (Black and Cleveland, 2011; Dalal and Bui, 2010; Perpelescu and Fukagawa, 2011), while the outer-kinetochore is thought to be structurally unstable and formed in early mitosis (Cheeseman and Desai, 2008; Maiato et al., 2004; McAinsh, 2014).

The outer kinetochore proteins and complexes include the KNL-complex (Spc105/Knl1), Mis12-complex (Dsn1, Nnf1, Nsl1 and Mis12) and the Ndc80-complex (Ndc80/Hec1, Nuf2, Spc24 and Spc25), which are known as the KMN network (Kim and Yu, 2015;

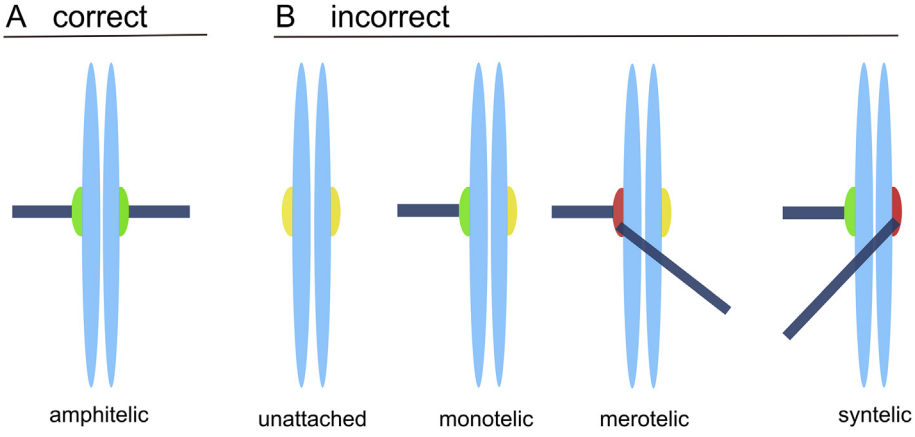

Fig. 1. Scheme showing different anchoring between chromosomes and microtubules. (A) Proper Bi-orientation chromosome segregation in anaphase requires all chromosomes to have amphitelic attachment, that is, both kinetochores of every chromosome must be attached to microtubules from opposite poles. (B) Before all chromosomes have established amphitelic attachment, chromosomes having no or erroneous attachments are frequent intermediates. Erroneous connections between microtubules and kinetochores spontaneously detach, facilitating proper re-attachment. Chromosomes showing merotelic attachment have a kinetochore which is simultaneously attached to microtubules from opposite poles. In contrast, chromosomes with syntelic attachment have both kinetochores connected to microtubules from the same pole.