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A mathematical model of CENP-A incorporation in mammalian centromeres

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ABSTRACT

Centromere Protein A (CENP-A) is a histone H3 variant found at mammalian centromeres. Unlike canonical histones which are incorporated at centromeres in S phase, CENP-A is deposited at centromeric chromatin in G1. Although recent studies have elucidated many of the molecular details associated with the CENP-A incorporation pathway, some aspects of the process are still not fully understood. CENP-A incorporation in G1 requires multiple assembly factors for its recruitment and maintenance. In this study, the first mathematical model of the CENP-A incorporation pathway is developed. The model is based on what is currently known about the pathway and is calibrated by comparing numerical simulations with experimental observations taken from the literature. The model succinctly collates a large body of knowledge accumulated in recent decades concerning the pathway and produces results that are consistent with experimental findings. It identifies possible gaps in what is currently known about the pathway and suggests possible directions for future research. It is envisaged that the model will be expanded upon and improved as more information concerning the pathway comes to light.

1. Introduction

The cell cycle refers to the periodic growth and division of a cell and it progresses through four phases [1,2]. In order of occurrence these are *G1*, *S*, *G2* and *M*. G1 and G2 are growth phases. S is the synthesis phase, during which the cell produces a second copy of the genetic information, contained in its *chromosomes*. M is the mitotic phase, the period when the chromosomes are divided between daughter cells as one cell splits to form two. The *centromere* is the locus that joins paired chromosomes, or *sister chromatids*, and has a number of important cellular functions. A schematic representation of a mitotic chromosome with the centromere labelled is shown in Fig. 1. The centromere serves as the site for the formation of the *kinetochore*, a large multi-protein structure that forms attachments with *microtubules*. The kinetochore and microtubules are also labelled in Fig. 1. Kinetochore-microtubule attachments form in mitosis and are required for chromosomes to be divided evenly between daughter cells. Once all kinetochore-microtubule attachments have been formed correctly, cohesion between sister chromatids is lost and the microtubules pull identical chromosomes to opposite ends of the cell.

Centromere Protein A (CENP-A) has long been recognised as a key component of the centromeres of higher eukaryotes [3–5]. Since its initial characterisation as a core histone variant [6], illumination of the role of CENP-A and the details surrounding its incorporation at centromeres has been the focus of much research. CENP-A differs from canonical histones in the manner and timing of its incorporation in centromeres. Canonical histones H2A, H2B, H3 and H4 are known to be incorporated in chromosomes during DNA synthesis. However, the timing of CENP-A incorporation depends on the organism in question and, in most cases, occurs outside of S phase [7–13].

The presence of CENP-A at centromeres is vital for the proper construction of the kintechore complex and, in turn, microtubule binding and correct segregation of sister chromatids in mitosis. Loss of CENP-A from centromeres results in defects in chromosome congression to the metaphase plate and missegregation in anaphase, which can lead to the formation of micronuclei [14]. On the other hand, overexpression of CENP-A has been implicated in the relapse of ER positive breast cancer [15], colorectal cancer [16], hepatocellular carcinoma [17], and could possibly be a common attribute of many cancers [18–21].

In mammals, the population of CENP-A molecules at a centromere is halved in S phase, when the replication fork passes through parental chromatin and CENP-A molecules are shared between the two daughter helices. In a newly formed daughter cell, CENP-A is first observed to associate with centromeres in early G1 [14,22,23]. This CENP-A is

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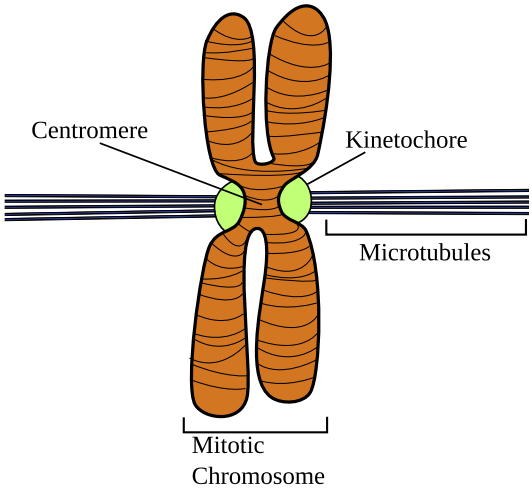

Fig. 1. A schematic representation of a mitotic chromosome with kinetochore-microtubule attachments. In mitosis, sister chromatids are joined at the centromere. Correct establishment of kinetochore-microtubule attachments is necessary for the error-free division of chromosomes.

then incorporated in centromeric chromatin through the remainder of G1 [24,25]. The manner in which CENP-A is replenished at centromeres in G1 can be broken into a number of distinct steps, which are now summarised. A schematic illustrating the various stages of CENP-A incorporation is given in Fig. 2.

Soluble CENP-A associates with *Holliday Junction Recognition Protein* (HJURP) and both proteins are produced at high levels in G2 phase, mitosis and early G1 phase [26–28]. HJURP is a CENP-A chaperone that is required for CENP-A deposition at centromeres. CENP-A deposition also requires that centromeres be first primed by the *Mis18 complex* [29] and the recruitment of Mis18 to centromeres has been shown to be dependent upon the presence of CENP-C [13,30]. Recent evidence suggests that Mis18 association with centromeres is restricted to G1 by Cdk activity [31]. Centromere priming likely involves some balance between acetylation and methylation [32–34]. CENP-A associates with centromeres in late M phase and early G1 phase [22,23]. In mid G1, Rsf-1 and SNF2h (the *RSF complex*) associate with centromeres, and are necessary for the retention of CENP-A at centromeres [24]. In late G1, a GTPase activating protein, *MgcRacGAP*, associates with centromeres and through the action of a GTP switch stabilises the newly incorporated CENP-A at centromeres [25].

A complete picture of the CENP-A incorporation pathway is currently lacking. In this paper, the known mechanisms of CENP-A incorporation are reviewed and a mathematical model based on these is formulated. The mathematical model presented herein uses a dynamical systems approach and contains two compartments, one for the nucleoplasm and another for centromeric binding sites. Parameter values are obtained from the literature, where available, or are estimated by comparing model output with experimentally observed behaviour.

As well as making quantifiable predictions concerning the process of CENP-A incorporation at centromeres, a model of the kind developed here is useful in consolidating the results of various experimental observations and provides an analytic framework with which to analyse the system. To date, the authors are not aware of any other mathematical model for this system.

2. Background biology and mathematical modelling

In this section, a detailed review of the CENP-A incorporation pathway, shown in Fig. 2, is presented. Following this, a mathematical model is developed to describe the pathway. In Section 3, the model results are discussed.

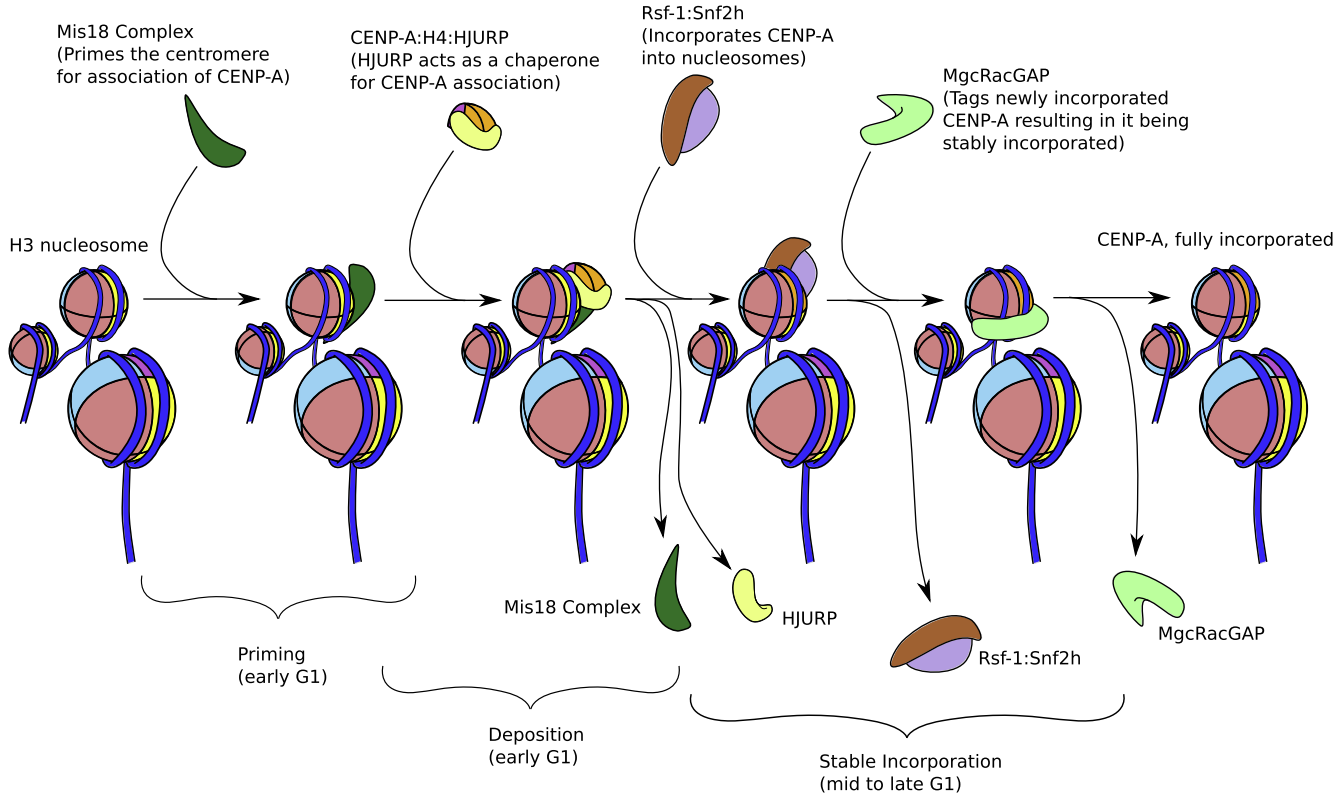

Fig. 2. The CENP-A incorporation pathway. This schematic is based on what is currently known about the system. The Mis18 complex primes centromeres for the deposition of CENP-A. Soluble CENP-A is complexed with H4 histones and the histone chaperone, HJURP. CENP-A becomes fully incorporated at nucleosomes, after deposition, through the actions of the RSF complex and MgcRacGAP. All of these processes are included in the modelling.