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Mini Review

Kinetochore, An Anchorage Site for The Dividing Chromosomes, Helps Maintain the Integrity of The Genome Over Generations

Akraam Ali and Ahtsham Ul Hassan*

School of Biological and Chemical Sciences, Queen Mary University of London, UK

Centre of Agricultural Biochemistry and Biotechnology, University of Agriculture, Faisalabd, Pakistan

***Corresponding author:** Akraam Ali, School of Biological and Chemical Sciences, Queen Mary University of London, UK

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Abstract

The continuity of life on this planet owes a lot to the efficient cell division of all organisms which in turn supports the survival of these organisms. During cell division, the chromosomes, a thread-like structure made of nucleic acid and proteins need to get duplicated before entering the actual division phase where the sister chromosomes are separated to ensure faithful distribution of genetic make-up among the progeny. This segregation/distribution of chromosomes is mainly regulated by kinetochore besides helping the cells avoid mis-segregation. In this mini review, we will briefly follow up the studies undertaken for a molecular mechanism involving the functions of kinetochore and will try to suggest what areas are more important to investigate than others regarding the cell cycle.

Keywords: Cell Division, Chromosomes, Kinetochore, Mitosis, Segregation, CPC, KMN

Abbreviations: CCAN: Constitutive Centromere Associated Network; DNA: Deoxyribonucleic Acid; Y2H: Yeast-Two-Hybrid; SAC: Spindle Assembly Checkpoint; CPC: Chromosomes Passenger Complex

Kinetochore and Centromere

The proper segregation of chromosomes requires timely and accurate attachment of kinetochore with microtubules as any anomalies involving this physical link resulted in abnormal chromosome segregation which in turn leads to various diseases. The kinetochore is a proteinaceous complex that is recruited to the centromere of the dividing chromosomes [1]. The electron microscopic structure of this complex found it with a structure having three layers with two being electron-dense while the third is transparent one positioned between dense layers [2]. It has been suggested that these electron-dense layers make up the two main components of kinetochore i.e., the inner kinetochore and out kinetochore [3]. The inner inetochore is itself composed of a subcomplex called Constitutive Centromere Associated Netwar (CCAN) having almost 16 protein subunits, whereas the outer kinetochore has the KMN, a network of three oteins namely, Knl1, Mis12, and Ndc80.

The centromere is a specific chromosomal region with which the inetochore binds during the cell cycle for ensuring the segregation of chromosomes [4]. All the centromeres, with one exception of budding yeast centromere, are mainly specified by an epigenetic element which means although they are made up of DNA bases, yet the vital determinant that distinguished them from other

sequences is something else rather than the DNA itself [5]. The most conserved epigenetic element is a histone H3 variant known as CENP-A. It has been suggested that the variation that CENP-A has involved major subunits of H3 octamer complex i.e., H4, H2A, and probably H2B [6].

Kinetochore as an Anchorage Site

Tanaka et. al. reported that kinetochores with their dual-layer complex make the physical binding of centromere with the microtubules evolving from opposite poles [7]. The molecular mechanism of how kinetochore proteins make this link possible remains poorly understood, however, it has been learned through cytological, biochemical, and computational experiments on model organisms, that the Inner Kinetochore (CCAN) proteins firstly recognize the CENP-A nucleosomes followed by the recruitment of other subunits to centromere [8]. The outer kinetochore complex containing the KMN network helps bind the incoming fiber of microtubules. These two interactions of CCAN and KMN with centromere and microtubules respectively make an interface between the sister chromatids and microtubules thereby leading to the accurate segregation of chromosomes in mitosis [9]. Most of the studies supporting such mechanisms being at play during cell division are based on in-vitro analyses where Yeast-Two-Hybrid (Y2H) has been employed to investigate these interactions, hence, in this review we have been suggesting the exploration of live systems for investigating these molecular pathways so that they can be referenced when it comes complex eukaryotic organisms.

Dynamic Changes in Kinetochore Morphology Ensure Equal Chromosomal Distribution

Kinetochore not only helps to get segregation of duplicated chromosomes before entering the M-phase of the cell cycle, but it also ensures the equal distribution among the progeny by regulating signaling for Spindle Assembly Checkpoint the SAC [10]. The structural changes in the kinetochore complex have been associated with the SAC signalling, the unattached or mal-attached chromosomes prompt the SAC mechanism which halts the entry of such chromosomes to the mitotic phase [11]. The Aurora B Kinase (AurB) being an active component of Chromosomes Passenger Complex (CPC) is a leading error correction player [12]. This enzyme forms a kinase gradient around the interior of centromeres and has a wide range of substrates with Ndc80 one of the members of the KMN complex being its specific substrate [13]. The mal-attachment of microtubules or loss of tension among outer kinetochore components including Ndc80 [14] which directly binds to the microtubules through its N-terminal domain places Ndc80 into a catalytic zone of Aurora B which phosphorylates the Ndc80 specific domain eventually destabilizing the microtubules binding with kinetochore [15].

Once the correct binding is accomplished, Ndc80 gets out of the Aurora B activity zone and to make it functional again by de-phosphorylation a Protein Phosphatase (PP1) [16] is employed and eventually, the dephosphorylated Ndc80 strengthens the microtubule-kinetochore attachment [17]. This is a putative mechanism of error correction, what we think might be another possible way of this feedback is not only the phosphorylation of Ndc80 but some other proteins may contribute to this end that needs to be investigated either via deletion or mutation of this Ndc80. Given the vital role, Ndc80 plays in fine-tuned chromosomal segregation thereby controlling the division of cells, what prompts the carcinogenic cells to bypass this mechanism? Understanding the mechanistic details of this process helps us to devise strategies aimed at curing various illnesses in general and avoiding the onset of such genetic abnormalities in particular.

Conclusion

The transmission of genetic material in an exquisite way is vital for proper cellular division. The kinetochore is the main player that not only properly segregates the duplicated chromosomes but also insures their symmetrical transfer among the progeny. The CCAN and KMN are the vital subcomplexes of the kinetochore. Ndc80 is involved in error correction pathways of the cell cycle. Although the pioneering studies elaborated the molecular details of some vital protein/s, a lot needs to be explored yet to understand the regulation of pathways involved in chromosomal segregation. Some key emerging avenues include tapping the Ndc80 for its interaction with other proteins regarding its role in error correction, understanding how this mechanism is compromised by cells undergoing uncontrolled division.

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Conflict Of Interest

None.

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