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Minireview

The Ndc80 complex: Hub of kinetochore activity

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Abstract **Kinetochores are protein scaffolds coordinating the process of chromosome segregation in mitosis. Kinetochore components are organized in functionally and topologically distinct domains that are designed to connect the sister chromatids to the mitotic spindle. The inner kinetochore proteins are in direct contact with the centromeric DNA, whilst the outer kinetochore proteins are responsible for binding to spindle microtubules. The conserved Ndc80 complex is implicated in several essential outer kinetochore functions, including microtubule binding and control of a safety device known as the spindle assembly checkpoint. Here, we describe how current work is contributing to unravel the complex endeavors of this essential kinetochore complex.**

Keywords: Kintochore; Centromere; Cancer; Aneuploidy; Hec1; Ndc80; Nuf2; Spc24; Spc25; Spindle assembly checkpoint; Microtubule

1. General remarks

The name ''mitosis'' describes the equational division of a cell, a process whose outline is similar in all eukaryotes [1]. In mitotic prometaphase, a microtubule-based structure named the spindle captures and aligns the replicated chromosomes (sister chromatids) on the spindle's equatorial plane. After alignment (metaphase), the sisters separate towards opposite spindle poles (anaphase), giving birth to two new cells (telophase and cytokinesis). A critical requirement for the seamless execution of this process is that chromosomes form stable attachments with spindle microtubules. The molecular machinery responsible for creating such attachments resides at kinetochores, scaffolds that contain ~100 or more proteins assembled around a nucleus of centromeric DNA [2,3]. Defects in chromosome attachment arise after interfering with the function of a large number of kinetochore proteins, most likely due to various, pleiotropic deleterious effects on the structural organization of the kinetochore. Specifically for this reason, and is spite of recent formidable progress in the elucidation of kinetochore composition and organization, it has been difficult to pinpoint specific proteins or protein complexes responsible for microtubule binding [4–7]. The application of strategies of biochemical reconstitution, and their combination with sophisticated imaging techniques and high-resolution structural approaches, has finally directed the search to the proteins that are directly involved in microtubule–kinetochore attachment. These studies, which we review here, identify the Ndc80 kinetochore complex (Fig. 1) as a key player at the kinetochore–microtubule interface.

2. Kinetochores in brief

Kinetochores assemble around selected DNA segments known as centromeres. The ''point'' centromeres of *Saccharomyces cerevisiae*'s are compact loci of ~150 bp of DNA that contain distinct *cis*-acting protein binding regions [2,8,9]. The centromeric DNA wraps around a specialized nucleosome marked by the presence of the centromere-specific Histone H3 variant Cse4 (known as CENP-A in metazoans). The Cse4/CENP-A-containing nucleosome is the scaffold on which the rest of the kinetochore is built (Fig. 2). The kinetochores of *Saccharomyces cerevisiae* bind a single microtubule. Most eukaryotes have extended ''regional'' centromeres, which encompass several kilobases of DNA and are packaged into heterochromatin [2,9]. The regional centromeres of *S. pombe* and of most metazoans sustain larger kinetochores that attach to fibers containing multiple microtubules (kinetochore- or K-fibers, usually containing 15–25 microtubules in human cells). Direct visualization of the kinetochore by electron microscopy in higher eukaryotes reveals a trilaminar disk, with an electron dense inner plate embedded in the centromeric chromatin, an electron opaque middle layer, and an electron dense outer plate engaged in end-on binding of the microtubule plus ends [2]. To understand the relationship between point and regional centromeres, it is important to state that the histone variant Cse4/CENP-A is not only present at centromeres of *S. cerevisiae*, but that it also marks the regional centromeres of higher eukaryotes. Several other kinetochore proteins known to interact with the Cse4/CENP-A nucleosome are also conserved in evolution [2,9]. This observation suggests that regional centromeres have a modular organization in which an array of

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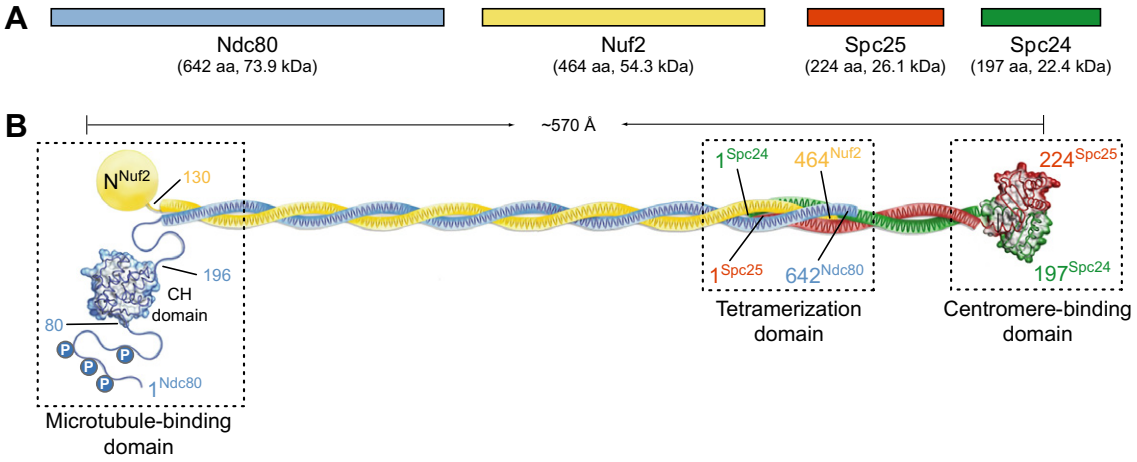

Fig. 1. General properties of the Ndc80 complex (A) Schematic view of the subunits of the Ndc80 complex, reporting their size and introducing coloring scheme used in other panels and figures. Rectangular shapes are drawn to scale. (B) Model of the Ndc80 complex including domains whose structure has been determined. The microtubule-binding domain includes the globular heads of Ndc80/Hec1 and Nuf2. The globular head of Ndc80/Hec1 contains a Calponin-homology domain [37]. It is unclear whether a similar domain is contained in the Nuf2 globular head. The Ndc80/Hec1 region N-terminal to the CH-domain contains several sites of phosphorylation by the Aurora B/Ipl1 kinase [27,37,38]. The entire central shaft is made of coiled-coils from Nuf2–Ndc80/Hec1 and Spc24–Spc25 dimers. These meet in a tetramerization domain where the four chains overlap.

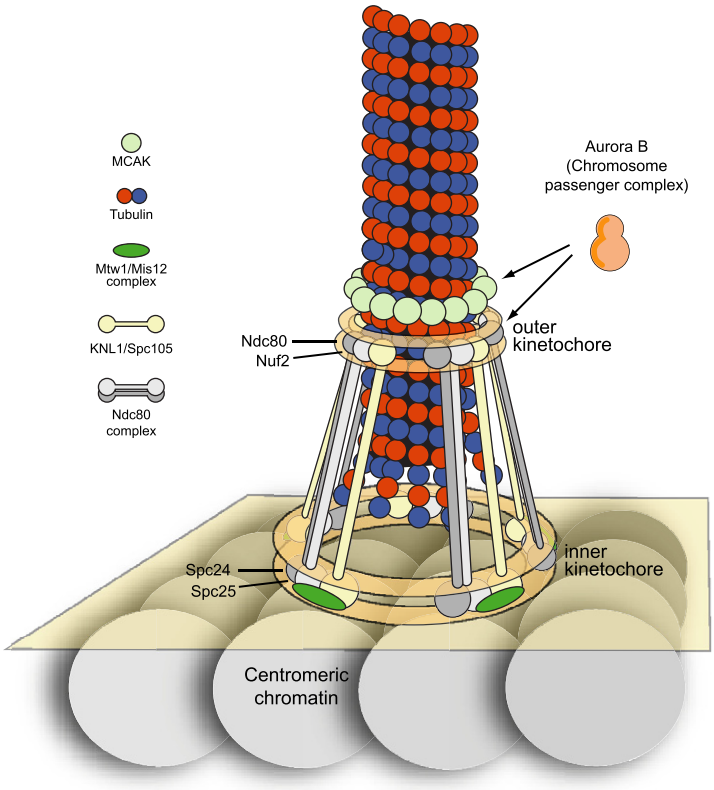

Fig. 2. Microtubule–kinetochore attachment. A stylized view of the microtubule–kinetochore interface. The inner plate rests on centromeric chromatin containing the histone H3 variant CENP-A. The Spc24–Spc25 sub-complex possibly mediates the interaction of the Ndc80 complex with the inner kinetochore (see text). The globular heads of Ndc80/Hec1 and Nuf2 are embedded in the outer kinetochore domain and interact directly with the microtubules. Mtw1/Mis12 might act as a linker between the Ndc80 complex and KNL1/Spc105. MCAK forms rings around microtubules and might act as a functional homologue of the Dam/DUO/DASH complex.

specialized Cse4/CENP-A containing nucleosomes, rather than the single one predicted to exist in *S. cerevisiae*, generate kinetochore "units" that co-orient to bind microtubules emanating from the same spindle pole [2].

3. Ndc80 at kinetochores

The Ndc80 complex is conserved from fungi to humans. It contains four protein subunits, known as Ndc80 (the human