Centromere cohesion: regulating the guardian

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Mitosis, a process in which duplicated chromosomes are segregated into two daughter cells, is the most spectacular event in cell cycle. In mitosis, cells undergo drastic rearrangement of cytoskeleton, lipid and chromosomes under amazingly strict temporal and spatial control so that genetic information is faithfully transmitted to daughter cells. Errors in mitosis result in aneuploidy and malignant transformation that are frequently linked with tumorigenesis. Mitotic regulation is achieved by an orchestration of a series of post-translation events including phosphorylation and proteolysis. Mitotic kinases, including Cdk1, Aurora, Polo, and NIMA family kinases, are undoubtedly the main conductors of this orchestration [1].

Cdk1, Aurora and Polo kinases have been relatively well studied while the precise role of NIMA family remains elusive. For a long time, the best studied NIMA member, Nek2 is categorized as a centrosomal kinase that regulates mitotic entry by controlling centrosome maturation and separation at the G2/M transition [2]. However, recent research suggests that Nek2 functions beyond the mitotic entry by regulating the mitosis surveillance machinery called spindle assembly checkpoint (SAC), and chromosome segregation. Chen *et al.* identified Hec1 as the first kinetochore protein that interacts with and is phosphorylated by Nek2 [3]. Kinetochore is a proteinaceous structure assembled on the outside of centromeric DNA in condensed chromosomes and is the site for microtubule attachment. Interference of Hec1 function causes severe chromosome missegregation. In their study, they showed phosphorylation of Hec1 by Nek2 is essential for faithful chromosome segregation in yeast, strongly suggesting a novel role of Nek2 in regulating kinetochore function. In addition, Yao's group found that Nek2A, an important Nek2 isoform, is localized to kinetochores in human cells [4]. They also demonstrated that Nek2A interacts with SAC proteins and plays a vital role for SAC signaling. These studies link Nek2 to a group

of regulators for SAC signaling and chromosome segregation. However, the precise role and the mechanism of Nek2 function remain to be investigated.

In the July issue of *Cell Research*, Yao and his colleagues, in an effort to understand the function of Nek2A, carried out a high throughput screen for Nek2A-interacting proteins and intriguingly the centromere guardian Sgo1 was identified [5]. Their study extends the cellular function of Nek2A to centromeric cohesion regulation and SAC signaling.

In mitosis, accurate regulation of centromere cohesion is critical for faithful chromosome segregation. From S phase the entire duplicated sister chromatids are held together by cohesin complex. At prometaphase, the cohesin complex on chromosome arm is dissociated through Plk1-mediated phosphorylation. However, cohesin complex at centromere is protected from phosphorylation and remains associated until anaphase onset, which ensures bipolar attachment and metaphase alignment of sister chromatids. The pulling force from bound microtubules and the resistance by centromere cohesion generate tension across sister kinetochores. Once tension is established on all the chromosomes, the SAC is turned off and the anaphase ensues. The mechanism for the protection of the centromere cohesin from dissolution at prometaphase is explained by the function of Sgo1. Sgo1 is a centromere protein that is identified with an essential role in centromeric cohesion protection during meiosis and mitosis in yeast as well as mitosis in vertebrates [6]. In human cells, Sgo1 is loaded onto centromeres in early mitosis and associated with centromeric cohesin complex [7]. This association blocks the Plk1-mediated phosphorylation of the centromeric cohesin and prevents its dissolution [8]. Upon the silencing of SAC, the anaphase-promoting complex is activated, leading to degradation of Sgo1 and securin. Securin degradation activates separase that cleaves the unprotected centromere cohesin complex.

Besides centromere cohesion protection, functional studies show that Sgo1 regulates spindle dynamics by acting as a microtubule stabilizer in vertebrates [7]. More importantly, genetic study in yeast indicates that Sgo1 directly acts as the long-sought tension sensor for the SAC control [9]. Even though the potential role of Sgo1 in tension sensing remains to be defined in vertebrates, it is reasonable to speculate vertebrate Sgo1 may have a similar function based on its high sequence and function conservation among different species [10].

In Yao's paper, Nek2A was identified as a novel mitotic regulator of Sgo1 in human cells. Nek2A phosphorylates Sgo1 and disruption of this phosphorylation in cells causes misaligned chromosomes and incorrect microtubule-kinetochore attachment but does not change Sgo1 localization [5]. Their results indicate that the kinase activity of Nek2A is required for faithful chromosome segregation mediated by Sgo1. Moreover their results imply a potential role of Sgo1 in the tension sensing in human cells as Sgo1 mutant that cannot be phosphorylated by Nek2A causes monotelic and syntelic microtubule attachment on kinetochores in cells, consistent with the phenotype of a failure in sensing tension on kinetochores. Thus, phosphorylation of Sgo1 by Nek2A provides another layer of regulation of Sgo1 in centromere cohesion and SAC control. On the other hand, their study also provides interesting insights on the function and regulation of Nek2A. It is known that Nek2 contains two isoforms: Nek2A and Nek2B. Both isoforms are induced during G2. However, the levels of Nek2A drop upon mitotic entry while the level of Nek2B remains until mitotic exit [2]. Although Nek2A can phosphorylate Sgo1 *in vitro*, it is unclear which kinase, Nek2A or Nek2B, is the physiological kinase for Sgo1 *in vivo*, given that Nek2A is degraded at prometaphase.

An interesting parallel is observed between centrosomal and centromeric cohesions with respect of their regulation by kinase and phosphatase. Parental and daughter centrosomes are held together through centrosomal cohesion

until mitotic entry and their separation is dependent on the balance between the activities of kinase Nek2A and phosphatase PP1A on centrosome protein C-Nap1 [2]. On the other hand, the centromere cohesion regulator Sgo1 requires phosphatase PP2A to localize to centromere. The current study by Yao's group raises the possibility that Nek2 may also contribute to the dissolution of centromere cohesion. In all, the present study by Yao's group provides a new direction in investigating the function and regulation of Nek2 and Sgo1.

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