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Two Birds with One Stone—Dealing with Nuclear Transport and Spindle Assembly

Spindle assembly and nuclear transport both utilize the same simple device: Ran-GTP-sensitive interaction of importin β and its cargo proteins. In this issue of *Cell*, Blower et al. (2005) report that one of these cargos required for spindle assembly turns out to be Rae1, previously known as an mRNA export protein. This study reveals the importance of RNAs in spindle structure.

Transporting macromolecules between the nucleus and cytoplasm is a critical issue for eukaryotic cells. Emerging pieces of evidence have shown that the players involved in nuclear transport are not just idle during M phase, when nuclear envelopes are broken down; they are used to form the elaborate spindle apparatus. Many of these findings were obtained by using the powerful *Xenopus* egg extract system, in which microtubule dynamics can be recapitulated even in the absence of the nucleus. Taking advantage of this experimental system, Blower and colleagues (Blower et al., 2005) demonstrate in this issue of *Cell* that Rae1, a protein which had previously been implicated in mRNA nuclear export, is required for spindle assembly.

Microtubules, the polymeric form of tubulin, are used to segregate eukaryotic chromosomes during cell division. The dynamic property of microtubules is a key feature of the machinery used to ensure accurate chromosome segregation during mitosis. For example, if sister kinetochores are attached to microtubules emanating from the same spindle pole, these microtubules are destabilized before reestablishing the desired configuration, in which sister kinetochores are correctly attached to opposing poles. At the same time, microtubules must be robust to maintain the sturdy bipolar structure of the spindle. To meet these opposing requirements, M phase microtubules are controlled so that they are highly dynamic and unstable, while only particular structures locally permit microtubule assembly and stabilization.

Two dominant spindle structures promote spindle microtubule assembly, the centrosomes and chromatin. Although centrosomes are found at spindle poles in many eukaryotic cells, some cells lack centrosomes but still form functional bipolar spindles. In these cells, chromatin promotes microtubule assembly and spindle formation. One of the best-characterized mechanisms that controls chromatin-induced microtubule assembly is the Ran-GTP pathway. Efforts to identify downstream targets of the Ran-GTP pathway have offered a glimpse of the mechanism by which chromatin induces microtubule nucleation and spindle assembly. Importin β, a protein playing a pivotal role in nuclear import, sequesters factors that promote microtubule assembly (reviewed in Harel and Forbes [2004]). Nuclear Ran-GTP liberates these microtubule assembly factors from importin β for spindle assembly during M phase just as it liberates cargo proteins from importin β for nuclear transport during interphase. Since, during M phase, RanGTP is generated by chromosomally bound RCC1 (a Ran GDP/GTP exchange factor), it has been suggested that a higher RanGTP concentration near chromatin promotes microtubule assembly (Karsenti and Vernos, 2001).

Previous studies have detected several spindle assembly-promoting factors that are sequestered by importin β via importin α, the cofactor of importin β that recognizes nuclear localization signals (NLS). These factors include microtubule-associated proteins, such as TPX2 and NuMA (references found in Harel and Forbes [2004]). Blower et al. (2005) report another microtubule assembly promoting activity that is sequestered by importin β, this time in an importin α-independent manner. After a heroic biochemical purification effort from *Xenopus* egg extracts, they reveal that this activity consists of a ribonucleoprotein (RNP) complex containing Rae1. Instead of importin α, Nup98 (a previously known Rae1-interacting protein) is used to facilitate Rae1 binding to importin β.

Rae1 was originally identified as a protein localized to nuclear pore complexes (NPCs) and is required for mRNA export from the nucleus in fission and budding yeasts (Murphy et al. [1996] and references therein). The mRNA export function of Rae1 is accompanied by another NPC protein, Nup98 (Pritchard et al., 1999). Curiously, Rae1 is homologous to the spindle checkpoint component Bub3, and studies with knockout mouse cells demonstrated that Rae1 and Bub3 have an overlapping function in the spindle checkpoint, although the same Rae1 knockout cells did not show any defects in mRNA export (Babu et al., 2003). Now, Blower et al. (2005) show that Rae1 is able to interact with microtubules and is required for spindle assembly. Rae1 contains a WD repeat, a β propeller structure that is often used for multiprotein complex formation. It is conceivable that Rae1 forms a variety of functional RNP complexes dependent on the biological context. In fact, Blower et al. (2005) report several proteins that associate with Rae1 in *Xenopus* egg extracts. Some of these proteins may specialize the function of the Rae1 complex.

Rae1 has another intriguing link to the spindle apparatus. Nup98, a component of the Rae1-containing RNP complex, is produced by autocleavage of its 98 kDa or 190 kDa precursors, which are generated

through alternative splicing from one gene (Fontoura et al., 1999). The other half of the protein processed from the 190 kDa precursor is Nup96, which is a component of the Nup107-160 subcomplex, the essential core of the NPC. Recently, Devos et al. (2004) hypothesized that this subcomplex is evolved from "protocoatomer," whose structure is used to curve intracellular membranes. Surprisingly, the Nup107-160 complex is recruited to kinetochores during mitosis (Loiodice et al. [2004] and references therein), although its kinetochore function remains a mystery. Since Nup96 acts as an NPC-docking module of Rae1-Nup98 complex (Hodel et al., 2002), it is tempting to speculate that the dynamic interaction between Nup98 and Nup96 may be used during M phase to control microtubule assembly and the spindle checkpoint.

Another important finding of Blower et al. (2005) is that RNAs play a translation-independent role in spindle assembly in M phase. The authors demonstrate that RNase-treated extracts do not support spindle assembly. The phenotypes caused by RNase treatment are not due to its indirect effect on protein translation, because protein translation inhibitors do not block spindle assembly in *Xenopus* egg extracts. Consistent with this finding, the authors show that RNA is required for the microtubule assembly activity of the Rae1-containing complex. However, the functional role of RNA in microtubule assembly remains speculative. As the authors suggest, an interesting hypothesis is that RNA may act as an efficient scaffold to assemble multiple factors required for spindle assembly. Since Blower et al. (2005) introduce a method to create RNase-treated extracts from which RNase is removed, it will be possible in the future to address the questions of whether the Rae1 complex is the only RNP complex required for spindle assembly and whether specific RNAs are involved in this process.

Unlike most man-made tools, many biological components do play multiple functions. We are far from understanding how this is possible. By learning the connection between nuclear transport and the spindle apparatus, we may be able to obtain some useful hints.

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