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Subcellular scaling: does size matter for cell division?

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Among different species or cell types, or during early embryonic cell divisions that occur in the absence of cell growth, the size of subcellular structures, including the nucleus, chromosomes, and mitotic spindle, scale with cell size. Maintaining correct subcellular scales is thought to be important for many cellular processes and, in particular, for mitosis. In this review, we provide an update on nuclear and chromosome scaling mechanisms and their significance in metazoans, with a focus on *Caenorhabditis elegans*, *Xenopus* and mammalian systems, for which a common role for the Ran (Ras-related nuclear protein)-dependent nuclear transport system has emerged.

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Introduction

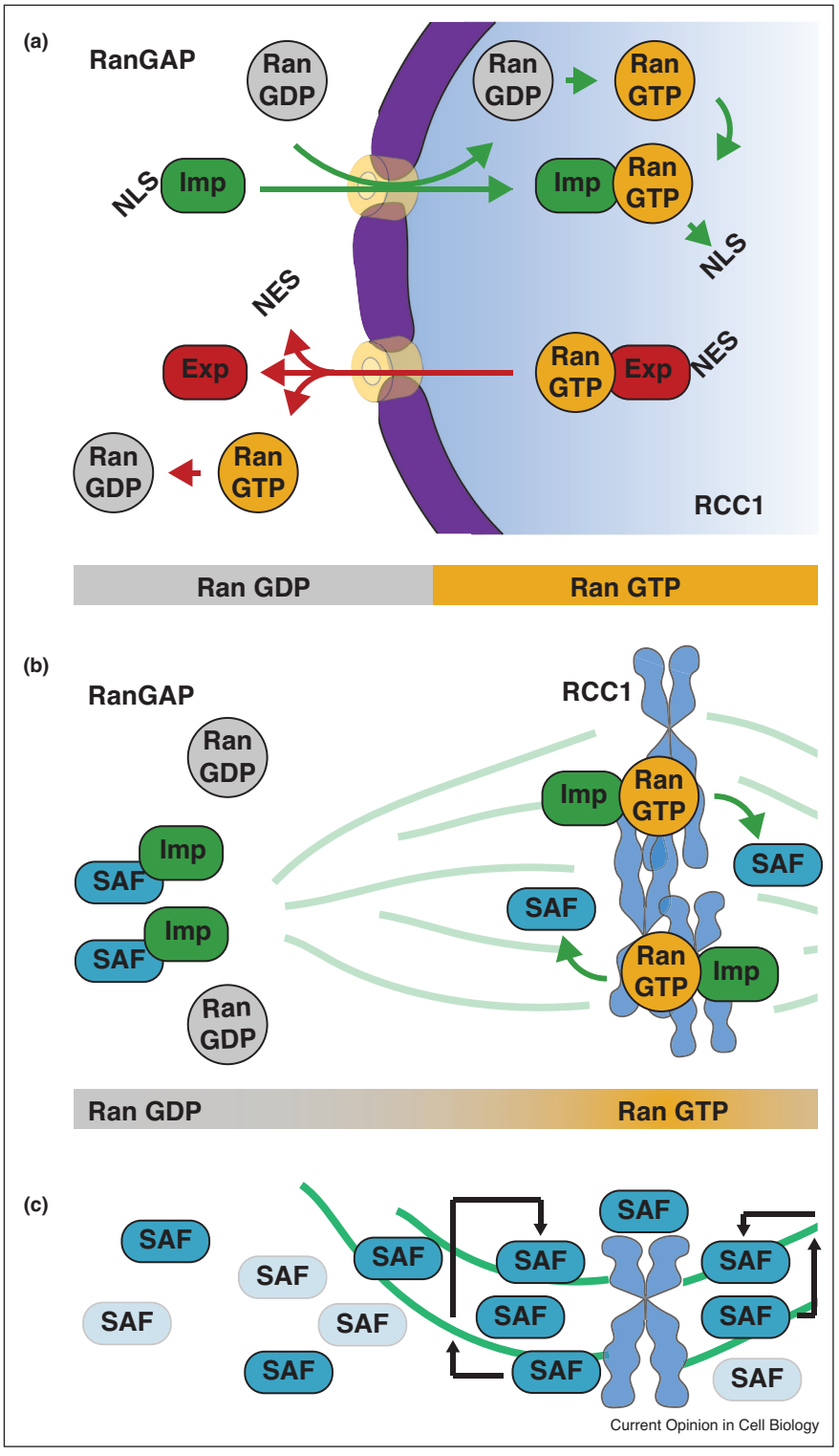
Absolute and relative size of biological entities varies widely, both within and among species at all levels of organization above the atomic/molecular: the organism, the cells that make up the organism, and the components of the cells. How does scaling occur so that everything fits and functions properly? Until recently, the control systems that a cell uses to regulate and coordinate the size of its internal structures were virtually unknown. One candidate coordinator is the small GTPase Ran and its downstream transport machinery, which are involved in many cellular processes in both interphase and mitosis, from nucleo-cytoplasmic transport to spindle morphogenesis to nuclear envelope assembly [1,2]. We will start with a brief overview of the Ran pathway and discuss recent work that elucidates mechanisms of subcellular scaling and the potential importance for cell function and division.

The RanGTP pathway and spindle assembly

RanGTP marks the genome in both interphase and mitosis and acts as a molecular switch. In the nucleus, Ran is concentrated in its GTP state due to the chromatin-associated RanGEF (Guanine nucleotide Exchange Factor) RCC1. In the cytoplasm, Ran is found in its GDP form due to the activity of cytoplasmic RanGAP (GTPase Activating Protein). RanGTP binds both importins and exportins, stabilizing the exportin–cargo interaction required for nuclear export, while releasing cargoes from importins. As a result, proteins with an NLS (Nuclear Localization Signal) are transported into the nucleus by importins and accumulate in the nucleus, while NES (Nuclear Export Signal)-containing proteins are transported out of the nucleus (Figure 1a).

During mitosis, RCC1 remains associated with the chromosomes following nuclear envelope breakdown, enriching RanGTP in the zone where the spindle will assemble. As RanGTP diffuses away from the chromatin, RanGAP in the cytoplasm converts it to RanGDP, creating a RanGTP gradient. Numerous NLS-containing SAFs (Spindle Assembly Factors) are released within this gradient where they contribute to spindle assembly by nucleating and organizing microtubules [2] (Figure 1b). A recent study in cultured cells has revealed an interesting feedback mechanism that results from the binding of RanGTP-activated SAFs to microtubules [3••]. Microtubule binding serves to concentrate microtubule nucleators on the forming spindle, amplifying microtubule polymerization and rendering the length of the spindle insensitive to the size of the Ran gradient (Figure 1c). This microtubule-dependent amplification mechanism would explain why increasing the amount of chromatin in the spindle, and therefore the amount of RCC1 and RanGTP, does not increase spindle length in *Xenopus* egg extracts [4], while increasing the amount of microtubule polymer by addition of a drug dramatically increases spindle size [5]. Importantly, however, NLS-containing SAFs that regulate microtubule nucleation and dynamics downstream of RanGTP, including TPX2 and kif2a, have been shown to act as scaling factors for centrosomes and/or spindles and whose activities are regulated by importin α [6–8]. Thus, the emerging concept is that while RanGTP acts as a trigger for spindle assembly, the complex interplay between SAFs, microtubules and importins contributes to spindle scaling. Mechanisms of spindle size regulation have been elucidated in a variety of systems, particularly *Xenopus*, and are discussed in detail elsewhere [2,9].

Figure 1



The RanGTP pathway and spindle assembly. **(a)** In interphase, Ran is GTP-bound in the nucleus due to the chromatin-associated RanGEF, RCC1, and GDP-bound in the cytoplasm due to cytoplasmic RanGAP. Proteins harboring an NLS are imported into the nucleus by importins and released when importins interact with RanGTP. Proteins containing an NES are exported out of the nucleus by RanGTP-bound exportins and released by GTP hydrolysis. **(b)** In mitosis, chromosome-bound RCC1 creates a Ran-GTP gradient near the chromosomes where NLS-containing SAFs are released from importins, promoting microtubule nucleation and stabilization. **(c)** Following microtubule nucleation by SAFs, the interaction between SAFs and microtubules leads to a feedback that further enriches SAFs on microtubules.