dorsal and ventral hypothalamic nuclei, which are regions regulating feeding behaviour and energy balance (Figure 1).

Overall, the hypothalamic RFamide systems (Kiss, GnIH, RFRP) are excellent candidates for modifying the proximate cue of photoperiod towards species-specific seasonal strategies and integrating energy balance information (food, fat, temperature) to the reproductive system. Describing second messenger pathways and mapping the neuroanatomical network of hypothalamic RFamide signaling will be the challenge for the near future. Comparison of mammal and bird species with different reproductive strategies will most certainly help to solve this intriguing puzzle of neuroanatomical mechanisms underlying optimal timing of hibernation and reproduction.

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http://dx.doi.org/10.1016/j.cub.2014.05.061

Nuclear Envelope Breakdown: Actin' Quick to Tear Down the Wall

Nuclear envelope breakdown in metazoan cells is thought to be facilitated by microtubules, which pull on the nuclear membranes. Unexpectedly, an F-actin meshwork helps to tear down the large nucleus of starfish oocytes and to prevent chromosome loss in meiosis.

Binyam Mogessie and Melina Schuh*

Every time a metazoan cell divides, its contents are completely reorganized. One of the most dramatic events during this reorganization is the demolition of the nucleus, which needs to be broken down so that the microtubule spindle can access the chromosomes. Decades of work have started to reveal the biochemical mechanisms by which the nucleus is disassembled (Figure 1A) [1–3]. Mitotic kinases, such as Cdk1/cyclin B, phosphorylate various proteins of the nuclear envelope. This first leads to the disintegration of nuclear pore complexes, which normally allow transport between the nucleus and the cytoplasm [4]. Subsequently, the nuclear lamina, a filament network that stabilizes the nucleus from inside, is depolymerized [5]. This gradual disassembly weakens the nuclear envelope, which eventually leads to a collapse of the nucleus and dispersion of the nuclear membranes into the endoplasmic reticulum. It has been suggested that this rapid and dramatic event of nuclear collapse, easily seen with a transmitted light microscope, is facilitated by forces generated by the cytoskeleton. So far, based on studies in mammalian fibroblasts, these mechanical forces have been thought to come primarily from microtubules: these attach to the nuclear envelope via the motor protein dynein, stretch the nucleus and tear holes into the nuclear membranes, which renders the physical barrier discontinuous [6,7].

Despite recent progress in understanding nuclear envelope disassembly, many questions remain to be answered. For instance,

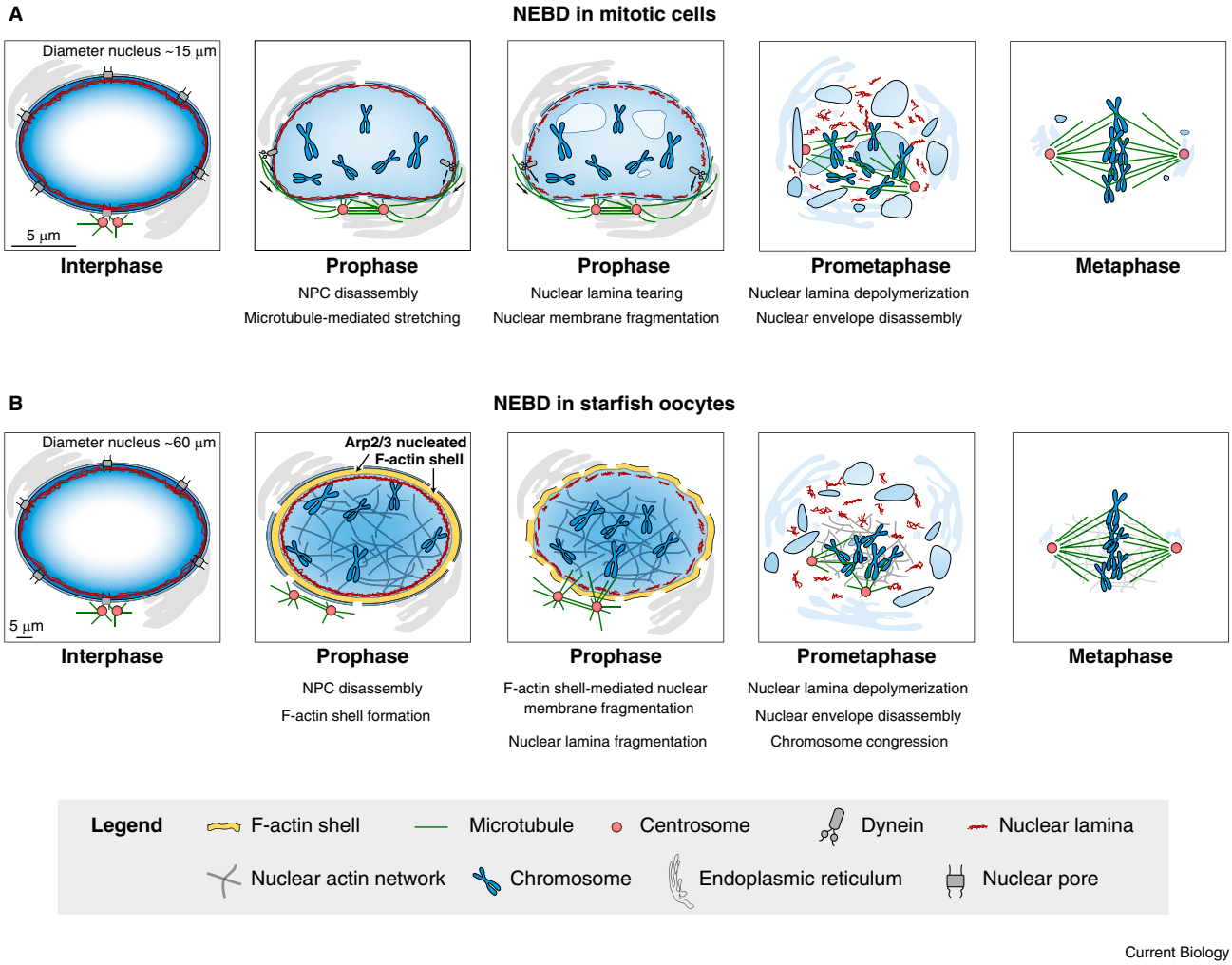

Figure 1. Nuclear envelope breakdown in starfish oocytes is driven by an F-actin shell.

(A) In mitotically dividing cells, the nuclear envelope is broken down by microtubule-mediated stretching forces that tear holes into the nuclear lamina and membranes. (B) In starfish oocytes, where microtubules are too short to bridge the entire nucleus, nuclear envelope breakdown is achieved by an Arp2/3 complex-nucleated F-actin shell that fragments nuclear membranes.

microtubules are not absolutely essential to break down the nucleus. In some cells, where nuclei are large, microtubules cannot even bridge the entire nuclear volume [8]. It seems possible that other cytoskeletal structures facilitate nuclear envelope breakdown (NEBD), but direct evidence for this model has been missing. As reported recently in *Current Biology*, Mori *et al.* [9] have now demonstrated an unexpected function for actin in breaking down the large nuclei of starfish oocytes (Figure 1B). Using an elegant set of experiments, they demonstrate that an Arp2/3 complex-nucleated F-actin shell disintegrates the nucleus and prevents the loss of chromosomes during meiosis.

Previous work had revealed a wave of actin polymerization underneath the nuclear envelope in starfish oocytes around the time of NEBD [8]. The actin structure formed in this process was termed ‘actin shell’, because it engulfed the entire nucleus; however, the function of the actin shell as well as the mechanism of its formation remained unclear. Mori *et al.* [9] first analysed how the actin shell was generated. As the density of actin in the shell was very high, they reasoned that it might be generated by the Arp2/3 complex. In contrast to formins, which assemble long, unbranched actin filament bundles, the Arp2/3 complex forms densely branched actin meshworks which cannot be resolved as individual filaments when observed by light microscopy. Indeed, Mori *et al.* [9] found that components of the Arp2/3 complex were recruited to the nuclear envelope just when the actin shell formed. Inhibition of the Arp2/3 complex revealed that the actin shell was indeed dependent on the Arp2/3 complex. The authors then went on to investigate the function of the actin shell. Strikingly, they found a strong correlation between actin shell assembly and nuclear membrane fragmentation: nuclear envelope regions where the actin shell had assembled fragmented soon after the actin polymerization wave had passed them.

From these observations, Mori *et al.* [9] reasoned that the actin shell might facilitate NEBD. In a series of acute

Arp2/3 complex inhibition experiments, they found that blocking actin shell assembly did indeed compromise NEBD. Their data suggest that the disintegration of nuclear pore complexes remained unaffected, but the second step of NEBD, in which nuclear membranes become fragmented, was severely impaired when the formation of the actin shell was blocked. The authors then used electron and high resolution light microscopy to investigate how actin might help to fragment the nuclear membranes. Interestingly, they observed unusual 'spike' like filament structures projecting through the nuclear envelope. Although the function of these spikes in NEBD is difficult to assess, it is tempting to speculate that they might help to pierce and to thereby fragment nuclear membranes. Consistent with this model, the spikes were frequently observed directly adjacent to areas of the nuclear envelope that were already fragmented.

But is the rapid fragmentation of the nuclear envelope by the actin shell also important to generate functional eggs? As disruption of the actin shell only delays NEBD without blocking it, one might expect that the egg is still fine. Interestingly, Mori *et al.* [9] found that the actin shell is required to prevent aneuploidy in starfish oocytes: When they blocked the formation of the actin shell, oocytes had severe difficulties in capturing all chromosomes on the microtubule spindle. Instead, chromosomes were lost in the nuclear region, resulting in aneuploidy. Together, these results demonstrate that the rapid fragmentation of the nuclear envelope is essential to segregate the chromosomes reliably in starfish oocytes.

A very interesting question that remains to be answered is whether the actin shell really just acts as a demolition machinery that tears down the wall, or whether it serves an additional purpose. The large nuclei of starfish oocytes are far more densely packed with nuclear pore complexes than fibroblast nuclei [9,10]. It seems possible that nuclear pore complexes are stored in the oocyte's nucleus to be readily available during the rapid mitotic divisions of the embryo. Thus, it will be interesting to investigate if the actin shell might have a function in preserving these components for post-meiotic reassembly of nuclei.

Another important question is whether the mechanism described by Mori *et al.* [9] is also relevant in mitotically dividing cells. These normally have smaller nuclei that are fully accessible by microtubules. Interestingly, similar actin shells that form along the nuclear envelope during NEBD have also been observed in early embryos of various echinoderm species, including sea urchin, starfish and sand dollars [9,11]. It is thus conceivable that early mitotic divisions in echinoderms also rely on an actin-dependent mechanism of nuclear envelope disassembly.

Whether actin also plays a role during NEBD in other eukaryotes remains to be investigated. It might of course be surprising if such an important function of actin in mitotic cells has previously been missed. However, most of our knowledge about NEBD in mitosis comes from studies in tissue culture cells such as fibroblast, whereas our bodies contain many specialized cell types, which strongly differ in size, morphology and nuclear volume. Furthermore, several recent studies have revealed unexpected functions for actin in nuclei — not only in oocytes, but also in various other cell types. For instance, a growing body of evidence suggests that nuclear actin has various functions in controlling transcription [12–15]; a nuclear actin meshwork is required to mechanically stabilize and organize the giant nuclei of *Xenopus* oocytes [16–18]; contractile actin networks in the nuclear area have been reported to transport chromosomes to the microtubule spindle in starfish oocytes [8]; and nuclear actin also functions as part of chromatin remodeling complexes [18,19]. Thus, actin takes over a wide variety of functions in nuclei. The work of Mori *et al.* [9] is a seminal contribution to our knowledge of nuclear actin function and expands the list to fragmentation of the nucleus in starfish oocytes.

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http://dx.doi.org/10.1016/j.cub.2014.05.059