Dynein at the nuclear envelope

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Most cellular organelles are positioned through active transport by motor proteins. This is especially important during cell division, a time when the organelles and genetic content need to be divided equally between the two daughter cells. Although individual proteins can attain their correct location by diffusion, larger structures are usually positioned through active transport by motor proteins. The main motor that transports cargoes to the minus ends of the microtubules is dynein. In nondividing cells, dynein probably transports or positions the nucleus inside the cells by binding to the nuclear envelope (NE; Burke & Roux, 2009). However, it appears that dynein also has important cell-cycle-regulated functions at the NE, as it is recruited to the NE every cell cycle just before cells enter mitosis (Salina *et al*, 2002; Splinter *et al*, 2010). Here, we discuss why dynein might be recruited to the NE for a brief period before mitosis.

During late G2 or prophase the centrosomes separate to opposite sides of the nucleus, but remain closely associated with the NE during separation. This close association is probably mediated through NE-bound dynein, which 'walks' towards the minus ends of centrosomal microtubules, thereby pulling centrosomes towards the NE (Splinter *et al*, 2010; Gonczy *et al*, 1999; Robinson *et al*, 1999). We speculate that close association of centrosomes to the NE might have several functions. First, if centrosomes are not mechanically coupled to the NE, centrosome movement during

separation will occur in random directions and chromosomes will not end up between the two separated centrosomes. In this scenario, individual kinetochores might attach more frequently to microtubules coming from both centrosomes (merotelic attachments), a defect that can result in aneuploidy, a characteristic of cancer. Second, centrosome-nuclear attachment also keeps centrosomes in close proximity to chromosomes, which might facilitate rapid capture of chromosomes by microtubules nucleated by the centrosomes after NE breakdown. This might not be absolutely essential, as chromosome alignment can occur in the absence of centrosomes. However, the spatial proximity of centrosomes and chromosomes at NE breakdown might improve the fidelity of kinetochore capture and chromosome alignment.

In addition, dynein has also been suggested to promote centrosome separation in prophase in some systems (Gonczy *et al*, 1999; Robinson *et al*, 1999; Vaisberg *et al*, 1993), although not in others (Tanenbaum *et al*, 2008). Perhaps dynein, anchored at the NE just before mitosis, could exert force on microtubules emanating from both centrosomes, thereby pulling centrosomes apart. However, this force could also be produced by cortical dynein and specific inhibition of NE-associated or cortical dynein will be required to test which pool is responsible.

Dynein has also been implicated in the process of NE breakdown itself, by promoting mechanical shearing of the NE. Two elegant studies showed that microtubules

can tear the NE as cells enter mitosis (Salina *et al*, 2002; Beaudouin *et al*, 2002). One possibility is that microtubules growing into the NE mechanically disrupt it. Alternatively, NE-associated dynein might 'walk' along centrosomal microtubules and thereby pull on the NE, tearing it apart. However, testing the exact role of dynein in NE breakdown is complicated by the fact that centrosomes detach from the NE on inactivation of dynein and centrosomal microtubules stop growing efficiently into the NE. Thus, selective inhibition of dynein function will also be required to test this idea.

Specific recruitment of dynein to the NE just before mitosis clearly suggests a role for dynein at the NE in preparing cells for mitosis. A major role of NE-associated dynein is to maintain close association of centrosomes with the NE during centrosome separation, which might be needed for efficient capture and alignment of chromosomes after NE breakdown, but additionally, NE-associated dynein could facilitate breakdown and contribute to centrosome separation in some systems.

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