The size-wise nucleus: nuclear volume control in eukaryotes

Michael D. Huber and Larry Gerace

Department of Cell Biology, The Scripps Research Institute, La Jolla, CA 92037

Eukaryotic cells have an “awareness” of their volume and organelar volumes, and maintain a nuclear size that is proportional to the total cell size. New studies in budding and fission yeast have examined the relationship between cell and nuclear volumes. It was found that the size of the nucleus remains proportional to cell size in a wide range of genetic backgrounds and growth conditions that alter cell volume and DNA content. Moreover, in multinucleated fission yeast cells, Neumann and Nurse (see p. 593 of this issue) found that the sizes of individual nuclei are controlled by the relative amount of cytoplasm surrounding each nucleus. These results highlight a role of the cytoplasm in nuclear size control.

One of the fundamental properties of eukaryotes is their ability to maintain cell sizes and organelle volumes that are appropriate for different growth and differentiation states. Although most organelles, such as the ER and mitochondria, can vary greatly in amounts, it has long been observed that cells maintain a roughly constant “karyoplasmic ratio” (the ratio of the nuclear volume to cell volume) (Wilson, 1925; Cavalier-Smith, 2005). This volume relationship is found in cells with widely different DNA contents, ranging from single-celled eukaryotes to mammalian cells. Now, a more penetrating look at this question has been taken in two studies involving quantitative morphometric analysis of yeast (Jorgensen et al., 2007; Neumann and Nurse, 2007). The nucleus is known to increase in volume through the cell cycle (for review see Umen, 2005), but how this is coupled to cell cycle progression and cell growth is largely mysterious. The cell size checkpoint in budding yeast requires that cells undergo a continuous increase in volume from G1 until M phase, extending the conclusions of Jorgensen et al. (2007). They also examined mutant strains blocked in cytokinesis, in which cells acquired multiple, unevenly distributed nuclei. In this situation, nuclei with a range of volumes were present in a single cell. Interestingly, the volume of each nucleus was directly proportional to the amount of “surrounding” cytoplasm. The nuclei located in central regions of these cells were crowded into a relatively small cytoplasmic area and were proportionally smaller than the peripheral nuclei, which occupied a greater cytoplasmic space.

To investigate the mechanisms of size control in these multinucleated cells, the authors mechanically displaced nuclei in the cells by centrifugation, and then evaluated the growth of individual nuclei in real time. Nuclei that were positioned within a disproportionately large amount of surrounding cytoplasm grew more rapidly than in normal mononucleated cells, up to the point where a N/C ratio of ~0.08 was achieved. By contrast, nuclei surrounded by small amounts of cytoplasm “waited” until the adjacent cytoplasmic volume became sufficiently large before they started growing. These results strongly suggest that cytoplasmic components directly and “dominantly” influence nuclear growth in fission yeast. An effect of the cytoplasm on nuclear size also was seen with metazoan systems, showing that the highly condensed avian erythrocyte nucleus undergoes dramatic swelling when fused to a proliferating cell (Harris, 1967), and that the heterochromatic nucleus of sperm grows continuously when introduced into the cytoplasm of Xenopus oocytes in vitro (Gurdon, 1976). The experiments with multinucleated yeast cells indicate that nuclear size control does not involve a diffusible cytoplasmic factor; otherwise, all nuclei within the
When two small daughter nuclei are formed from a parent nucleus (Fig. 1). During yeast mitosis, the peripheral ER–NE connection is morphologically continuous with the outer nuclear membrane intact. In both higher and lower eukaryotes, the peripheral ER lamina, yeast undergo a closed mitosis in which the NE remains intact. The peripheral ER lamina is involved in the control of nuclear size and shape (for review see Gruenbaum et al., 2005; Worman and Courvalin, 2005; Brandt et al., 2006). When does aberrant nuclear structure contribute to cellular dysfunction, and when is it simply a consequence of it? Although many different factors are likely to be involved in nuclear size control in eukaryotes, the tools of genetics and cell biology should soon begin to expand on this issue.

Submitted: 23 October 2007
Accepted: 25 October 2007

References

Brandt, A., F. Papagiannouli, N. Wagner, M. Wilsch-Brauninger, M. Braun, E.E. Furlong, S. Loseth, C. Wenel, F. Pilot, N. Vogt, et al. 2006. Developmental control of nuclear size and shape by Kugelkern and Kurzkern. *Curr. Biol.* 16:543–552.

Cavalier-Smith, T. 2005. Economy, speed and size matter: evolutionary forces driving nuclear genome miniaturization and expansion. *Ann. Bot. (Lond.)* 95:147–175.

Gruenbaum, Y., A. Margalit, R.D. Goldman, D.K. Shumaker, and K.L. Wilson. 2005. The nuclear lamina comes of age. *Nat. Rev. Mol. Cell Biol.* 6:21–31.

Harris, H. 1967. The reactivation of the red cell nucleus. *J. Cell Sci.* 2:23–32.

Jørgensen, P., N.P. Edgington, B.L. Schneider, I. Rupes, M. Tyers, and B. Futcher. 2007. The size of the nucleus increases as yeast cells grow. *Mol. Biol. Cell.* 18:3523–3532.

Neumann, F.R., and P. Nurse. 2007. Nuclear size control in fission yeast. *J. Cell Biol.* 179:593–600.

Newport, J.W., K.L. Wilson, and W.G. Dunphy. 1990. A lamin-independent pathway for nuclear envelope assembly. *J. Cell Biol.* 111:2247–2259.

Santos-Rosa, H., J. Leung, N. Grimsey, S. Peak-Chew, and S. Siniossoglou. 2005. The yeast lipin Smp2 couples phospholipid biosynthesis to nuclear membrane growth. *EMBO J.* 24:1931–1941.

Starr, D.A., and J.A. Fischer. 2005. KASH 'n Karry: the KASH domain family of cargo-specific cytoskeletal adaptor proteins. *Bioessays.* 27:1136–1146.

Umen, J.G. 2005. The elusive sizer. *Curr. Opin. Cell Biol.* 17:435–441.

Wilson, E.B. 1925. The karyoplasmic ratio. In *The Cell in Development and Heredity.* Third edition. The Macmillan Company, New York. 727–733.

Worman, H.J., and J.C. Courvalin. 2005. Nuclear envelope, nuclear lamina, and inherited disease. *Int. Rev. Cytol.* 246:231–279.

Yang, L., T. Guan, and L. Gerace. 1997. Lamin-binding fragment of LAP2 inhibits increase in nuclear volume during the cell cycle and progression into S phase. *J. Cell Biol.* 139:1077–1087.

Zink, D., A.H. Fischer, and J.A. Nickerson. 2004. Nuclear structure in cancer cells. *Nat. Rev. Cancers.* 4:677–687.