Apoptosis is now considered to be a crucial part of the normal repertoire of tissue function. In multicellular organisms, groups of cells generally operate together as functional units, and tissue homeostasis is maintained by a delicate balance of cell removal through apoptosis, and replacement via proliferation. Although this programmed form of cell death occurs daily and extensively as part of normal tissue turnover, it is also involved in profound aspects of tissue remodeling. An extreme example is in the developing hand, where the removal of swathes of mesenchymal cells is required for digit formation. Apoptosis en masse can be used to great effect in normal adult physiology, nowhere being as dramatic as in the reproductive system. Billions of breast epithelial cells, for example, are removed at weaning when the gland is remodeled to a resting state from a lactational one; and apoptosis occurs cyclically in the glands of breast and endometrium during the menstrual cycle. These processes are tightly controlled by hormones and by local micro-environmental signals, some from extracellular matrix.

Since there are few events more important to species survival than a well executed delivery of the newborn after a successful pregnancy, it comes as no surprise to learn that the birth process involves well orchestrated biochemical and cellular changes in placental tissue. A paper from Jerome Strauss III's group reports in this issue of *The Journal* that apoptosis is prominent in the preparation of fetal membranes for rupture during labor in the rat (1). The rat amnion consists of a triple layer of simple epithelium, connective tissue, and fibroblasts. A second membrane, the visceral yolk sac (or chorion laeve in human), surrounds the amnion and both break during delivery. Electron microscopy of the physical changes occurring over the last few days of pregnancy had already indicated that the amnion weakens dramatically on day 21, the day of parturition (2). This is associated with deterioration and detachment of the amnion epithelial cells, and internalization of desmosomes. In addition, loss of collagen from the underlying connective tissue occurs, coinciding with upregulation of matrix metalloproteinase expression and activity. Both the type IV collagenase, MMP-9, and an interstitial collagenase are activated on days 20 and 21, probably contributing to the breakdown of both basement membrane and connective tissue.

The authors have now shown convincingly that there is extensive apoptosis in the amnion epithelium and that this is timed to occur on day 21 just before parturition, adding another layer of complexity to preparation of fetal membranes for labor (1). Although the mechanism for initiating the whole program is not clear, one possibility is that hormonal alterations trigger a process in which degradation of the amnion is coordinated with other events that lead to expulsion of the newborn fetus, such as activation of myometrial contraction. But could apoptosis act as the final trigger for parturition? This question is not yet answered, but since apoptosis does not occur in the neighboring yolk sac membrane, it may just be a consequence of other changes in the amnion. In the breast, specific interactions between epithelial cells and basement membrane are required for suppression of apoptosis (3), and since MMPs are upregulated during involution of the gland (4), it is possible, though not yet proven, that their activation is causally related to the apoptosis that occurs at this time. It will be important to identify whether altered MMP expression and the resulting changes in amnion basement membrane induce apoptosis in the epithelium directly, or whether it is triggered by another mechanism.

Are these findings relevant to obstetric medicine? Neonatal intensive care places a major burden on the health care industry. Commonly, preterm labor follows premature rupture of the membranes, a problem that may result from infection, cervical incompetence, inherited collagen mutations, smoking, or dietary insufficiency (5, 6). As in the rat, the subepithelial collagenous matrix of human amnion makes an important contribution to the strength of the placental membranes (7, 8). But humans are larger than rats and are upright, so the mechanical load is greater, especially over the cervix where the chorioamnion normally breaks (8). Attempts to relate membrane rupture to reduced levels of collagen in the term chorioamnion have met with mixed results, although morphological studies indicate that widespread apoptosis and degeneration do not occur in human amnion at term (8). Nonetheless, it cannot be excluded that weakening of the membranes may result from more localized changes in the tissue. Examination of spontaneous rupture sites has produced evidence of local morphological alterations including thinning of the trophoblast layer of the chorion (9), but this approach cannot distinguish postrupture changes from those that might have been causative. As so often in comparative reproductive biology, an animal model has stimulated an important hypothesis that will need to be carefully tested in human, and may even lead to treatment in cases of women at risk of premature rupture of the membranes.

Charles H. Streuli
School of Biological Sciences
University of Manchester
and
John D. Aplin
Department of Obstetrics and Gynaecology and School of Biological Sciences
University of Manchester

References

1. Lei, H., E. Furth, R. Kalluri, T. Chiou, K. Tilly, J. Tilly, K. Elkon, J. Jeffrey, and J. Strauss III. 1996. A program of cell death and extracellular matrix degradation is activated in the amnion prior to the onset of labor. *J. Clin. Invest.* 98:1971–1978.

2. Paavola, L., E. Furth, V. Delgado, C. Boyd, C. Jacobs, H. Lei, and J. Strauss III. 1995. Striking changes in the structure and organization of rat fetal membranes precede parturition. *Biol. Reprod.* 53:231–338.

3. Pullan, S., J. Wilson, A. Metcalfe, G. Edwards, N. Goberdhan, J. Tilly, J. Hickman, C. Dive, and C. Streuli. 1996. Requirement of basement membrane for the suppression of programmed cell death in mammary epithelium. *J. Cell Sci.* 109:631–642.

4. Talhouk, R., M. Bissell, and Z. Werb. 1992. Coordinated expression of

extracellular matrix-degrading proteinases and their inhibitors regulates mammary epithelial function during involution. *J. Cell Biol.* 118:1271–1282.

5. Aplin, J., S. Campbell, P. Donnai, J. Bard, and T. Allen 1986. Importance of vitamin C in maintenance of the normal amnion: an experimental study. *Placenta.* 7:337–389.

6. Kitzmiller, J. 1984. Preterm premature rupture of the membranes. *In* Preterm Birth: Causes, Prevention and Management. F. Fuchs, and P. Stubblefield, editors. Macmillan Publishing Co., New York. 298–322.

7. Bourne, G. 1962. The human amnion and chorion. Lloyd-Luke (Medical books), London. 276 pp.

8. Aplin, J., S. Campbell, and T. Allen 1985. Human amnion epithelial extracellular matrix: ultrastructure, composition, and deposition. *J. Cell Sci.* 79: 119–136.

9. Malak, T., and S. Bell. 1994. Structural characteristics of term human fetal membranes: a novel zone of extreme morphological alteration within the rupture site. *Br. J. Obstet. Gynaecol.* 101:375–386.