Book Review

Mammary development in health and disease: Biochemical Society Symposium 63

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Mammary Development and Cancer. Edited by P.S. Rudland, D.G. Fernig and S.J. Leinster. Portland Press, London, UK: 1997. Pp. 344. ISBN: 1 85578 087 9. UK £65.00/US \$110.50.

As a non-essential glandular organ developing at puberty, the mammary gland offers special opportunities for developmental research. It can serve as a model for various epithelial tissue systems, developing at the beginning of ovarian oestrogen secretion from small 'Anlagen' associated with the teats. Since the mammary gland undergoes cyclical phases of development in oestrus, but also in response to pregnancy and involution, it provides a model for physiological apoptosis. Finally, because of the importance of the breast cancer problem, tumor formation represents an important counterpoint to apoptosis in the gland. More than in any other significant tissue at risk for tumor formation, in the mammary gland these alternative fates stand out as topics of study.

Biochemical Society Symposium 63 was held in the Spring of 1996. The compiled papers presented at the meeting represent a cross-section of topics: from transcription factors, signal transduction, to dairy science and breast cancer metastasis. The authors are all highly qualified. In several cases papers present overviews and intuitive composite pictures of mammary development arrived at in decades of research in this field. These composites are original and gripping to read. In particular the organizers and editors, especially Philip Rudland and colleagues have distinguished themselves with constructive review contributions: Chapter 1 (Growth and differentiation of the normal mammary gland and its tumors), Chapter 15 (Induction of a variety of preneoplasias and tumors in the mammary glands of transgenic rats) and Chapter 24 (Use of DNA transfer in the induction of metastasis in experimental mammary systems). Additional outstanding conceptual contributions I found fascinating and useful came from Paul Edwards (Chapter 2: control of the three-dimensional growth pattern of mammary epithelium: Role of genes of the *wnt* and *erbB* families studied using reconstituted epithelium) and from the Docherty Group (Chapter 25: Matrix metalloproteinases and metastatic cancer).

Thus far little work has been published about the expression of 'death' genes in the mammary gland such as *fas*, *fas* ligand or caspases. This volume will not alter this deficit. The concern of most investigators of physiological apoptosis has been regulation. How does the tissue know when to initiate apoptosis in cells no longer

needed? This sounds an easy question, almost trivial, but is central to apoptosis in any developmental context. Whereas we have learned that the 'execution' phase of apoptosis looks the same largely without differences among tissues, the 'initiation' phase seems highly variable, with almost unique factors and situations governing onset or entry into apoptosis. In three chapters devoted to the question of how the mammary gland adapts in its structure and milk output to the needs of progeny, several experiments and hypotheses for explaining the regulation of programmed cell death in the mammary gland are discussed.

Because apoptosis in the mammary gland is physiological, and can be massive, involving the majority of cells in the tissue, as in involution, or can be confined just to a few cells in individual alveoli of lactating glands, regulation in this system must be capable of acting very selectively, locally and with a short half-life. The chapters dealing with regulation contain insights likely to have general significance for apoptosis phenomena. Regulation will ultimately be a key issue in the normal developmental situations where apoptosis comes into play.

We know about several early signals for impending apoptosis in the mammary gland: upregulation of *fos*, *jun* and *p53* genes. Taking a simplistic view, one might imagine that changes in systemic lactogenic hormone levels might regulate the onset of apoptosis. As usual, the simplistic view is certainly false.

Malcolm Peaker (Chapter 6: Local control of the mammary gland) introduces the biological problem and explains why local control of lactation must apply. Dairy farmers have been aware for many years, that more complete milking at one gland increases its output relative to others less milked. Individual glands neglected in the milking process, involute individually. From this bit of history, Peaker details experiments which were aimed at deciding between two main alternatives for local control: distension, or pressure caused by accumulated milk, or alternatively, the presence of an 'inhibitor' which, accumulating with milk, down-regulates further milk secretion. The results have proved ambivalent, since pressure, for example produced by isotonic lactose injected into the

ducts, will down-regulate milk secretion (and presumably initiate involution). At the same time, elegant experiments have shown the existence of at least one sort of inhibitor, called FIL, for 'feedback inhibitor of lactation'.

Peaker warns of the danger of interpreting lactational physiology across species barriers, but he ends his contribution with a delightful anecdote which convincingly shows the power of local mammary regulation. The marsupials certainly confound our imagination. Peaker's expression of progeny production 'by conveyor belt' sums up the peculiarity of the marsupials nicely. A marsupial mother is lactating simultaneously in two mammary glands, one at maximal output for young at heel, and a second, producing small quantities of milk (of different composition) for the infant in the pouch. Indeed, the regulation is complex.

Colin Wilde (Chapter 7: Autocrine regulation of milk secretion) continues the theme of FIL, describing it as a molecular entity. Most importantly for me, he makes a solid connection between FIL as an inhibitor of milk secretion and FIL as an inducer, under appropriate conditions, of programmed cell death. His discussion of mammary regulation stresses the distinction between regulation of demand with fine control of milk output, and terminal regulation at milk stasis as an entry into involution. He introduces the significance of insulin-like growth factor binding proteins, such as the IGF-BP-5 which is up-regulated in apoptosis during mammary involution. In Wilde's concept FIL regulates daily milk output, inducing changes in cell number as needed in the alveoli, but is not in itself an apoptosis inducer. Involution, occurring in response to high FIL coupled with prolonged distension,

is a phenomenon regulated in a complex and also species-specific fashion, by a network of inter-related influences/factors.

A further highly significant contribution brings together distension, Ca^{2+} mobilization, FIL and apoptosis. Robert Burgoyne (Chapter 8: Role of calcium in the pathway for milk protein secretion and possible relevance for mammary gland physiology) shows that Ca^{2+} availability is essential for casein secretion, and that mechanical stimulation leads to activation of 'stretch-activated' membrane channels for Ca^{2+} entry. He speculates on a mechanism by which distension could act together with FIL to initiate apoptosis. Distension of alveoli due to milk accumulation would lead to a stretch-activated response which can involve emptying the Ca^{2+} stores in the endoplasmatic reticulum with consequences for casein synthesis, but also possibly for initiation of apoptosis.

While the precise pathway of apoptosis initiation cannot yet be described, the complexity of the process, the fine regulation, and some of the players have been discussed here in a collection providing some broad overviews. Rudland adds a final piece to the puzzle, the strange fact that pre-neoplastic hyperplasias fail to undergo involution or apoptosis, lactating consequently for up to 6 months after pregnancy. Clearly cessation of milk secretion is linked to apoptosis, and as an alternative to proliferation, apoptosis is absent or at least minimized in developing tumors. How all these pieces will eventually merge to present us with a coherent picture is a question that will keep us working for a few more years. Mammary biology will remain a useful avenue for proceeding toward some more complete understanding of apoptosis.