Preface

Wendy V. Ingman

Published online: 3 July 2014
© Springer Science+Business Media New York 2014

In 1994, Pollard and Henninghausen reported the unexpected observation that mice genetically deficient in a cytokine called colony-stimulating factor 1 (CSF1) failed to lactate [1]. As this cytokine is essential for normal macrophage proliferation, differentiation, survival and motility, deficiency in CSF1 caused these mice to be largely devoid of resident tissue macrophages. Investigation of this defect demonstrated that macrophages regulate developmental processes in the mammary gland, such that the absence of macrophages perturbed branching morphogenesis during pregnancy and led to a failure of lactation. Until this time, macrophages were known as immune system cells involved in phagocytosis, the presentation of antigens to generate adaptive immune responses and as effector cells that assist in elimination of bacterial and viral infections. That paper, published in the Proceedings of the National Academy of Sciences USA, went largely unnoticed by mammary gland biologists until 1997, when Dr Pollard was invited to speak at a Jackson Labs meeting on “Animal models in breast cancer” (Pollard, personal communication). Further studies on CSF1-deficient mice demonstrated the significance of macrophages in mammary branching morphogenesis, and finally led to widespread acceptance of the critical role these immune system cells play in normal mammary gland development. These discoveries eventually became a paradigm for the developmental roles of macrophages in other tissues, in regulating epithelial cell development and tissue complexity.

It has been 20 years since Pollard and Henninghausen’s landmark discovery, and macrophages are now recognised as

essential cells involved in all stages of mammary gland development. Indeed, we now appreciate that macrophages provide support for epithelial duct morphogenesis during puberty, ovarian cycling and pregnancy, and promote epithelial cell apoptosis and tissue remodelling during post-lactation mammary gland involution. Furthermore, similarities have emerged between the roles of macrophages in normal mammary gland development and in tumour progression, lending support to the concept that tumours hijack normal developmental processes to support their inappropriate and unconstrained growth. Thus, the roles of macrophages in the mammary gland extend beyond support for normal developmental processes, to their participation in the promotion of breast tumour progression and metastasis. As an essential regulator of macrophage function, the cytokine CSF1 therefore has a pivotal role in mammary gland health and disease, reviewed by Sullivan and Pixley.

Increasingly recognised are the roles of other components of the immune system, apart from macrophages, in regulation of mammary gland morphogenesis and breast cancer. Both innate and adaptive arms of the immune system, as well as a number of soluble secreted factors and intracellular immune signalling pathways, are essential components of the microenvironment that support mammary gland development. Inflammatory mediators such as nuclear factor kappa B and nitric oxide promote mammary involution, and may regulate milk yield during lactation, as proposed by Ingman et al. Furthermore, the role of mammary stromal cells in modulating the immune microenvironment is increasingly appreciated. Complex interactions between the immune microenvironment and fibroblasts and adipocytes, reviewed by Unsworth et al. and Brown respectively, are implicated in the promotion of normal mammary gland morphogenesis and homeostasis, and can affect cancer risk and the progression of established tumours. A number of cytokines secreted by the mammary epithelium direct the function of macrophages and thereby

W. V. Ingman (✉)
Discipline of Surgery, School of Medicine, The Queen Elizabeth
Hospital, University of Adelaide, Woodville, Australia
e-mail: Wendy.ingman@adelaide.edu.au

W. V. Ingman
Robinson Research Institute, University of Adelaide, Adelaide,
Australia

regulate mammary morphogenesis and cancer development, reviewed in this issue by Sun and Ingman. Boyle and Kochetkova further the concept of the immune microenvironment as significant in promotion of breast cancer by highlighting recent evidence supporting their proposal for an “immuniche” that supports breast cancer stem cells.

The critical roles of immune cells in mediating the morphological changes that occur in the mammary gland over the course of adult life pose unique immunological challenges for this tissue. Inflammation can promote tumorigenesis, and cancer cells must avoid destruction by the immune system in order to survive [2]. Therefore, the involvement of immune cells in normal mammary gland morphogenesis is potentially of great significance to breast cancer risk and growth of incipient tumours in this microenvironment. The involvement of immune cells and inflammatory mediators such as cyclooxygenase 2 in the tissue remodelling that occurs during mammary gland involution is a specific example of how normal mammary gland developmental processes result in a microenvironment that promotes tumour development. Fornetti et al. highlight potential new approaches to prevent and treat breast cancers that arise during the involution period with immunotherapeutic agents. Immune system factors may also contribute to increased breast cancer risk associated with menstrual cycling, where regulation of the immune

microenvironment by fluctuations in the hormones estrogen, progesterone and prolactin is discussed by Need et al.

This special edition of the *Journal of Mammary Gland Biology and Neoplasia* is focused on the immune microenvironment in mammary gland development and cancer. The issue is a timely analysis of all that has been discovered on the contribution of the immune system to mammary gland health and disease. These reviews highlight the cutting edge research that promises the next 20 years will see many exciting new developments in this field. Indeed, it is encouraging to see the emergence of fresh ideas that challenge old paradigms and propose new directions for novel immunotherapies to prevent and treat breast diseases. Many thanks to the contributors and reviewers who lent their expertise to this edition, their enthusiasm and hard work made it a pleasure to compile these reviews.

References

1. Pollard JW, Hennighausen L. Colony stimulating factor 1 is required for mammary gland development during pregnancy. *Proc Natl Acad Sci U S A*. 1994;91(20):9312–6.
2. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011;144(5):646–74.