Preface

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Although it has been known for some time that full-term pregnancy at an early age reduces the lifetime risk of developing breast cancer, women of all ages have a transient increase in breast cancer risk after a recent pregnancy. Traditionally, breast cancers diagnosed during pregnancy and within close proximity to parturition have been called pregnancy associated breast cancer or PABC. Newer epidemiologic data indicate that the transient elevation in risk for breast cancer after pregnancy peaks as late as seven years post-partum, providing a compelling argument for extending the definition of PABC to include these cases. Importantly, PABC has a poor prognosis and patients succumb to metastatic disease. The complexity of the relationships between age at first birth and breast cancer incidence curves implicate pregnancy in cancer initiation as well as promotion of existing lesions. To date, the poor prognosis of PABC is best explained by progression of pre-existing disease. The notion that pregnancy promotes metastasis of tumors already present could be the result of factors associated with post-lactational regression (involu-

tion) of the mammary gland. Experimental evidence in support of this notion was provided by xenotransplantation studies with MDA-MB-231 cells mixed with extracellular matrix (ECM) isolated from actively involuting rat mammary glands or with ECM from nulliparous rats and injected into the mammary fat pad of immunocompromised mice. Metastases to lung, liver and kidney were significantly increased in cells injected with involution ECM compared to nulliparous ECM, providing evidence that the microenvironment of the involuting gland is permissive for dissemination and metastasis of tumour cells. These experimental data, in combination with several microarray analyses revealing that involution is associated with an acute phase and inflammatory response, provided the first plausible explanation for the high metastatic rate of PABC. That is, the post-partum involuting microenvironment, while physiologically normal, shares similarity to the cancer microenvironment. Cancer has been described as a wound that never heals and involution likens to a wound healing process. Thus, involution may provide the environment necessary for tumour cell dissemination.

In this issue of JMGB&N, we present a series of review articles that discuss different aspects of involution and the implications for breast cancer progression. In the first article, Traci Lyons, Pepper Schedin and Virginia Borges review epidemiologic and clinical studies of PABC and summarize data indicating that PABC can be divided into two distinct subtypes; breast cancers diagnosed during pregnancy and those diagnosed after parturition. Their assessment of these published studies supports the hypothesis that breast cancers present during the involution period have poorer prognosis than cancers diagnosed and treated during pregnancy.

Torsten Stein presents an original paper, based on previous microarray work that identified a wound-healing

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transcriptome profile associated with involution. He hypothesised that the involution profiles may provide prognostic power for breast cancer. This was indeed found to be the case when correlated with the low and high metastatic activity sets within the NKI 295 breast cancer dataset. Specifically, the two clusters of genes that were expressed either throughout the first 4 days of involution (C5) or were differentially regulated at day 3 involution (Inv3) were both found to be independent prognostic indicators. Genes common to both Inv3 and C5 include those involved in copper ion homeostasis and hypoxia regulated genes, in addition to secreted factors that were associated with poor survival. Promoter analysis of upregulated genes identified HIF-1 as the most overrepresented transcription factor having putative binding sites in 24 genes. Based on these gene expression profiles, novel targets for prevention of PABC are proposed.

Sara Pensa, Christine Watson and Valeria Poli tackle the question of the role of the inflammatory and acute phase response in involution and how this could promote breast cancer in the context of the paradoxical role of the transcription factor Stat3 as a mediator of involution and a promoter of breast tumorigenesis. The functional complexities of Stat3 as an activator of both inflammatory and anti-inflammatory responses and as a promoter of both apoptosis and tissue remodeling are discussed.

Members of TGF-beta are also highly unregulated during involution. Kathleen Flanders and Lalage Wakefield review the roles of specific isoforms of TGF-beta in wound healing models and cancer, providing insight into putative functions of TGF-beta members during involution and promotion of PABC.

The contribution macrophages may play in PABC is discussed in the review by Jenean O'Brien and Pepper Schedin. Clinical and experimental data are summarized that provide a compelling argument for alternatively activated or M2-like macrophages being key contributors to the tumor-promoting milieu of the involution microenvironment.

That milk secretion is not the final differentiated state of the mammary alveolar cells is a relatively new concept.

Recent work has suggested that during involution the secretory mammary epithelial cells become amateur phagocytes, or efferocytes, with the primary role of apoptotic cell clearance. The article by Jenifer Monks and Peter Henson reviews evidence that the mammary epithelial cell undergoes efferocyte differentiation immediately post-weaning and explores what is known of the signaling involved in this differentiation event. They speculate on why these cells may be particularly susceptible to transformation and/or metastatic progression.

Involution is associated with extensive protease activity. Peter Kreuzaler and Christine Watson discuss the role of cathepsins, a large family of serine proteases, in involution and breast cancer. A number of studies have examined expression of specific cathepsins in breast cancer tissues along with expression of their endogenous inhibitors. It is evident that breast tumors upregulate both expression and secretion of specific cathepsins that can degrade components of the tumour microenvironment and facilitate metastasis. Expression profiles of cathepsins during the mammary pregnancy/lactation/involution cycle suggest that a subset of these could have a specific function in involution. The few studies that have been carried out to address this are reviewed and suggest a role for cathepsins in both phases of involution although much higher activity is associated with the second phase, in concert with the extensive tissue remodelling that occurs at this time.

Derek Radisky and Lynn Hartmann present an overview of the genetically modified mice that have involution phenotypes (either accelerated or delayed involution) and discuss the consequences of gene deletion or overexpression on tumor development. They raise some interesting points about new data that suggest age-related lobular involution in humans can protect against breast cancer.

We hope these reviews stimulate further research endeavours into the mechanisms responsible for the poor prognosis of PABC. Hopefully such research will lead to targeted therapies and alleviate morbidity and mortality associated with breast cancer diagnosed in new mothers. Our Best, Pepper Schedin and Christine Watson