Self-Organization and Pattern Formation in Mammary Gland Development

Yao-li Chuang[1], Michael T. Lewis[2], Zhihui Wang[1], Vittorio Cristini[1] and Arnaud Chauvière[3]

***Short Abstract* — Mammary morphogenesis is a highly coordinated collective development of a multicellular system, mediated by exchanging various endocrine and paracrine signals. We attempt to understand the underlying physics of the process by constructing, validating, and analyzing mathematical models at various scales. Studying the process of mammary morphogenesis may further elucidate the emergence of breast tumors, where normal mechanisms leading to healthy duct formation are believed disrupted.**

***Keywords* —mammary gland development, tissue morphogenesis, pattern formation, self-organization.**

I. Introduction

THE formation of mammary ductal network is a unique process, which undergoes most of the development after birth. During the embryonic stage, epithelial cells form several early mammary buds, and the development is halted after birth until it resumes at puberty in response to estrogens [1,2]. Local cellular interactions, mediated through various endocrine and paracrine signals, are believed essential for the mammary duct network development. Despite recent success in identifying such essential mediators [3], the underlying mechanisms leading from cellular interactions to mammary morphogenesis are still unclear. Here we attempt to understand the process by constructing experimentally driven mathematical models that can be used to test various physical hypothesis regarding mammary tissue morphogenesis.

II. Method

We adopted a multiscale approach to study the mammary gland development from the coarsest scale to the finest scale. We started with a cell population model capable of estimating the elongation rate of the duct growth. We next proceeded to a spatiotemporal model explaining the cell distribution patterns observed in myoepithelial layers, and then to cell-scale agent-based model to investigate mammary duct morphogenesis.

A. Population model

The duct was divided into eight compartments from the terminal end bud (TEB) to the mature duct. The proliferation and apoptosis rates of various cell species in each region were measured experimentally. The duct elongation rate were deduced from the population balance and corroborated by the actual experimental measurements.

B. Tissue-scale spatiotemporal model

Based on the proliferation/apoptosis rules in the population model, we further extended the previous compartment model to include finer spatial resolution. The spatiotemporal model enabled us to incorporate the diffusion process of paracrine signaling molecules, from which heterogeneous cell distribution patterns may emerge through symmetry breaking.

C. Cell-scale agent-based model

While we imposed geometry constraints for the previous models, the dynamic formation of ductal geometry can be simulated by cell aggregation patterns due to cell-cell interaction. We incorporated cell adhesion and cell polarity in a cell-scale agent-based model (ABM) to investigate cell aggregation patterns. The goal is to integrate the ABM to the spatiotemporal model to construct a hybrid continuum-discrete model for dynamical mammary duct formation.

III. Summary

We developed mathematical models appropriate for each scale when we went from the cell population level to the cellular interaction level. At each level, we corroborated model predictions with experimental observations, while further analysis of the model elucidated the necessary components for the next level. We hope that understanding the formation of healthy mammary glands may also reveal the secrets regarding carcinogenesis, where some mechanisms and pathways in normal tissue development are hijacked or bypassed during cancer development.

Acknowledgements: This work is funded by NIH-PSOC grant 1U54CA143907-01.

[1]Department of Pathology, University of New Mexico, Albuquerque, NM, USA. E-mail: ychuang, vcristini, zwang@salud.unm.edu

[2] Baylor College of Medicine, Houston, TX, USA. E-mail: mtlewis@bcm.edu

[3]Another Department, Université Joseph Fourier, Grenoble, France. E-mail: Arnaud.Chauviere@imag.fr

References

[1] Närhi K (2012) Canonical Wnt signaling in hair and mammary gland patterning and development. PhD thesis, University of Helsinki.

[2] Sternlicht MD (2006) Key stages in mammary gland development: The cues that regulate ductal branching morphogenesis. *Breast Cancer Research* **8(201)**, 1–11.

[3] LaMarca HL and Rosen JM (2007) Estrogen regulation of mammary gland development and breast cancer: amphiregulin takes center stage. *Breast Cancer Research* **9(4)**, 1–3.