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PREFACE

Mammary Gland Development & Breast Cancer; Connecting the Dots by Non-Coding RNAs

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The intriguing discovery that small non-coding RNAs called microRNAs played a key role in regulating cancer turned many heads towards finding such roles for other types of non-coding RNAs. These other types of non protein coding RNAs include transcribed ultraconserved regions (T-UCRs), small nucleolar RNAs (snoRNA), PIWI-interacting RNAs (piRNAs), large intergenic non-coding RNAs (lincRNAs) and the heterogeneous group of long non-coding RNAs (lncRNAs). We are now at the tip of the iceberg and in an exciting time to begin to finally connect the dots between normal mammary development and breast cancer by elucidating the roles of non-coding RNAs. This represents the next major frontier in understanding gene regulation during normal development and how these regulatory processes have been altered in breast cancer.

We have been fortunate to bring together a number of outstanding experts in the field to review the current knowledge and share their views and research on this exciting new field.

Dr. Yossi Yarden's review describes the role of microRNAs in fine tuning and buffering - noise in complex signaling networks. He proposes that cancer progression is due to leaky activation of signaling pathways, when immediately downregulated miRNAs (ID-miRs) are aberrantly expressed. Further studies will be required to discover how cancers simultaneously regulate large assemblies of miRNAs that share critical cellular functions implicated in cancer, e.g., cell cycle progression and cellular migration.

Hannan Elsarraj and colleagues focus on miR-146a/b, another one example of a microRNA that may function in buffering or fine tuning of signaling networks including those induced by inflammatory cytokines such as INFγ and IL-1 as well as those involved in normal mammary development such as prolactin, estrogen and progesterone. Interestingly, a miR-146a/b polymorphism has been linked to diverse cancers including breast, gastric, glioblastoma, and thyroid cancers highlighting another example of how aberrant regulation of a single microRNA with pleiotropic role in normal homeostasis may predispose to diverse cancers.

Suling Liu and Max P. Wicha present their intriguing hypothesis that normal and malignant stem cells may exist in transition between mesenchymal and epithelial states and that the interconversion between these two states may be regulated by microRNAs. These investigators will soon publish a manuscript showing that mir-93, mir-100 and mir-22 may be important regulators of the epithelial to mesenchymal (EMT) and mesenchymal to epithelial (MET) stem cell states. They suggest that future cancer therapies should target microRNAs, which regulate different cancer stem cell states.

Complementing the chapter by Liu and Wicha, Jennifer Richer focuses on the mechanisms by which some miRNA families (i.e., miR-200 and miR-221/222) exert opposing effects on EMT thus regulating crucial processes in cancer development and progression including migration/invasion, resistance to anoikis/survival, and metastasis. MiRNA families such as miR-200 and miR221/222, which exert

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opposing effects on cellular plasticity may also regulate the differentiation states of breast cancers by promoting the development of luminal vs. basal breast cancer subtypes.

Scott Valasayan reviews the various steps in the invasion-metastasis cascade and how miRNAs and other non-coding RNAs regulate these processes. This review also highlights recently discovered competing endogenous RNAs (ceRNAs), which function by competing with other mRNAs for miRNA binding motifs thus upregulating rather than dampening expression of target mRNAs. Finally the translational potential of non-coding RNAs for the diagnosis and treatment of human breast cancers is discussed.

Li Ma discusses recent findings on the role of non-coding RNAs including miRNAs and lncRNAs during normal mammary gland development, specifically focusing on the regulation of estrogen, progesterone and prolactin signaling, as well as mammary stem and progenitor cells. Other highlights include the role of lncRNAs in breast cancer progression and the use of miRNA expression profiling as more precise predictors of breast cancer outcome.

The review by Amy Shore and colleagues emphasizes the role of lncRNAs in normal mammary development as well as in stepwise progression of mammary tumorigenesis. This review highlights the role of a specific lncRNA, PINC, in alveolar progenitor cell differentiation, as well as discussing the general mechanisms by which lncRNAs and lincRNAs may regulate gene expression.

Zuoren Yu and Richard Pestell summarize the role of miRNAs in breast cancer progression and onset by regulating distinct cell-cycle checkpoints including cyclins, CDKs, CDK inhibitors and G2-M checkpoints. Furthermore, the evolving role of other non-coding RNAs such as piRNA and snoRNA in breast cancer is discussed. They provide several examples of successful delivery of miRNA for treatment of various cancers including breast, non-small-cell lung and liver cancers thus demonstrating the promise of miRNA as future anti-cancer therapies.

In summary this is an exciting time for the study of non-coding RNAs in mammary gland development and breast cancer and we anticipate many new and exciting findings will be forthcoming in the future. We hope that the scientific community finds this issue helpful.