Dynamics of estrogen stimulated regulatory networks in breast cancer

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***Short Abstract* — Expression of the estrogen receptor α (ERα) is the most significant predictor of breast cancer severity and survival. ERα is overexpressed in the majority of breast tumors, and acts as a transcriptional regulator by cyclically binding to promoter regions and controlling both mitogenic and anti-metastatic pathways. microRNAs and alternative polyadenylation also play a role in the ERα regulatory network, further enriching the potential dynamics by introducing post-transcriptional regulation. Using a network modeling approach, we are examining the dynamics of coding and non-coding genes in the MCF7 estrogen response by integrating mRNA, microRNA, and 3'UTR expression profiles.**

***Keywords* — Estrogen response, microRNA, alternative polyadenylation**

I. Background

DESPITE advances in screening and treatment, breast cancer remains a leading cause of cancer and mortality in women worldwide [1]. The estrogen receptor plays a key role in breast cancer both as a biomarker of cancer severity, and as a therapeutic target to reduce tumor mass [1]. However, recent studies have demonstrated that estrogen signaling also protects tumors against metastatic transformation, suggesting that current therapeutics (ERα antagonists) have the potential to lead to tumor transformation [2].

ERα binds to estrogen and transcriptionally regulates expression of its targets [1]. In addition to ERα-responsive genes, several ERα-stimulated microRNAs (miRNAs) have been identified that post-transcriptionally regulate both ERα and its targets [1]. Also, alternative polyadenlyation (APA) alters the length of the 3' untranslated region (UTR) of mRNAs; thus gaining or eliminating miRNA target sites. While studies have shown that APA differs across cell types and tissues [3], it has not yet been globally investigated in response to a stimulus. It is known that ERα interacts with numerous co-factors to regulate transcription, and stimulates expression of several 3'-end processing proteins [4]. Therefore, we hypothesize that miRNA networks exert temporal control of ERα signaling, thereby regulating the timing and extent of specific cellular responses to estrogen.

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II. Methods

To identify both coding and non-coding components in ERα regulatory networks, we examine a time course of RNA-seq and small RNA-seq data from MCF7 cells exposed to 10mM estradiol. Analysis of RNA-seq data using the DaPars algorithm [5] combined with 3'-end sequencing [3] allows us to infer APA sites and 3'-UTR usage. Together these data allow us to construct a regulatory map detailing the genes and miRNAs that play a role in estrogen signaling. By studying this map we can: (1) identify temporally regulated genes, miRNAs, and 3'-UTRs; (2) predict miRNA master regulators of ERα-stimulated pathways; and (3) identify candidate therapeutic targets that will interfere with the ERα's mitogenic pathways without eliminating its anti-metastatic functions.

III. Conclusions

Numerous genes and miRNAs respond to estrogen-stimulation, and detailed analysis of ERα occupancy at known targets has shown that the receptor cyclically binds to promoters and initiates bursts of transcriptional activity. ERα-targets such as *TFF1* and miRNA-21 both cycle following estrogen stimulation. Genome-wide profiling of both coding and non-coding transcripts will provide an unprecedented systems-level understanding of the temporal contribution of miRNAs to the estrogen response in breast cancer cells. Finally, these data will provide a dynamic map of predicted novel regulators of the estrogen response that will guide future therapeutic strategies for breast cancer.

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