Steroid Hormones and Receptors
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Endocrine Response And Resistance Is Driven By Novel Transcriptional Co-Regulator Activity In Invasive Lobular Carcinoma Of The Breast
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Invasive lobular carcinoma of the breast (ILC) affects ∼40,000 US women annually and is a top ten most diagnosed cancer in women. ∼95% of ILC express estrogen receptor alpha (ER), but ILC is associated with poor long-term outcomes and anti-estrogen resistance, suggesting ER function is distinct in ILC cells. We reported that MDC1 (mediator of DNA damage checkpoint 1) is an ILC-specific ER co-regulator required for ER-driven proliferation, and that MDC1 knockdown dysregulates the ER transcriptome in ILC. Mechanisms of MDC1 co-regulator activity are unknown, but must be defined to understand endocrine response and resistance in ILC.

To understand MDC1 co-regulator functions, we profiled ER/MDC1 genomic binding (ie. "cistrome") using CUT&RUN in ER+ ILC cell line MDA MB 134VI (MM134). We identified ∼2500 binding sites each for ER and MDC1, but only ∼8% of sites were bound by both factors. However, using BETA to integrate cistrome and transcriptome data predicted that both ER and MDC1 activate estrogen-regulated genes with over half of direct ER target genes also direct MDC1 targets (p=9.8x10-375). Among shared ER: MDC1 direct target genes (n=760), 58% had MDC1 binding in the promoter region with ER bound at nearby enhancers, while only 15% were linked to shared ER: MDC1 binding sites, suggesting MDC1 primarily facilitates promoter access for ER-bound enhancers. Further, MDC1 knockdown reduced ER binding at enhancer sites at ER: MDC1 target genes, implicating MDC1 in regulating chromatin access.

Importantly, MDC1 does not have known enzymatic activity to directly regulate chromatin structure. We profiled MDC1-interacting proteins in ILC cells by RIME (Rapid immunoprecipitation mass spectrometry of endogenous proteins), and determined whether knockdown of putative ER: MDC1 partners disrupted ER function. This identified the SWI/SNF complex protein BRG1 (SMARCA4) as a critical ER: MDC1 partner. BRG1 was required for ILC cell growth, and BRG1 knockdown specifically suppressed ER regulation of MDC1-dependent ER target genes.

Taken together, our data suggest that in ILC cells, MDC1 facilitates ER access to and activity at target gene promoters. The BRG1 SWI/SNF complex is a putative ER: MDC1 partner and mediator of MDC1 co-regulator functions. Ongoing research is focused on understanding how MDC1 regulates ILC-specific ER activity by licensing access to ILC-specific target genes, and the role of the SWI/SNF complex in mediating genomic ER: MDC1 activity.

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