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Review

Estrogen receptor-mediated long-range chromatin interactions and transcription in breast cancer

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ABSTRACT

Estrogen induces the binding of ERα to thousands of locations in the breast cancer genome, preferring intergenic and distal regions rather than near the promoters of estrogen-regulated genes. With recent technological innovations in mapping and characterization of global chromatin organization, evidence now indicates ERα mediates long-range chromatin interactions to control gene transcription. The principles that govern how ERα communicates with their putative target genes via chromosomal interactions are also beginning to unravel. Herein, we summarize our current knowledge on the functional significance of chromatin looping in estrogen-mediated transcription. ERα collaborative factors and other players that contribute to define the genomic interactions in breast cancer cells will also be discussed. Defects in chromatin organization are emerging key players in diseases such as cancer, thus understanding how ERα-mediated chromatin looping affects genome organization will clarify the receptor's role in estrogen responsive pathways sensitive to defects in chromatin organization.
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1. Introduction

ERα has been one of the most extensively profiled transcription factors in genomic studies. The initial ChIP-chip study on MCF7 cells using arrays covering chromosomes 21 and 22 provided a partial genome-wide view of ERα binding (Carroll et al., 2005). Since then, the complete genomic landscape of ERα binding has been determined after estrogen stimulation in different breast cancer cell lines (Carroll et al., 2005, 2006; Lin et al., 2007; Welboren et al., 2009; Ross-Innes et al., 2011; Theodorou et al., 2013), in the presence of antagonists including tamoxifen and fulvestrant (Welboren et al., 2009), as well as growth factors such as EGF (Lupien et al., 2010). The tissue specific binding behavior of ERα in different tissues including bone (Krum et al., 2008) and uterus (Hewitt et al., 2012) has also been described. Furthermore, the effect of post-translational modifications by kinases such as AKT and PKA on the genome-wide recruitment of ERα (Bhat-Nakshatri et al., 2008; de Leeuw et al., 2012) and ERα binding with respect to other nuclear receptors such as ERβ have been evaluated (Liu et al., 2008).

The binding of ERα has also been examined in much greater detail recently by assessing its profile in the absence of essential cofactors (*e.g.* knockdown of a transcription factor, followed by ChIP-seq of ERα) such as FOXA1 (Hurtado et al., 2008), TLE1 (Holmes et al., 2012) and GATA3 (Theodorou et al., 2013). In addition, the binding profile of ERα in the context of other protein factors have been determined through sequencing of re-ChIP samples (*e.g.* ChIP of ERα followed by additional ChIP of a separate transcription factor, or vice versa) such as RARα (Ross-Innes et al., 2010). Among all the genome-wide ERα binding studies performed to date, two key observations have emerged. First, ERα binds across the genome, but does so preferentially at distal regions, away from the proximal promoters of the estrogen-regulated genes. Second, the recruitment of ERα to chromatin is determined by essential collaborative factors binding in close proximity to the receptor. Collectively, these studies suggest that ERα and its collaborative factors may play important roles in mediating long-range chromatin interactions to regulate gene transcription.

The spatial organization of our genome is not random, but is instead organized into distinct three-dimensional chromosome conformations that has profound effects on numerous key biological processes, including gene transcription (Hakim and Misteli, 2012). Recent advances in the tools for capturing long-range chromatin interactions have allowed researchers to begin mapping and understanding the basic principles that govern the control of gene expression by distal regulatory elements within chromatin loops. For example, ENCODE data on the chromatin interaction landscape of gene promoters across multiple cell lines suggests that long-range chromatin interactions within cells are widespread (Sanyal et al., 2012). Furthermore, several protein factors have been identified and characterized as functionally important in the mediation of chromatin interactions (Cai et al., 2006; Wendt et al., 2008). The misregulation of these protein factors can cause global alterations in chromatin structure (Zhang et al., 2012) and changes in genome stability (Misteli, 2010).

With respect to estrogen signaling in breast cancer cells, findings from recent genomic and molecular studies suggest distal regulation of transcription appears to be a key mechanism used by ERα (Dietz and Carroll, 2008). In this review, we will highlight methods and technologies for studying these chromatin interactions in ERα-regulated transcription and describe the chromatin interaction network defined by ERα in breast cancer cells. We will also summarize our current knowledge on the molecular principles that govern the way ERα and cofactors contribute to the dynamic spatial genomic interactions and transcriptional responses in the nucleus. Finally, we will discuss the biological significance of these chromatin loops and how these observations may translate to further our understanding of breast cancer biology.

2. Methods to examine ERα-mediated long-range chromatin interactions

Our current understanding of ERα-mediated chromatin organization in breast cancer cells has been driven to a large extent by two main techniques for capturing and mapping long-range chromatin interactions: (1) non-ChIP based methods such as interphase fluorescent *in situ* hybridization (FISH) (Solovei and Cremer, 2010) and chromosome conformation capture (3C) (Dekker et al., 2002), and (2) ChIP based methods including ChIP-3C (Carroll et al., 2005) and *Chromatin* Interaction Analysis by Paired-End Tag Sequencing (ChIA-PET) (Fullwood et al., 2009). In this section, we will briefly review these two types of assays and discuss their main advantages and disadvantages. In addition, we will describe recent advances in methods that have been used for the characterizing of long-range chromatin interactions.

2.1. Non-ChIP based methods to capture long-range chromatin interactions

In FISH, the relative nuclear position of genes, genomic regions or even whole chromosomes are detected by the hybridization of fluorescently labeled DNA probes to nuclei fixed on glass slides which are then visualized by fluorescence microscopy (Solovei and Cremer, 2010). The FISH assay has been used extensively to understand the spatial interactions of chromosomes in numerous systems such as the interaction between the immunoglobulin and β-globin loci (Kosak et al., 2002; Ragoczy et al., 2006). The main advantage of FISH is that it provides information regarding how frequently chromatin domains overlap at the single cell level (Gondor et al., 2008). Its disadvantage, however, is its general low resolution in detecting intra-chromosomal interactions that are close to each other (Gondor et al., 2008; van Berkum and Dekker, 2009).

To examine chromatin interactions at higher resolution, the 3C assay is the preferred technique. For example, chromatin interactions have been reported at numerous estrogen-regulated genes including *RET* (Tan et al., 2011), *PR* (Boney-Montoya et al., 2009), *ERBB2* (Hurtado et al., 2008), *CTSD* (Bretschneider et al., 2008), *CA12* (Barnett et al., 2008), *BCL2* (Perillo et al., 2008), *P2RY2* (Fullwood et al., 2009), *SIAH2* (Fullwood et al., 2009), *GREB1* (Deschenes et al., 2007; Fullwood et al., 2009) and *TFF1* (Pan et al., 2008; Zhang et al., 2010; Theodorou et al., 2013). The current 3C method is largely based on the concept of proximity ligation from the Nuclear Ligation Assay (Cullen et al., 1993). Briefly, the protein mediated chromatin interaction is first captured by formaldehyde crosslinking. Subsequently, the protein–chromatin complexes are digested with restriction enzyme and proximally ligated. Higher order chromatin interactions are then detected by qPCR using site-specific primers on the newly formed junctions. While the 3C assay has provided researchers with the opportunity to understand the frequency of proximity between two DNA fragments, as captured by formaldehyde crosslinking, the method is laborious and requires some prior knowledge of the interacting sequences or regions. To expand the scope of detecting long-range chromatin interactions, derivatives of the 3C assay have been developed through the coupling of the 3C material to either microarray hybridization (*e.g.* chromosome conformation capture-on-chip (4C) (Simonis et al., 2006)) or next generation sequencing (*e.g.* Hi-C (Lieberman-Aiden et al., 2009)).

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