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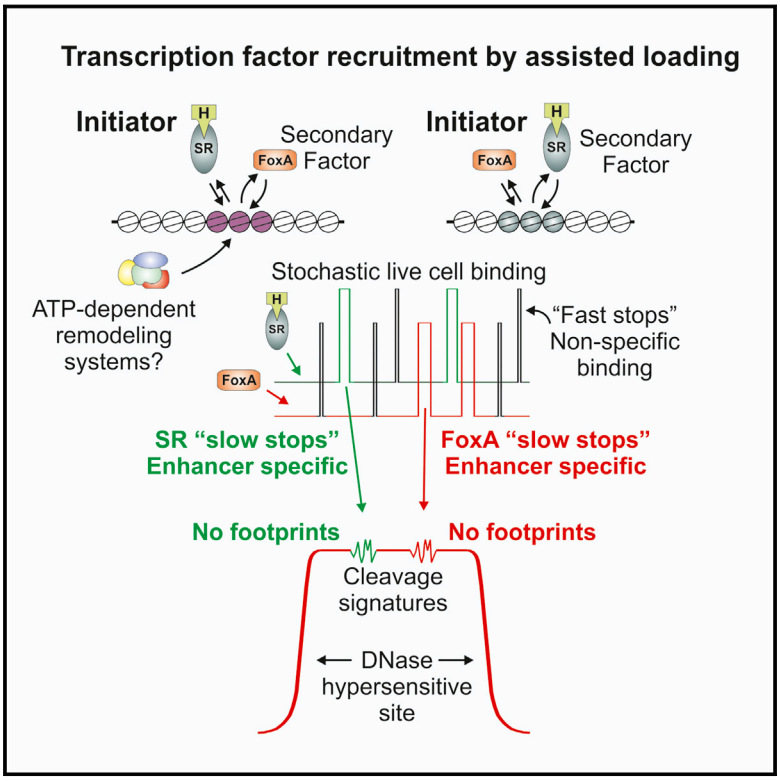
Steroid Receptors Reprogram FoxA1 Occupancy through Dynamic Chromatin Transitions

Graphical Abstract



Highlights

- Binding patterns for the FoxA1 pioneer factor can be modulated by steroid receptors
- Interactions of FoxA1 with chromatin in live cells are highly dynamic
- The FoxA1 factor fails to produce significant footprints at chromatin-binding sites
- Redistribution of FoxA1 binding occurs through a dynamic assisted loading mechanism

Authors

Erin E. Swinstead, Tina B. Miranda, Ville Paakinaho, ..., Lars Grøntved, Diego M. Presman, Gordon L. Hager

Correspondence

hagerg@exchange.nih.gov

In Brief

Single-molecule tracking reveals that a transcription factor, FoxA1, that has been characterized as a pioneer chromatin binder associates with DNA more dynamically than expected and that its role in promoting DNA binding of steroid receptors can in some instances be reciprocated, with the steroid receptors promoting binding of FoxA1

Accession Numbers

GSE72252

Swinstead et al., 2016, Cell *165*, 593–605
April 21, 2016
http://dx.doi.org/10.1016/j.cell.2016.02.067

CellPress

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Steroid Receptors Reprogram FoxA1 Occupancy through Dynamic Chromatin Transitions

Erin E. Swinstead,[1,4] Tina B. Miranda,[1,4] Ville Paakinaho,[1] Songjoon Baek,[1] Ido Goldstein,[1] Mary Hawkins,[1] Tatiana S. Karpova,[1] David Ball,[1] Davide Mazza,[2] Luke D. Lavis,[3] Jonathan B. Grimm,[3] Tatsuya Morisaki,[1,5] Lars Grøntved,[1,6] Diego M. Presman,[1] and Gordon L. Hager[1,*]

[1]Laboratory of Receptor Biology and Gene Expression, Building 41, 41 Library Drive, NCI, NIH, Bethesda, MD 20892, USA
[2]Istituto Scientifico Ospedale San Raffaele, Centro di Imaging Sperimentale e Università Vita-Salute San Raffaele, 20132 Milano, Italy
[3]Janelia Research Campus, Howard Hughes Medical Institute, 19700 Helix Drive, Ashburn, VA 20147, USA
[4]Co-first author
[5]Present address: Department of Biochemistry and Molecular Biology, Colorado State University, Fort Collins, CO 80523, USA
[6]Present address: Department of Biochemistry and Molecular Biology, University of Southern Denmark, 5230 Odense M, Denmark
*Correspondence: hagerg@exchange.nih.gov
http://dx.doi.org/10.1016/j.cell.2016.02.067

SUMMARY

The estrogen receptor (ER), glucocorticoid receptor (GR), and forkhead box protein 1 (FoxA1) are significant factors in breast cancer progression. FoxA1 has been implicated in establishing ER-binding patterns though its unique ability to serve as a pioneer factor. However, the molecular interplay between ER, GR, and FoxA1 requires further investigation. Here we show that ER and GR both have the ability to alter the genomic distribution of the FoxA1 pioneer factor. Single-molecule tracking experiments in live cells reveal a highly dynamic interaction of FoxA1 with chromatin in vivo. Furthermore, the FoxA1 factor is not associated with detectable footprints at its binding sites throughout the genome. These findings support a model wherein interactions between transcription factors and pioneer factors are highly dynamic. Moreover, at a subset of genomic sites, the role of pioneer can be reversed, with the steroid receptors serving to enhance binding of FoxA1.

INTRODUCTION

Pioneer factors (PFs) have been described as a class of proteins that penetrate closed chromatin to create accessible binding sites for general transcription factors (TFs) during development (Zaret and Carroll, 2011). The forkhead box protein 1 (FoxA1) has been shown to interact with compact chromatin, modulating chromatin structure as an early event. Upon chromatin binding, FoxA1 is thought to initiate nucleosome binding via the winged-helix domain that it shares with the H1 linker histone and induce nucleosomal rearrangements by a mechanism independent of ATP-dependent remodeling complexes. These transitions in turn result in an increase in the accessibility of DNA-binding elements (Bernardo and Keri, 2012; Cirillo et al., 1998, 2002). This mechanism has been widely implicated for the recruitment of steroid receptors (SRs) (Bernardo and Keri, 2012; Eeckhoute et al., 2006; He et al., 2012; Hurtado et al., 2011), specifically for the estrogen receptor (ER) and androgen receptor (AR) in breast and prostate cancer cells, respectively. Early studies reported that FoxA1-binding sites overlap with ~50% of ER-binding sites (Carroll et al., 2005) and that FoxA1 is required for at least half of all ER-binding events in MCF-7 breast cancer cells (Carroll et al., 2005; Laganière et al., 2005). Later findings via genome-wide analysis (Carroll et al., 2006; Lupien et al., 2008; Hurtado et al., 2011) have been interpreted in support of this general model. In addition, it has been reported that inhibition of ER produces no change in FoxA1 genomic binding patterns (Lupien et al., 2008; Hurtado et al., 2011). These investigations have either focused on a small number of binding locations or compared FoxA1 binding only between unstimulated cells and cells treated with an ER antagonist (Hurtado et al., 2011; Lupien et al., 2008). Contrary to these findings, an independent study reported that upon knockdown of ER, FoxA1 binding is lost at many unstimulated ER-binding sites (Caizzi et al., 2014), evidence that ER may in fact regulate binding of FoxA1.

More recently it was demonstrated that multiple TFs can modulate each other's binding patterns through a mechanism termed dynamic assisted loading. In this model, one factor can induce accessibility for another through the recruitment of ATP-dependent remodeling complexes that create transient open chromatin states (Biddie et al., 2011; Grøntved et al., 2013; Miranda et al., 2013; Voss et al., 2011), allowing the secondary factor to bind. This model is distinguished from the classic pioneering concept by three important parameters: (1) the initiating and secondary binding factors can reverse roles, depending on the local chromatin environment, (2) residence times for the binding factors are quite short, measured in seconds (s), and (3) a central role for ATP-dependent remodeling proteins is proposed (Voss and Hager, 2014; Voss et al., 2011).

Here, we show that activation of either ER or the glucocorticoid receptor (GR) induces the reprograming of the chromatin landscape in breast cancer cells and results in the recruitment of FoxA1 to a subset of sites that were previously inaccessible. In addition, we find no evidence of FoxA1, ER, or GR footprints within DNase I hypersensitive (DHS) sites in multiple breast