CHAPTER SEVEN

FOXP1 and Estrogen Signaling in Breast Cancer

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Abstract

Breast cancers are considered to be primarily regulated by estrogen signaling pathways because estrogen-dependent proliferation is observed in the majority of breast cancer cases. Thus, hormone therapy using antiestrogen drugs such as tamoxifen is effective for breast cancers expressing estrogen receptor α (ERα). However, acquired resistance during the endocrine therapy is a critical unresolved problem in breast cancer. Recently, a forkhead transcription factor FOXA1 has been reported to play an important role in the regulation of ERα-mediated transcription and proliferation of breast cancer. Interestingly, immunohistochemical analysis of breast cancer specimens has revealed that nuclear immunoreactivities of FOXP1 as well as those of FOXA1 are positively correlated with hormone receptor status, including ERα and progesterone receptor. In particular, the double-positive immunoreactivities of FOXP1 and FOXA1 are significantly associated with a favorable prognosis for survival of breast cancer patients receiving adjuvant tamoxifen therapy. The functions of FOXP1 and FOXA1 have been characterized in cultured cells; further, similar to FOXA1, FOXP1 is assumed to be a critical transcription factor for ERα signaling, and both forkhead transcription factors can serve as predictive factors for acquired endocrine resistance in breast cancer.

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1. INTRODUCTION

Estrogen is a sex steroid hormone that regulates various cellular events through its cognate estrogen receptor α (ERα), which functions as a transcription factor that activates the transcription of its target genes (Platet, Cathiard, Gleizes, & Garcia, 2004). Clinically, ERα is noted as the defining feature of luminal breast cancer, which accounts for a large portion of breast cancers. Luminal breast cancer is generally treated with endocrine therapy using classical antiestrogen agents such as tamoxifen, which acts as an antagonist for ERα in breast cancer cells. Because of the sensitivity to endocrine therapy, ERα-positive luminal breast cancer is considered to have better prognosis than ERα-negative breast cancer. However, resistance to antiestrogen therapies is often acquired in a substantial fraction of recurrent breast cancers. Identification of the factors involved in the mechanisms underlying endocrine resistance, recurrence, or poor prognosis of breast cancer will be useful for understanding the exact pathophysiology of the disease and for developing alternative diagnostic methods and treatment specific to the disease.

The transcriptional activity of ERα is regulated by a number of regulatory cofactors, including chromatin-remodeling complexes, coactivators, and corepressors (Hall & McDonnell, 2005). Moreover, several transcription factors, including those belonging to the forkhead box (FOX) family, modulate the transcriptional activity of ERα. In particular, as described in detail below, FOXA1 plays a crucial role in the ERα-mediated transcription in breast cancer cells (Carroll et al., 2005; Hurtado, Holmes, Ross-Innes, Schmidt, & Carroll, 2011; Lupien et al., 2008). In addition, recent clinicopathological and *in vitro* studies have shown that another member belonging to the FOX family, FOXP1, is closely related to the biology of breast cancer (Ijichi et al., 2012; Shigekawa et al., 2011). This chapter focuses on the potential role of FOXP1 compared to that of FOXA1 in the pathophysiology of breast cancer and discusses the clinical relevance of these forkhead factors in the disease, particularly in association with hormone therapy.

2. FOXP1 AND FOXA1 IN ERα-POSITIVE BREAST CANCER CELLS

FOXP1 and FOXA1 are transcription factors, which belong to the FOX family that includes a conserved forkhead DNA-binding domain

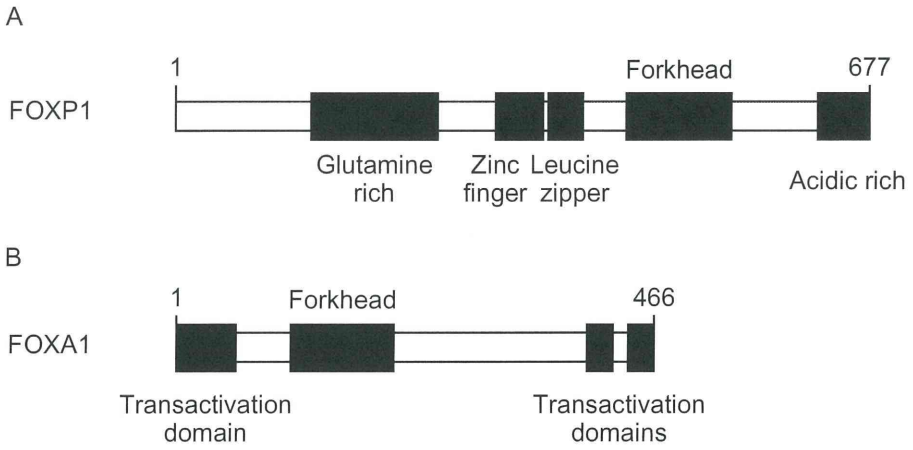

Figure 7.1 Schematic representation of the domain structure of forkhead box transcription factor FOXA1 and FOXP1 proteins. (A) FOXP1 structure. Forkhead domain is located in the C-terminal region of the FOXP1 protein. Zinc finger and leucine zipper domains, responsible for dimerization of FOXP1, are located in the central region. (B) FOXA1 structure. Forkhead domain is located in N-terminal region of FOXA1 protein. Three transactivation domains are located in both terminal regions.

(Fig. 7.1; Li, Weidenfeld, & Morrisey, 2004; Wang, Lin, Li, & Tucker, 2003). Recently, genome-wide studies with an aim of identifying ERα- and androgen receptor (AR)-binding sites have shown that FOXA1 plays a role in regulation of the nuclear receptor-mediated gene networks (Carroll et al., 2005, 2006; Lupien et al., 2008). FOXA1 is recognized as a pioneer transcription factor because binding of FOXA1 to chromatin DNA facilitates subsequent recruitment of ERα and AR to the genome (Grange, Roux, Rigaud, & Pictet, 1991; Lupien et al., 2008). Genome-wide mapping of ERα-, AR-, and FOXA1-binding events in breast and prostate cancer cells using high-throughput sequencing has further uncovered the involvement of several collaborative factors, including TLE1 and activator protein 2γ (AP-2γ), in the nuclear receptor-mediated transcription (Holmes et al., 2012; Tan et al., 2011). In breast cancer cells, several FOX family transcription factors may contribute to the ERα-mediated transcription by directly interacting with the ERα protein, as exemplified by FOXA1 and FKHR/FOXO1 (Carroll & Brown, 2006; Schuur et al., 2001).

Recent studies have shown that FOXP1 and FOXA1 play critical roles in estrogen signaling and in the biology of ERα-positive breast cancer (Ijichi et al., 2012; Shigekawa et al., 2011). These studies showed an upregulation in the expressions of *FOXP1* and *FOXA1* mRNAs induced by 17β-estradiol (E2) stimulation in ERα-positive MCF-7 cells. The

upregulation of both genes was observed in the early phase (3 h) after E2 stimulation, which suggests that both FOXP1 and FOXA1 are transcriptionally regulated by the estrogen in breast cancer cells. In addition, Giguère and his colleagues reported that estrogen upregulates the levels of FOXA1 protein 4–8 h after E2 stimulation (Laganière et al., 2005). Consistent with these findings, the findings of genome-wide chromatin immunoprecipitation (ChIP) analysis based on microarrays (ChIP-chip) showed three and two functional estrogen receptor-binding sites (ERBSs) within the *FOXP1* and *FOXA1* gene loci, respectively, in the genome of MCF-7 cells (Carroll et al., 2005). Conventional ChIP assay showed more than twofold enrichments of estrogen-dependent recruitment of ERα in these ERBSs, which suggested that the recruitment of ERα in the *FOXP1* and *FOXA1* loci contributes to the estrogen-dependent transcription of both *FOX* genes.

Further, FOXP1 and FOXA1 have been shown to serve as transcription factors that directly regulate the ERα-mediated transcription. Luciferase reporter analysis using a vector containing an estrogen-responsive element (ERE, ERE-tk-*luc*) showed that overexpression of either FOXP1 or FOXA1 significantly stimulated the ERα-mediated transactivation in MCF-7 cells in response to estrogen. siRNA-mediated knockdown of FOXA1 reduced ERα-mediated transactivation in the presence or absence of estrogen in MCF-7 cells. Consistent with these observations, the results of other studies showed upregulation of known estrogen-responsive genes, including *SHP* (Lai, Harnish, & Evans, 2003) and *LRH-1* (Annicotte et al., 2005), in FOXP1-overexpressing MCF-7 cells treated with estrogen. Similarly, the contribution of FOXA1 to ERα-mediated transcription was further confirmed by the FOXA1 siRNA-dependent reduction in estrogen-induced expressions of prototypic ERα target genes, progesterone receptor (*PgR*), and growth regulation by estrogen in breast cancer 1 (*GREB1*) (Ghosh, Thompson, & Weigel, 2000; Kastner et al., 1990). These observations suggest that both FOXP1 and FOXA1 stimulate ERα transcription activity in response to estrogen.

The mutual transcriptional regulations of *ERα* and *FOX* genes indicate that both FOXA1 and FOXP1 have the potential to promote estrogen-dependent proliferation of breast cancer cells. Moreover, FOXA1 also upregulates the migration of MCF-7 cells. These findings suggest that FOXP1 and FOXA1 regulate ERα in a positive feedback manner and play crucial roles in the estrogen-dependent cellular responses of ERα-positive breast cancer cells (Fig. 7.2).

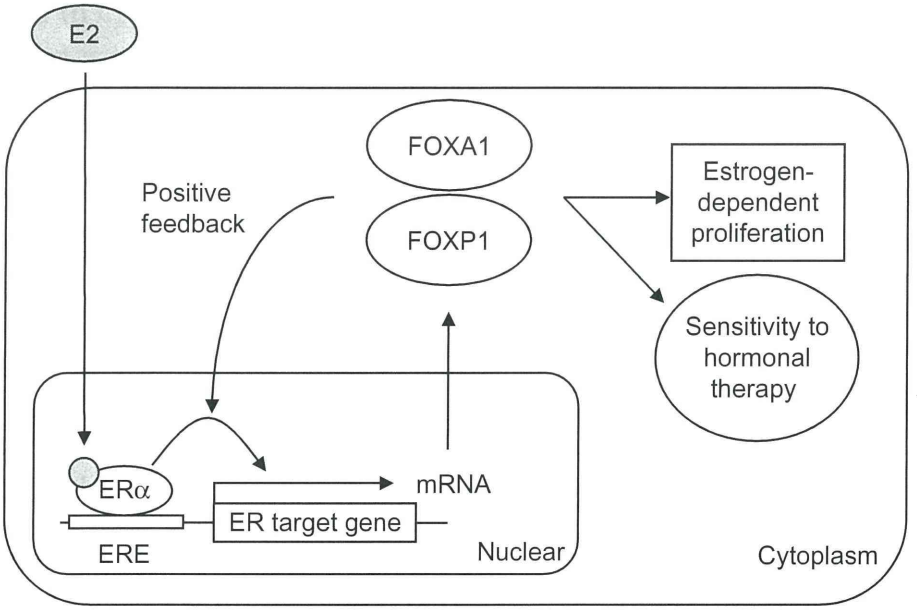

Figure 7.2 Model for cellular functions of FOXP1 and FOXA1 in estrogen signaling. *FOXP1* and *FOXA1* are primary target genes for estrogen receptor α (ERα) and regulate the ERα-mediated transcription in a positive feedback manner. FOXP1 and FOXA1 promote estrogen-dependent proliferation of breast cancer cells and contribute to the sensitivity to hormone therapy.

3. CLINICOPATHOLOGICAL SIGNIFICANCES OF FOXP1 AND FOXA1 IN ER-POSITIVE BREAST CANCER

Recent global gene expression studies on breast cancer have shown that high FOXA1 expression was positively correlated with the status of hormone receptors ERα and PgR and negatively correlated with histological grade and proliferation markers (Badve et al., 2007; Habashy et al., 2008; Thorat et al., 2008). In addition, FOXA1 expression was associated with better prognosis of cancer-specific survival, which indicated that FOXA1 can serve as a predictor for good prognosis of breast cancer (Badve et al., 2007; Habashy et al., 2008; Thorat et al., 2008; Wolf et al., 2007). On the basis of gene expression profiling studies, researchers have classified breast cancers into the following five intrinsic subtypes with unique molecular characteristics and prognostic significance (Perou et al., 2000; Sørlie et al., 2001): luminal A and B, HER2+/ERα−, basal-like, and normal-like subtypes. Luminal subtypes A and B are ERα-positive breast cancers, distinguishing subtype A from B by its higher levels of ERα and better prognosis of the patients (Sørlie et al., 2001). Among these subtypes, FOXA1

expression is best associated with luminal subtype A and FOXA1 immunoreactivity is shown as a significant predictor of cancer-specific survival for patients with ERα-positive tumors (Badve et al., 2007; Mehta et al., 2012). The prognostic relevance of FOXA1 in the breast cancers with relatively low risk will be useful for the determination of therapeutic methods (Badve et al., 2007; Thorat et al., 2008).

Altered expression of FOXP1 is associated with various types of tumors, including breast cancer (Banham et al., 2001, 2007; Barrans, Fenton, Banham, Owen, & Jack, 2004; Bates et al., 2008; Craig et al., 2011; Fox et al., 2004; Goatly et al., 2008; Hoeller, Schneider, Haralambieva, Dirnhofer, & Tzankov, 2010; Prown et al., 2008; Sagaert et al., 2006; Takayama et al., 2008; Wang et al., 2004; Zhang et al., 2010). FOXP1 immunoreactivity may be associated with the immunoreactivity of ERα and PgR in breast cancer, which may predict favorable prognosis in patients (Banham et al., 2005; Rayoo et al., 2009). A recent study showed that FOXP1 immunoreactivity was significantly enhanced in breast cancer samples for tamoxifen-treated patients without relapse, compared with samples for those with relapse within 5 years after surgery (Shigekawa et al., 2011). It was also demonstrated that a positive immunoreactivity for either FOXP1 or FOXA1 significantly correlated with better relapse-free and overall survivals for breast cancer patients with adjuvant tamoxifen therapy, compared with either FOXP1- or FOXA1-negative immunoreactivity (Ijichi et al., 2012). Univariate and multivariate proportional analyses showed that the relapse-free and overall survival rates were associated with FOXA1 and FOXP1 immunoreactivities. For the relapse-free survival, either FOXP1 or FOXA1 immunoreactivity was found to be a significant prognostic predictor through univariate analysis ($P=0.001$ and 0.002, respectively), whereas only FOXP1 immunoreactivity was a better prognostic predictor based on multivariate analysis ($P=0.026$). On the other hand, neither FOXP1 nor FOXA1 was significantly associated with overall survival by multivariate analysis. Notably, double-positive FOXP1 and FOXA1 immunoreactivities were significantly associated with more favorable prognosis for the relapse-free and overall survivals compared with either FOXP1- or FOXA1-negative immunoreactivity based on multivariate analyses ($P=0.002$ and 0.002, respectively). These findings suggest that the combined analyses of the FOXA1 and FOXP1 immunoreactivities provide powerful prognostic indicators for the patients with ERα-positive breast cancers treated with adjuvant tamoxifen therapy.

Carroll and his colleagues showed that FOXA1 also plays a role in the differential ER-binding events in the tumors with a poor outcome (Ross-Innes et al., 2012). Notably, an siRNA-mediated knockdown study showed that ERα signals, including ERα occupancy and estrogen-dependent cell growth, are FOXA1 dependent in both tamoxifen-sensitive and tamoxifen-refractory MCF-7 cells (Hurtado et al., 2011). Further studies are required to answer the question whether the ER/FOXA1-driven growth is associated with tumor recurrence in various stages of the disease.

4. CONCLUSIONS AND FUTURE DIRECTIONS

A recent genome-wide study using ChIP analysis with high-throughput sequencing revealed that FOXA1 is a critical transcription factor that contributes to most of the ERα-chromatin interactions and estrogen-dependent changes of gene expression (Hurtado et al., 2011). FOXA1 influences genome-wide chromatin accessibility of ERα in response to different ligands, including both estrogen and tamoxifen (Hurtado et al., 2011). Thus, FOXA1 is considered as a major determinant for estrogen–ERα activity and endocrine response in breast cancer cells. Since FOXP1 exhibits functions analogous to those of FOXA1 in the ER-mediated transcription and its immunoreactivity has a clinicopathological significance along with FOXA1 immunoreactivity in breast cancer, it is assumed that FOXP1 also plays an important role in the regulation of ERα activity and tamoxifen responsiveness in breast cancer, functioning cooperatively with FOXA1. Future genome-wide studies of FOXP1 binding as well as ERα and FOXA1 occupancy will elucidate the precise interactions of these transcription factors in the ERα-mediated signaling pathways.

In summary, *FOXP1* and *FOXA1* are primary ERα target genes and critical transcription factors that regulate the ERα activity. Both FOX proteins will be potential biomarkers for the prediction of breast cancer prognosis. Pharmacological modulation of FOXP1 and FOXA1 activities may be clinically useful in the prevention and/or treatment of breast cancer.

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