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New insights into the role of FOXA1 in breast cancer

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Abstract

Globally, breast cancer (BC) is the most prevalent form of cancer in women. In Egypt, breast cancer is the most common cancer in women, making up 37.7% of the 12,000–13,000 new cases that occur annually. The FOXA1 gene encodes the forkhead family protein known as forkhead box A1 (FOXA1). According to recent research, FOXA1 may develop into an oncogene during the growth of tumors such as gliomas, non-small cell lung cancer, and hepatocellular carcinoma. Both the functional implications of FOXA1 mutations and the involvement of FOXA1 in carcinogenesis are still unknown. Therefore, it is crucial to investigate the relationship between FOXA1 expression and the development of breast cancer as well as the therapeutic response to endocrine therapy in cases of breast carcinoma.

Keywords: Breast cancer, Forkhead box, FOXA1

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1. Introduction

The forkhead box gene family is named for the Drosophila gene fork head, mutations in which cause defects in head fold involution, resulting in a characteristic spiked head appearance [1]. The forkhead protein contains a 110-amino acid motif that is conserved from yeast to man and which functions as a DNA-binding domain [2]. More than 100 FOX genes have been found and categorized into subfamilies, and genetic studies have demonstrated the biological significance of many of these genes [3]. It has been discovered that many genes are altered in human diseases. The vertebrate FOXA subfamily of Fox transcription factors, which includes FOXA1, FOXA2, and FOXA3, has the closest evolutionary relationship with the original Drosophila protein fork head [4]. In the fifteen years since its discovery, the FOXA family has been demonstrated to be critical in many processes during development and postnatal life [5].

2. The FOXA protein family history and structure

The Forkhead box protein family contains over fifty transcriptional regulators which is distinguished by the presence of the highly conserved "forkhead" DNA-binding domain. Numerous biological processes, including development, proliferation, and longevity, are influenced by these proteins [6]. The forkhead proteins FOXA, FOXC, FOXM, FOXO, and FOXP are significant participants in the pathways that suppress tumor growth and cancer [7]. Upregulation of FOXM1 and FOXC family members is frequently observed in multiple carcinomas, including those of the lung, prostate, pancreas, and breast [8-9]. The FOXA protein family was first identified based on specific DNA binding activity for the promoters of the transthyretin (Ttr), α1-antitrypsin (Serpina1), and albumin (Alb1) genes found in liver nuclear extract [4]. Because of this, the genes were formerly known as hepatocyte nuclear factor-3 (HNF-3) α, β, and γ. However, in 2000, the nomenclature of all vertebrate genes containing a forkhead box was standardized [10]. Most FOXA target genes currently known are involved in the function of terminally differentiated cell types, including lung epithelium, hepatocytes, glucose transporters and enzymes involved in glucose metabolism, and surfactant proteins. These cell types include alb1 and protein C [5].

2.1. FOXA1 (Forkhead box A1)

A member of the forkhead transcription factor family, Forkhead box A1 was formerly known as Hepatocyte Nuclear Factor 3-α (HNF3-α) and has a number of roles in metazoan development [11]. The growth and differentiation of multiple organs, such as the liver, kidney, pancreas, lung, prostate, and mammary gland, is influenced by FOXA1 [10-13].

2.2. FOXA1 and Mammary Gland Development

FOXA1 and ER Are Coordinately Expressed during Mammary Gland Development. Breast cancer can be considered a caricature of normal mammary gland development, and the advancement of breast cancer is also linked to a number of crucial developmental variables, including estrogen receptor (ER) [14]. Like ER, FOXA1 is expressed in distinct compartments during the morphogenesis of the mammary gland. FOXA1 expression in the developing postnatal gland is confined to the body cells of the terminal end bud, which contain the luminal progenitor cells. Mirroring the expression pattern of ER, FOXA1 is expressed in the virgin gland's ductal epithelial cells as the gland grows. While ER and FOXA1 are co-expressed in ductal epithelium, there is a reduction in their expression in alveolar structures, a further decrease in their expression during pregnancy, and an undetectable increase in their expression when lobulo-alveologenesis begins. After involution, ER and FOXA1 expression is progressively restored [15-16].

2.3. FOXA1 expression in human malignancy

Due to the discovery of both pro- and anti-tumourigenic properties, the function of FOXA1 in human cancer is still not fully understood. It has been suggested that FOXA1 and FOXA2 may have a protective role in pancreatic cancer. According to clinical analyses, the expression of FOXA1 and FOXA2 is inversely correlated with the progression and/or aggressiveness of the disease; for instance, the expression of these proteins is commonly lost in poorly differentiated disease, but it is easily detected in normal epithelium and precancerous lesions [17]. On the other hand, research on thyroid cancer has revealed FOXA1 to be a putative oncogene, which is overexpressed and/or amplified in approximately 70% of cases [18]. According to Agarwal et al., (2021), nuclear FOXA1 staining was primarily seen in thyroid tumors that were poorly differentiated and was linked to a high proliferative index [19]. According to Li et al., FOXA1 was also found to be overexpressed or amplified in oesophageal and lung cancers, respectively. However, larger clinical cohorts are required to confirm the expression and significance of FOXA1 in these tumor types [20]. Metastatic prostate cancer specimens demonstrated high nuclear FOXA1 staining in 89% of tissues as compared with 19% of patient-matched primary tumour samples [21]. According to Jain et al., FOXA1 colocalized with androgen receptor (AR) in every sample, and its levels were positively connected with tumor size, extraprostatic extension, and lymph node metastasis [22]. Independent research found that the FOXA1 gene is amplified in a subset of clinical samples and confirmed that the FOXA1 gene is enriched in metastatic tissue at the 14q21.1 chromosomal locus [23]. Based on these data, FOXA1 is strongly linked to prostatic adenocarcinoma metastatic disease. In breast cancer, high FOXA1 expression positively correlates with outcome, but the potential impact of such expression is variant, dependent on ERα status and tumour molecular subtype [24]. Clinical studies involving over 3500 primary invasive ductal carcinomas demonstrated positive FOXA1 staining in ~86% of all specimens, and expression was positively correlated with favourable prognosis [25]. Accordingly, low FOXA1 correlated with established markers of poor prognosis including high grade, increased tumour size, basal tumours and nodal metastasis [26]. As in normal breast tissues, there is a strong co-expression of FOXA1 and ERα in luminal breast cancer, and like ERα expression, high FOXA1 staining is associated with favourable prognosis in luminal disease [27-28]. Recent studies have uncovered an unexpected role for FOXA1 in a subtype of ERα-negative disease, positively correlated with favourable prognosis [29]. Accordingly, low FOXA1 correlated with established markers of poor prognosis including high grade, increased tumour size, basal tumours and nodal metastasis [29].

2.4. Roles of FOXA1 in Breast Cancer

The mechanistic basis for how FOXA1 triggers transcriptional cascades involved in both development and disease is provided by its capacity to remodel heterochromatin. In particular, FOXA1 is needed for ER-positive breast tissue and for the development of the mammary gland [24]. According to earlier research, FOXA1 can function as a repressor or as a growth stimulant. It is a pioneer factor that binds to chromatinized DNA, opens the chromatin, and promotes ERα binding to target genes like TFF1 (trefoil factor 1; pS2) as a stimulator. FOXA1 is necessary for the expression of ER mRNA and protein in breast cancer cells and directly binds to the ESR1 (oestrogen receptor 1) promoter in addition to regulating ER activity [15]. When taken as a whole, these findings demonstrated that FOXA1 is necessary for both ER expression and activity [30]. Two mechanisms that have been identified as potential repressors that could contribute to growth inhibition are the inhibition of metastatic progression and the differential regulation of the ER pathway [24]. Research has demonstrated that over-expression of FOXA1 can impede the spread of metastatic disease by affecting the expression of p27, a cell cycle inhibitor associated with breast cancer gene 1(BRCA1), and by enhancing the expression of E-cadherin. To reduce the number of cells, FOXA1 binds to the p27 promoter and works in concert with BRCA1, the gene that increases the risk of breast cancer. In a similar vein, FOXA1 directly promotes the transcription of the E-cadherin gene (CDH1), and this in turn reduces the ability of breast cancer cells to migrate by increasing the expression of E-cadherin. It is suggested that FOXA1 plays ER-independent roles in determining a more differentiated luminal cell phenotype because CDH1 activation happens in the absence of ER. Conversely, FOXA1 slowed the growth of ERα-positive cells by blocking the ER pathway [31]. The crosstalk between FOXA1 and ER has been proposed to favor the expression of genes associated with differentiation rather than those associated with proliferation because of the intricate interactions between ER and the signaling pathways that are associated with it [32]. Therefore, over-expressed ER and well-differentiated breast cancer, which indicate a good prognosis in breast cancer, may be caused by FOXA1. Furthermore, even in those who have developed tamoxifen resistance, FOXA1 has been shown to be crucial for the cellular response to the drug [33]. Therefore, a molecular explanation for the association between FOXA1 and a favorable prognosis in breast cancer may be offered by these new findings in addition to the observations of the inhibited role.

2.5. FOXA1 as a Therapeutic Target in Breast Cancer

FOXA1 inhibits the migration and invasion of tumor cells, which are more primitive phenotypes. Consequently, it might be advantageous for patient outcomes to inhibit

FOXA1 function in breast cancer. It's unclear, though, if FOXA1 can be used as a therapeutic target in this illness. In breast cancer, pharmacological inhibition of FOXA1 is supported by multiple lines of evidence. First, the majority of breast cancer diagnoses are luminal breast cancer, for which FOXA1 is a critical determinant of estrogen receptor signaling and required for cell cycle progression and proliferation [28,34-36]. Poorer patient outcomes result from FOXA1's dysregulated expression and function, which is caused by amplification, mutation, or upregulation. This resistance also occurs to endocrine and HER2-targeted therapies [37-39]. Second, FOXA1 chromatin binding may be reprogrammed by (Nuclear Receptor) NR crosstalk, which may also be linked to therapy resistance and the activation of compensatory pathways [40-42]. Poorer patient outcomes have been linked to increased FOXA1 expression's ability to suppress the tumor immune response [43-45]. Last but not least, using genetic methods to suppress FOXA1 expression within leads to a reduction in the growth of tumor cells, a reversal of treatment resistance, and an increase in the tumor immune response. All of these findings support the management of breast cancer by blocking FOXA1.

4. Conclusions

In summary, there is adirect link between FOXA1 and human malignancies particularly breast cancer suggesting a potential role in therapy requiring further research for concrete associations and therapeutic possibilities.

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