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SAM pointed domain containing ETS transcription factor: A Pro- and Anti-Oncogenic agent in Breast Cancer

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ABSTRACT: SPDEF (SAM pointed domain containing ETS transcription factor) maintains homeostasis and differentiation of epithelial tissues and heritable alteration in cancer. SPDEF is a prostate-derived ETS factor that has been demonstrated to have a role in normal cell growth and development and also in cell survival. This transcription factor also plays a significant role in possessing dual malignancy characteristics. Breast cancer (BC) is a complex heterogeneous disease associated with multiple structures that have risen to become the leading source of cancer death in women worldwide. SPDEF has been linked to a variety of characteristics of BC. The mechanism governing SPDEF's pro- and anti-oncogenic effects in the BC state is yet unknown. If SPDEF is shown to significantly affect breast cancer, comprehension of its molecular mechanisms would be necessary to target it therapeutically. It is challenging to create treatments that regulate SPDEF activity while reducing side effects. In this study, we reviewed SPDEF's role as a multipurpose agent in expression levels, the regulation process in BC development, and its role in BC diagnosis, therapy, and prediction. Knowing SPDEF duality has assisted in getting knowledge into tumor biology as well as giving new BC treatment targets a new perspective.

Keywords: Breast Cancer, ETS, SPDEF, Oncogene, Tumor suppressor gene.

INTRODUCTION

Breast cancer (BC) is malignant cell growth in the breast cells. BC is the most commonly diagnosed cancer in women around the world. It is the leading cause of female deaths globally, comprising almost one-third of all malignancies in females. BC can occur in women at any age after puberty but with increasing rates in later life (Rodney and John 2003). It may metastasize to other parts of the body. The lymphatic system is the primary route of metastasis, which produces and transports the white blood cells which fight the cancer cells (Zhou *et al.,* 2021). It affects approximately 1 out of 8 women during their lifetime and is also sometimes seen in men (Nadia *et al.,* 2019). It is a worldwide medical issue and subsequently, the number of cases has increased over the past few decades. Breast cancer cases and mortality rates are expected to increase in the next 5-10 years (Greaney *et al.,* 2015). According to WHO 2020, there were 2.3 million women diagnosed with breast cancer. According to the Indian Council of Medical Research (ICMR) National Cancer Registry Programme, it is estimated that there will be 1,62,468 new cases of breast cancer and 87,090 deaths due to breast cancer in India in 2021. The incidence of breast cancer in India varies by region, with higher rates observed in urban areas compared to rural areas. The age-adjusted incidence rate of breast cancer in India is 25.8 per 100,000 women. Molecular heterogeneity of breast cancer causes hindrances in understanding mechanism research and the development of molecularly targeted drugs clinically. To organize this variability, several BC categorizations have been developed (Bray *et al.,* 2018).

Based on the presence or lack of specific biomarkers including hormone receptors, the human epidermal growth factor receptor 2 (HER2), and proliferation markers, breast cancer can be divided into several molecular subtypes. Breast cancer is classified into the following subtypes: luminal A, B, HER2, and Basal-like/Triple-negative according to the most widely used classification method (Zepeda *et al.,* 2008). Luminal A subtype is characterized by the presence of estrogen receptor (ER) and/or progesterone receptor (PR) and low levels of HER2. It is typically associated with a good prognosis and is sensitive to hormone therapy. The Luminal B subtype is also characterized by the presence of ER and/or PR but has higher levels of HER2 and/or proliferation markers such as Ki-67 (Cheang *et al.,* 2009). It is generally associated with a poorer prognosis than Luminal A and may require more aggressive treatment. The HER2-enriched subtype is characterized by the overexpression of HER2 and is typically associated with a poor prognosis. However, it can be effectively treated with HER2-targeted therapies such as trastuzumab. Basal-like/Triple-negative subtype

is characterized by the absence of ER, PR, and HER2 and is typically associated with a poor prognosis. It is more common in younger women and African American women, and there are currently no targeted therapies available for this subtype.

Research suggested that Her^{2+} BC is caused by overexpression of Her2 and is more invasive than estrogen receptor-positive (ER^{+}) BC (Isobe *et al.,* 1986). Other than this, based on pathogenicity, the most common BC with higher relative incidence include Invasive ductal carcinoma (IDC), Invasive lobular carcinoma (ILC), Tubular carcinomas (TC), Invasive Micropapillary Carcinoma (IMPC), Mucinous carcinoma, etc.

The heterogeneity of BC occurs mainly due to the dual nature of genes. Targeting one gene for specific cancer can be crucial but simultaneously it may also promote the growth and proliferation of other cells leading to tumorigenesis. Hence understanding the dual nature of genes will contribute to the treatment of different BC subtypes. In tumorigenesis, two antagonistic cancer regulatory genes are involved i.e., OCG (Oncogenes) and TSG (Tumor suppressor genes). OCGs can cause uncontrolled growth in normal cells and finally become cancer cells whereas TSGs prohibit normal cells from becoming cancer cells (Yang *et al.,* 2007). Interestingly, several genes exhibit both cancer-causing and tumor-suppressive properties such as p53, KMT2D, ARID1A, etc. (Soussi *et al.,* 2015; Malkin 1990; Ortega 2015; Sun *et al.,* 2017 and Zhang *et al.,* 2021). It is necessary to study the dual character of such genes to promote the development of cancer research. SPDEF gene is important for normal cell growth, development, survival, and function. However, its role in BC is debatable as SPDEF acts both as OCG or TSG. This review focuses on highlighting the dual role of SPDEF as TSG and OCG in breast cancer.

A. Structure of SPDEF

The SPDEF transcription factor family belongs to an ETS family that is the largest transcription factor family in animals (Nunn *et al.,* 1983). SPDEF gene is present on chromosome 6p21.31, reverse strand, and consists of 6 exons with a total length of 1895 nucleotide bases. SPDEF has been determined for its role in cancer development and progression. The initial ETS gene was recognized as a viral oncogene in the avian-transforming retrovirus E26 (Sharrocks, 2001). The SPDEF protein is made up of 335 amino acids. SPDEF differs from other ETS proteins in that it primarily comprises a SAM pointed domain and an 88-amino acid ETS domain. Moreover, the SPDEF protein's ETS entity chooses to bind to GGAT instead of the GGAA core, unlike some other ETS TFs (Oettgen *et al.*, 2000). One study claim that during viral infection, SPDEF contributes to mucus formation (Bao, and Wang, 2022).

B. Phosphorylation as Major Post-Translational Modification (PTM) in SPDEF Gene

The regulation of SPDEF genes is done by activation of extracellular signal-regulated kinase/mitogen-activated protein kinase (ERK/MAPK), phosphorylation. Post-translational modifications (PTMs) such as phosphorylation can play important roles in regulating the activity and function of SPDEF.

SPDEF contains putative phosphorylation locations for protein kinase C, 2 AKT phosphorylation sites, 2 tyrosine kinase phosphorylation sites, and 8 MAPK phosphorylation sites (Oettgen *et al.,* 2000). The loss of SPDEF protein, which is caused by cell cycle kinase CDK11p58, increases prostate cancer cell invasion and migration. Cancer cell migration and invasion are prevented by SPDEF overexpression or CDK11p58 protein expression suppression. The direct interactions between growth arrest and DNA damage-inducible 45 (GADD45) and CDK11p58 decreases CDK11p58 activity, SPDEF phosphorylation and degradation, and eventually inhibit prostate cancer cell migration and invasion (Tamura *et al.,* 2016). To establish the full degree of SPDEF phosphorylation as well as the role of phosphorylation in SPDEF activity modulation, more evidence will be needed in the future.

C. Summarization of SPDEF Expression Profile

Dissimilar to other transcription factors of the ETS family, it is elucidated that SPDEF is significantly expressed in both normal and malignant tissues (prostate, breast, intestine, colon, tracheal, eye, head, and neck) having high epithelial content. SPDEF expression in these tissues may play a key role in its development function. In normal tissues, SPDEF expression is well understood but the expression in BC is not clear (Oettgen *et al.,* 2000; Ghadersohi *et al.,* 2001; Sood *et al.,* 2007; Turcotte *et al.,* 2007; Gupta *et al.,* 2011 and Wang *et al.,* 2021).

SPDEF expression profiles in various BC cell lines and tissues have been widely studied. Findlay evaluated the expression of SPDEF mRNA and protein in multiple BC cell lines. Some cell lines expressed detectable levels of both SPDEF mRNA and protein, whereas others had SPDEF mRNA, but little or no detectable levels of protein (Findlay *et al.,* 2008).

In another study, the down-regulation of SPDEF protein in MCF-7 breast tumor tissues was inversely related to the expression of survivin. Significant levels of survivin were expressed by the silencing of SPDEF, which increases MCF-7 breast cancer cell growth in vitro. This indicates that SPDEF protein levels in the BC cell line inhibit tumorigenesis (Ghadersohi *et al.,* 2006). Xiao *et al.*, reported that GRIK3 (Glutamate receptor, ionotropic kainate 3) enhanced cell proliferation, migration, and invasion activities by downregulating SPDEF/CDH1 (Cadherin 1) in M. D. Androgen-Metastasis breast cancer (MDA-MB-231) and MCF-7 cell lines (Xiao *et al.,* 2019). This study indicates that SPDEF/CDH1 and GRIK3 mediate cell proliferation, migration, and invasion of breast cancer cells.

SPDEF expression was found to be prevalent in cancers of the lumen endothelial cell lineages, such as luminal, $Her2^{+}$, and apocrine subtypes of luminal BC. Triple-negative breast cancer (TNBC), on the other hand, expresses very low SPDEF (Sood *et al.,* 2009). Similarly, Ye *et al.,* studied the differential expression of SPDEF in multiple subtypes of BC and found that non-TNBC cells had high SPDEF mRNA whereas

TNBC cells had low SPDEF mRNA levels (Ye *et al.,* 2020).

Several studies have shown that SPDEF expression alone is insufficient to cause invasive activity in BC. Increased levels of SPDEF expression, however, could start transformation activity or sensitize cancerous cells, leading to further outcomes such as RTK (receptor tyrosine kinase) amplification or mutation activation to accelerate tumor development (Gunawardane *et al.,* 2005). When working with oncogenes, SPDEF can accelerate tumor progression in all aspects, including cellular mobility, invasiveness, and non-anchored proliferation of breast epithelial cells. It is revealed that SPDEF may involve in the occurrence or development of early BC. When compared to early tumors, advanced cancers have lower SPDEF mRNA expression, which is often compatible with SPDEF down-regulation and the detection of low protein levels (Turcotte *et al.,* 2007).

The tendency for SPDEF expression to decline during tumor advancement suggests that SPDEF may serve a variety of purposes at various periods of BC development, further demonstrating the dual function of SPDEF (Feldman *et al.,* 2003; Tsujimoto *et al.,* 2002). Also, the amounts of mRNA and proteins are not necessarily correlated. It might result from a post-translational modification mechanism like the control of miRNAs or the quick degradation of SPDEF (Findlay *et al.,* 2011; Oettgen *et al.,* 2000). Conversely, some BC cell lines, like HCC-1428, have high levels of SPDEF mRNA but low levels of SPDEF protein. It could be a result of SPDEF breakdown (Turcotte *et al.,* 2007). It is noticeable that the protein is independent of its transcript size in MDA-MB-231 (Findlay *et al.,* 2008). Overall, the available evidence suggests that the role of SPDEF in cancer is likely to be context-dependent and may vary depending on the cancer type and stage. More research is needed to fully understand the mechanisms by which SPDEF regulates cancer progression and to determine its potential as a therapeutic target in cancer.

D. Function of SPDEF in Breast Cancer

SPDEF is a highly conservative ETS transcription factor that helps in the regulation of several biological activities, involving cell proliferation, differentiation, death, transformation, motility, and invasion, and is expected to play a substantial role in oncogenesis (Findlay *et al.,* 2013; Dittmer 2003; Oikawa and Yamada 2003; Seth and Watson 2005). All of these studies concluded that SPDEF exhibits dual functionality. OCGs are derived by the activation of proto-oncogenes whereas TSGs cause cancer if they are inactivated. In the hundreds of BC examined thus far, SPDEF gene activation and inactivation mutations are infrequent (Nik *et al.,* 2016). According to the cellular hierarchy in normal mammary gland development, the basal myoepithelial, luminal ductal, and luminal alveolar mature cell types grow from progenitor and stem cell precursors through controlled specification, proliferation, and differentiation (Kordon and Smith 1998; Stingl *et al.,* 2006). The basal versus luminal breast cancer subtypes, which are two different subtypes of human breast cancer, appears to have developed from the equivalent normal cells with unique gene expression profiles (Sorlie *et al.,* 2003; Weigelt *et al.,* 2008). Despite these developments, it is still unclear how certain molecular processes control lineage selection, proliferation, and differentiation in healthy breast tissue and how breast cancer heterogeneity arises. Understanding the function of certain transcription factors in typical mammary gland development is still in its early stages. As the breast tumor progressed, SPDEF protein expression revealed that individual samples varied substantially in terms of staining intensity and the proportion of cells that stained positively. The development from normal breast tissue to carcinoma, however, was commonly accompanied by an increase in the expression of SPDEF protein, and this was further supported in the vast majority of matched samples of benign breast and tumor tissues from the same patients (Tamura *et al.,* 2016). Such as SPDEF expression in breast tumors raises the possibility of its involvement in mammary gland development and the pathogenesis of breast cancer.

The role of SPDEF in breast cancer also varies according to the molecular subtype of the disease. The reduction of SPDEF protein in TNBC cell lines, which has been connected to the inhibition of SPDEF mRNA translation by miR-204 and miR-510, suggests a tumor migration of the TNBC cell line, (MDA-MB-231) (Feldman *et al.,* 2003; Turner *et al.,* 2007). On the other hand, excessive SPDEF mRNA expression is associated with poor overall survival in ER+ breast tumors (Sood *et al.,* 2017; Sood *et al.,* 2009). The ER antagonists, tamoxifen and fulvestrant, as well as basal apoptosis, were all made more sensitive when SPDEF was knocked down in several luminal cell lines. The significance of this discovery was confirmed by a genome-wide short hairpin RNA (shRNA) screen of several breast cancer cell lines, which recognize SPDEF and Forkhead box A1 (FOXA1) as the two most crucial genes necessary for the development and survival of luminal/HER2 cell lines (Marcotte *et al.,* 2016).

Overall, the function of SPDEF in breast cancer is complex and context-dependent, with both tumor-suppressive and oncogenic functions reported. Further research is needed to fully understand the molecular mechanisms underlying the role of SPDEF in breast cancer and to identify potential therapeutic targets for this disease.

E. Progression and Proliferation

SPDEF appears to be a crucial component in regulating tumor growth and proliferation. According to the study, SPDEF and ER^+ luminal BC exhibit a significant inverse relationship ER^-cooperating factors including FOXA1 and GATA3 are also directly recruited to the SPDEF gene region. In ER^+BC cells, it has been demonstrated that SPDEF is a direct target of ER, FOXA1, and GATA3. GATA3 and FOXA1 regulate the co-expression of SPDEF and ER. GATA3 suppresses SPDEF transcription mediated by the ER and plays a negative function in SPDEF regulation. FOXA1 on the other hand, stimulates ER-mediated SPDEF transcription and cell proliferation (Buchwalter *et al.,* 2013). SPDEF may act as an oncogene in ER^+ breast cancer by promoting the proliferation and growth

of cancer cells through the activation of the ER pathway. Higher SPDEF expression was associated with better prognosis in ER+ breast cancer patients, and SPDEF enhanced ER function and the growth of ER^+ breast cancer cells in vitro and in vivo. The SPDEF function can expedite the malignant transformation of cancer cells as well as support cancer cells' ability to survive. SPDEF can promote tumor progression and invasion by overexpression of p62 in BC. p62 (also known as SQSTM1) is a protein involved in various cellular processes, including autophagy, signaling, and cell migration. SPDEF upregulates p62 transcription by binding immediately to at least two locations on the p62 promoter, suggesting that SPDEF may operate as a p62 co-activator and drive p62 overexpression in BC (Thompson *et al.,* 2003). In vivo, p62 depletion has also been shown to prevent BC metastasis and diminish tumorigenicity (Li *et al.,* 2017). Patients with p62 overexpression in TNBC are more likely to have lymph node-positive and lymphoid metastasis (Luo *et al.,* 2013). p62 can promote breast cancer invasion and metastasis by activating signaling pathways involved in cell migration and extracellular matrix remodeling. SPDEF-induced p62 expression may contribute to breast cancer progression and could be a potential target for therapy.

F. SPDEF Functions as a Tumor Suppressor Gene by Inhibiting of Cell Growth and Proliferation

It is well known that SPDEF plays BC development but some studies have also revealed SPDEF has a tumor-suppressor effect. As a transcription factor, SPDEF regulates the transcription of the gene it specifically targets downstream. It has been shown that survivin, a novel member of the inhibitor of apoptosis (IAP) protein family, plays a role in encouraging carcinogenesis. The survivin gene is a putative PDEF transcription factor downstream target. In MCF-7 breast cancer cells, ectopic expression of PDEF reduces survivin expression and its promoter activity *in vitro* and the creation of xenograft tumors *in vivo*. SPDEF silencing, on the other hand, can increase survivin expression, which promotes the proliferation of MCF-7 BC cells in vitro and the formation of xenograft tumors in vivo (Ghadersohi *et al.,* 2008).

Another study found that SPDEF regulates the transcription of p21/CIP1 in breast cancer cells and that this regulation is necessary for SPDEF to inhibit cell proliferation. Specifically, SPDEF was found to bind to the p21/CIP1 promoter region and activate its transcription, leading to increased expression of p21/CIP1 and subsequent inhibition of cell cycle progression and cell proliferation. Additionally, the study showed that SPDEF overexpression in breast cancer cells inhibited tumor growth and metastasis in a mouse model of breast cancer. Overall, this study provides evidence for the importance of PDEF in the regulation of cell proliferation and tumor progression in breast cancer through the transcriptional regulation of p21/CIP1. Cell cycle studies revealed SPDEF development in the G1/S phase without affecting apoptosis. Nevertheless, p21 silencing reverses the SPDEF growth inhibition in vitro and in vivo (Schaefer *et al.,* 2010). Maspin (mammary serine protease inhibitor), uPA (Urokinase plasminogen activator), VASP (Vasodilator-stimulated phosphoprotein), and SLUG are a few of the SPDEF direct downstream effector genes discovered over the years that are involved in the negative control of BC migration, invasion, and metastasis. Identification and characterization of a serine protease inhibitor called Maspin, which is capable of suppressing the growth and invasion of cancer cells *in vitro* and *in vivo*. Maspin inhibits the activity of a protease called urokinase-type plasminogen activator (uPA), which is known to play a role in cancer cell invasion and metastasis. By inhibiting uPA, Maspin can block the spread of cancer cells and prevent the formation of new tumors. Maspin is frequently down-regulated throughout the progression of BC (Sager *et al.,* 1997). SPDEF exerts its effects on breast cancer cells and found that SPDEF downregulates the expression of a protein called survivin, which is known to play a role in cell survival and resistance to chemotherapy. By reducing survivin expression, SPDEF can increase the sensitivity of breast cancer cells to chemotherapy drugs. In addition to in vitro studies, conducted *in vivo* experiments using xenograft models of breast cancer. Overexpression of SPDEF in breast cancer cells led to a significant reduction in tumor growth in mice. SPDEF has been shown to modulate the Maspin promoter favorably and influence Maspin expression (Ghadersohi *et al.,* 2007). Maspin expression is reduced in inflammatory breast cancer (IBC) primarily due to the loss of SPDEF, which might also lead to tumor cell invasion and metastasis. In addition, several studies have shown that Maspin, a type II TSG, can reduce the development, motility, invasion, and metastasis of various malignancies, including BC (Hendrix 2000; Zhang *et al.,* 1997 & Zou 1994). Cell proliferation and adhesion are regulated by the uPA ligand and its membrane-bound receptor, uPAR (Choong and Nadesapillai 2003; Han *et al.,* 2005). In a variety of ways, SPDEF's negative control of uPA can alter the capacity of cancer cells to migrate (Kruger *et al.,* 2000). uPA is a primary transcription target of SPDEF-negative regulation, according to numerous studies (Turner *et al.,* 2008). uPA is triggered on the exterior of MDA-MB-231 cells and can transform surface plasminogen to plasmin (Andronicos and Ranson 2001). Plasmin can not only destroy extracellular matrix (ECM) elements directly, but it can also directly or indirectly activate matrix metalloproteinase (MMP), which can speed up ECM destruction (Ramos *et al.,* 1999). SPDEF-downregulated uPA may stop the basement membrane from degrading. Second, SPDEF-depleted uPA causes a compensatory rise in uPAR mRNA transcription in IBC cells. It turns out that increased soluble uPAR may inhibit BC cell metastasis by inhibiting several urokinase system functions, including tumor development and proteolysis (Turner *et al.,* 2008). The combination of the uPA/uPAR system plays a key role in intracellular signal transduction, including interactions with tyrosine kinase, the EGFR signaling pathway, and members of the signal-related integration family (Chapman and Wei 2001). Downregulation of

uPA by SPDEF may diminish uPAR binding, alter intracellular signaling patterns, and hence impede cell motility. Vasodilator-stimulated phosphoprotein (VASP) is an actin-binding protein that helps to connect signaling pathways to the actin cytoskeleton (Bear *et al.,* 2002). VASP is a presumed target gene for SPDEF, according to bioinformatics studies. Turner *et al.* (2008) have confirmed that SPDEF directly upregulates VASP *in vitro* (Kruger *et al.,* 2000). When up-regulated VASP is positioned on the cell membrane, many lamellipodia can be generated, which can slow cell movement and has a phenotype similar to SPDEF re-expression (Lin *et al.,* 2004). Snail family zinc finger 2 (SLUG) is a component of the SNAIL superfamily, as well as its high transcription in breast cancers, is linked to the invasive basal phenotype. SLUG is highly expressed in BBC, which is an aggressive subtype of breast cancer characterized by poor prognosis and lack of response to hormonal and targeted therapies. SLUG regulates the BBC phenotype, and found that SLUG regulates the expression of genes involved in cell adhesion, migration, and invasion. They also found that SLUG expression is associated with increased tumor-initiating cell (TIC) activity, which is thought to contribute to the aggressive nature of BBC (Storci *et al.,* 2008). Furthermore, SLUG is inversely associated with E-cadherin expression and is a crucial event–promoting EMT in a variety of tumor types (Jethwa *et al.,* 2008). SPDEF has been found to regulate downstream substrates of SLUG in both SLUG-dependent and SLUG-independent ways, implying a vital involvement in EMT regulation. During carcinogenesis, E-cadherin is also recognized to be a transcription target of SLUG. Low levels of SPDEF can relieve E-cadherin repression by inhibiting SLUG directly, and this is a crucial interaction in preventing the migratory phenotype (Findlay *et al.,* 2011).

Endogenous 19-25 nucleotide non-protein coding RNAs called miRNAs play a dual role in tumor growth (Siegel *et al.,* 2014). Even though many studies on miRNAs have been conducted in BC, only a few have concentrated on miRNAs that link with SPDEF mRNA. Findlay *et al.,* revealed that SPDEF is actively governed by two types of miRNAs (miRNA-204 and miRNA-510), that can inhibit SPDEF mRNA from being translated, leading to the loss of SPDEF protein production and encouraging tumors to become more aggressive. Extrinsic SPDEF transcription can also prevent miRNAs from becoming overexpressed (Findlay *et al.,* 2008). The tumor suppressor gene SPDEF, whose mRNA levels are decreased in invasive breast cancer cells, also inhibits cell migration and invasion when it is re-expressed (Feldman *et al.,* 2003). SPDEF are important factors that can inhibit cancer cell migration, invasion, and metastasis by regulating the expression of genes involved in cell adhesion and motility.

G. Double Agent SPDEF: A Potent Breast Cancer Diagnostic Marker

Oncologists are searching for novel BC genes that can be used as early diagnostic or prognostic markers. The dual-functional SPDEF has been identified as a potential biomarker for breast cancer diagnosis and prognosis. SPDEF expression is often decreased in breast cancer tissues compared to normal breast tissues, and low SPDEF expression is associated with poor prognosis and increased risk of metastasis. Furthermore, SPDEF expression is associated with specific breast cancer subtypes, with higher expression in luminal A and B subtypes and lower expression in basal-like and HER2-positive subtypes (Ye *et al.,* 2020). SPDEF expression was discovered in 86 clinical specimens and then evaluated using receiver–operator curves to determine the sensitivity and specificity with which SPDEF expression may predict an association of ER-positive (ROCs). ER^+ was the result, with a sensitivity of 98.3% (58/59) and a specificity of 76.9% (20/26) The area under the curve (AUC) is 0.902 when SPDEF production is at or above the MCF-7 level (Turcotte *et al.,* 2007).

SPDEF has an impact on the prognosis of BC patients. In 246 individuals with ERBC, increased SPDEF expression was linked to a shorter overall survival (OS), whereas SPDEF expression was not linked to disease-free survival (DFS). However, multivariate analysis revealed that SPDEF transcription is a substantial independent prognostic factor for OS (Cao *et al.,* 2018; Cao *et al.,* 2018). In addition, three separate data sets were retrieved from the GEO and Array Express databases and examined using Kaplan-Meier analysis. The findings revealed that elevated SPDEF expression is linked to a poor prognosis in ER^+BC patients. When SPDEF is a constant factor in ER^+BC, SPDEF is a significant determinant of survival in the Cox regression model, which is similar to earlier studies (Turner *et al.,* 2007; Sood *et al.,* 2009).

H. Future Perspective of Double Agent: SPDEF in Treatment of Breast Cancer

The directed therapy concept has helped in a new era of tumor chemotherapy, which is now widely employed to treat a variety of molecular subtypes of BC. HER2-positive breast cancer is a subtype of breast cancer that is characterized by overexpression of the human epidermal growth factor receptor 2 (HER2). HER2-targeted therapies such as trastuzumab and pertuzumab have been shown to improve survival in patients with HER2-positive breast cancer. In this study, a total of 808 patients with HER2-positive metastatic breast cancer were randomized to receive either pertuzumab, trastuzumab, and docetaxel or placebo, trastuzumab, and docetaxel.

In conclusion, the study demonstrated that the combination of pertuzumab, trastuzumab, and docetaxel is an effective and safe treatment option for patients with HER2-positive metastatic breast cancer. The results of this study have led to the approval of this combination therapy for the treatment of HER2-positive metastatic breast cancer (Swain *et al.,* 2015). Endocrine therapy and selective adjuvant chemotherapy are still the most common treatments for luminal BC and selective adjuvant chemotherapy. The inclusion of a targeted medication in endocrine treatment has lately opened up new treatment options for individuals with luminal BC. DFS in this cohort has improved with the

addition of everolimus to exemestane (Baselga *et al.,* 2012).

Because tumor cells differ from one another and multiply as a result of treatment, they have a poor therapeutic impact or cause substantial damage. Furthermore, tumor heterogeneity is linked to genes with multiple functions. As a result, identifying the best tumor candidate antigen depending on this dual nature will aid in the establishment of tumor-targeted therapy.

Her2 is now the primary antibody-mediated immunotherapeutic target for BC, which is crucial for the treatment of the disease (Mittendorf *et al.,* 2008). Targeting OCG and its linked pathways is likely to lead to the development of new medications, particularly antibodies and small synthetic compounds, according to existing therapeutic usage (Osborne *et al.,* 2004). Furthermore, because SPDEF is expressed in a restricted number of healthy human tissues, SPDEF-based anti-tumor therapies are expected to have little toxicity in important normal tissues (Sood *et al.,* 2017).

SPDEF, as a transcription factor, can also have a considerable impact on the biological features of tumors by causing large-scale alterations in gene expression, and these altered genes could code for cell surface or secreted chemicals that influence the behavior of the tumor and stromal cells nearby (Sood *et al.,* 2007). These findings support SPDEF as a promising new potential antigen for the treatment of luminal BC. Meanwhile, Sood *et al.,* discovered that SPDEF is immunogenic and intolerant in female BC patients and that the SPDEF sequence contains HLA-A2-binding peptides that could trigger HLA-A2-restricted T cell responses. The peculiarities of ER expression in BC and their implications for endocrine therapy support this theory. Similarly, using SPDEF-targeted vaccines/immunotherapy to eradicate SPDEF-expressing cells from BC should not only destroy SPDEF-expressing tumor cells but also change the tumor microenvironment and slow tumor development (Sood *et al.,* 2010). SPDEF is also required for luminal BC cell survival and endocrine resistance models, suggesting that it may have therapeutic relevance in BC patients receiving endocrine therapy (Marcotte *et al.,* 2016).

As a result, SPDEF may be an excellent option for co-targeting with endocrine therapy in the treatment of BC patients with endocrine resistance (Sood *et al.,* 2017). Even though no clinical trials on SPDEF targeted therapy have been published, these considerations suggest that SPDEF's potential as a novel luminal breast cancer antigen should be studied. Future research should reframe the "SPDEF gene" by taking into account each mRNA, regulatory RNA, protein isoform, and post-translational modification from the same genomic locus instead of solely thinking that SPDEF is a TSG or an OCG in BC to better understand tumor biology and choose targets for various cancer subtypes for effective therapy.

I. Application of SPDEF Gene Expression in Various Cancers Types

SPDEF plays a role in cancer cell migration in various cancers (breast, prostate, ovarian, colon, and hepatocellular cancer). Joshua reported that hypermethylation of SPDEF promoter has been identified in breast cancer cells (Joshua *et al.,* 2012). An mRNA microarray analysis study showed that the expression of SPDEF influenced more than 300 genes including mucin 16 (MUC16), anterior gradient 2 (AGR2), and chloride channel calcium activated 1 (Clca1). IL-13 treatment induced by MUC5AC, AGR2, and Clca1 was reduced in SPDEF knockout human airway epithelial cells.

In colon cancer cells to activate the goblet cell genes by Notch signal inhibitors, the knockdown of SPDEF also repressed the expression of mucin (MUC2) and anterior gradient homolog 2 (AGR2) (Chen *et al.,* 2009). SPDEF is a molecular switch for E-cadherin expression that promotes prostate cancer metastasis. In a few studies, SPDEF genes were found to be involved as an oncogenic driver in prostate cancer (Tamura *et al.,* 2016) whereas others have noted SPDEF as a tumor metastasis suppressor (Steffan *et al.,* 2012; Cheng *et al.,* 2014). Several reports suggested that SPDEF should be considered a tumor-suppressor gene in prostate cancers. Loss of SPDEF in PCa is associated with worse clinical outcomes and poor differentiation. Knockdown of SPDEF gave rise to enhanced prostatic cell migration, invasion, and metastasis.

The majority of prostate cancer samples had SPDEF expression levels that were higher than those of normal prostatic epithelium, indicating that SPDEF was elevated in cancer. In 80% of prostate cancer samples, nuclear SPDEF expression was found; it was rated as weak in 26.4%, moderate in 40.1%, and strong in 13.5% of instances (Meiners *et al.,* 2019). In human bladder cancer, SPDEF acts as a tumor suppressor (Tsui *et al.,* 2016). SPDEF was downregulated in hepatocellular carcinoma (HCC) (Guo *et al.,* 2020). It is also reported in a study that SPDEF prevents the development of colon cancers. By interfering with β-catenin's interactions with TCF1 and TCF3, as well as the regulation of cell cycle genes, SPDEF causes CRC (colorectal carcinoma) cells to enter a quiescent state (Yuan *et al.,* 2017). SPDEF downregulates carcinoma progression by transcriptionally activating NR4A1. SPDEF acts as a tumor suppressor by transcriptionally activating NR4A1 in head, neck squamous cell carcinoma. SPDEF upregulates pancreatic ductal adenocarcinoma (PDA) (Wang *et al.,* 2021).

CONCLUSION

SPDEF has drawn a lot of attention due to its role in oncogenesis and growth. The concept of SPDEF has been problematic in the dichotomy of cancer-regulatory genes. It is more feasible to treat SPDEF as a dual-functional gene after thoroughly summarising current findings, which will aid in understanding breast cancer heterogeneity and facilitate future research. The mechanism underlying SPDEF's regulation must be investigated given that we have a better understanding of its dual-functional nature. This is crucial for developing personalized therapy for each BC subtype. In the not-too-distant future, SPDEF could become a

novel diagnostic and therapeutic target in breast cancer biology.

FUTURE SCOPE

Investigating SPDEF's role in cancer initiation and metastasis may lead to the development of targeted therapies. It may be examined to alter SPDEF expression or activity to stop cancer cell proliferation, invasion, or metastasis. Understanding how SPDEF affects drug resistance pathways in cancer cells may help in the fight against drug resistance.

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