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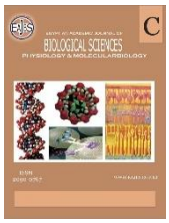

Caveolin-1 As A Novel Therapeutic Target For Breast Cancer: A Review Article

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ABSTRACT

Numerous different cell groups, such as endothelial cells, pericytes, macrophages, mesenchymal stem cells, smooth muscle cells, and stromal fibroblasts, can be found in the tumor microenvironment Caveolin-1, which is also referred to as caveolin, Cav-1, or VIP21 is a structural membrane protein that has been demonstrated to suppress breast tumor growth and metastasis. Numerous studies have determined Cav-1 as a potential therapeutic target for breast cancer due to its inhibitory effects on cancer-associated pathways. In preclinical studies, expressed Cav-1 has been demonstrated to prevent breast tumor cell invasion, and the lack of stromal Cav-1 is linked to early breast cancer development. According to certain research, Cav-1 may also inhibit the late phase of autophagy via HIF-1 in triple-negative breast cancer. Furthermore, Cav-1 has been demonstrated to prevent breast tumor stem cells' self-renewal ability and aerobic glycolysis activity. These data show that Cav-1 may play an important function in breast tumor inhibition, as a possible target for treatment of breast cancer.

INTRODUCTION

Tumor Microenvironment:

Numerous different cell groups, such as endothelial cells, pericytes, macrophages, mesenchymal stem cells, smooth muscle cells, and stromal fibroblasts, can be found in the tumor microenvironment (Mj and D 2001; Mj *et al.*, 2002). The stromal fibroblasts appear to undergo reprogramming through interactions with cancer cells in this scenario, adopting a more myo-fibroblastic phenotype (Rønnov-Jessen and Bissell 2009). These cells, which are becoming increasingly commonly known as cancer-associated fibroblasts (CAF), can encourage the progression and metastasis of tumors, though the precise mechanism by which they do so is still largely unknown (Orimo *et al.*, 2005; Orimo and Weinberg 2006). Additionally, this tumor microenvironment (also known as the cancer stroma) has more angiogenic elements and a higher influx of inflammatory cells (Watnick 2012). It's interesting to note that tumor-associated fibroblasts (TAF) respond similarly to fibroblasts that repair wounds. They have increased contractility, promoted angiogenesis, and boosted epithelial growth by secreting cytokines, growth factors, and extracellular matrix (ECM) (Watnick 2012). Neither natural quiescence nor apoptosis occurs in CAFs, as is the case during wound closure instead, they stay activated (Watnick 2012). It is already well acknowledged that the tumor microenvironment is crucial to the appearance and growth of breast cancer (Tlsty and Hein 2001; Kalluri and Zeisberg 2006a). The tumor stroma may encourage spread and metastasis, two malignancy-related hallmarks that are to blame for the failure of cancer treatments, recurrence, and mortality.

A significant percentage of the tumor microenvironmental components, such as the extracellular matrix (ECM) (Chen and Che 2014), pericytes (Glenney and Zokas 1989), endothelial cells, immune and inflammatory cells (Razani *et al.,* 2002a), and secreted diffusible growth factors/cytokines, are cancer-associated fibroblasts (CAFs) (Dvorak *et al.,* 2011).Several studies have found that CAFs are important for the development of cancer. According to reports, CAFs continue to play a significant part in the remodeling of the ECM, which has an impact on the growth, survival, and movement of tumor cells (Chun *et al.,* 2006; Yu *et al.,* 2014; Zhou *et al.,* 2014; Kan *et al.,* 2014). Also, activated CAFs produce extracellular matrix components, matrix metalloproteinases, hepatocyte growth factor, epidermal growth factor, collagen types I and IV, extra domain fibronectin, and basic fibroblast growth factor (Kalluri and Zeisberg 2006b; De Wever et al. 2008). Additionally, CAFs exhibit the capacity to advertise the growth of neighboring tumor cells and inhibit tumor cell apoptosis.

Main Text:

Breast Cancer:

Breast cancer is an extremely prevalent and diverse form of cancer that primarily affects women, causing over two million new cases and approximately 630,000 deaths worldwide in 2018 (Gp *et al.,* 2018). While researchers have typically concentrated their efforts on understanding the development of cancerous epithelial cells, they have paid relatively little attention to the role of the neighboring stroma or microenvironment (Elsheikh *et al.,* 2008). Genetic changes *in vivo* that enable a cell to obtain "transformed" properties, that is uncontrolled cell proliferation, the capacity to evade apoptotic pathways, greater invasiveness, the capacity to undergo metastasis, and the capacity to evade immune detection, are what is known as the multistep process of carcinogenesis (Cotran *et al.,* 1999). These genetic changes may be the product of acquired somatic changes made throughout a cell's lifetime or inherited germline transmission. Breast cancer is a neoplastic disorder that is extremely heterogeneous at both the molecular and clinical levels. It consists of various molecular subtypes, each of which typically correlates to a different prognosis and therapeutic responsiveness (Minafra *et al.,* 2012, 2014; Bravatà *et al.,* 2013a, b). Although treatment strategies for BC have lately made significant progress as shown in Figure 1 (Tremont *et al.,* 2017; Moo *et al.,* 2018; Zughaibi *et al.,* 2022), death and recurrence rates are still too high (Rl *et al.,* 2015). According to new research, phosphorylation of Cav-1 may be important in activating a cancer cell survival pathway. This discovery could lead to the creation of new cancer treatment strategies (Jiang *et al.,* 2022). It will be essential to comprehend the unique immunomodulatory mechanisms of the breast cancer microenvironment in order to develop novel therapeutic strategies (Hanamura *et al.,* 2023). The tumor's epithelial components have received most of the attention in the research of breast cancer up until lately, with the surrounding tumor stroma receiving little consideration. The way breast cancer is viewed is changing as a result of new data that points to a crucial interaction between the mammary epithelia and the nearby tumor stroma.

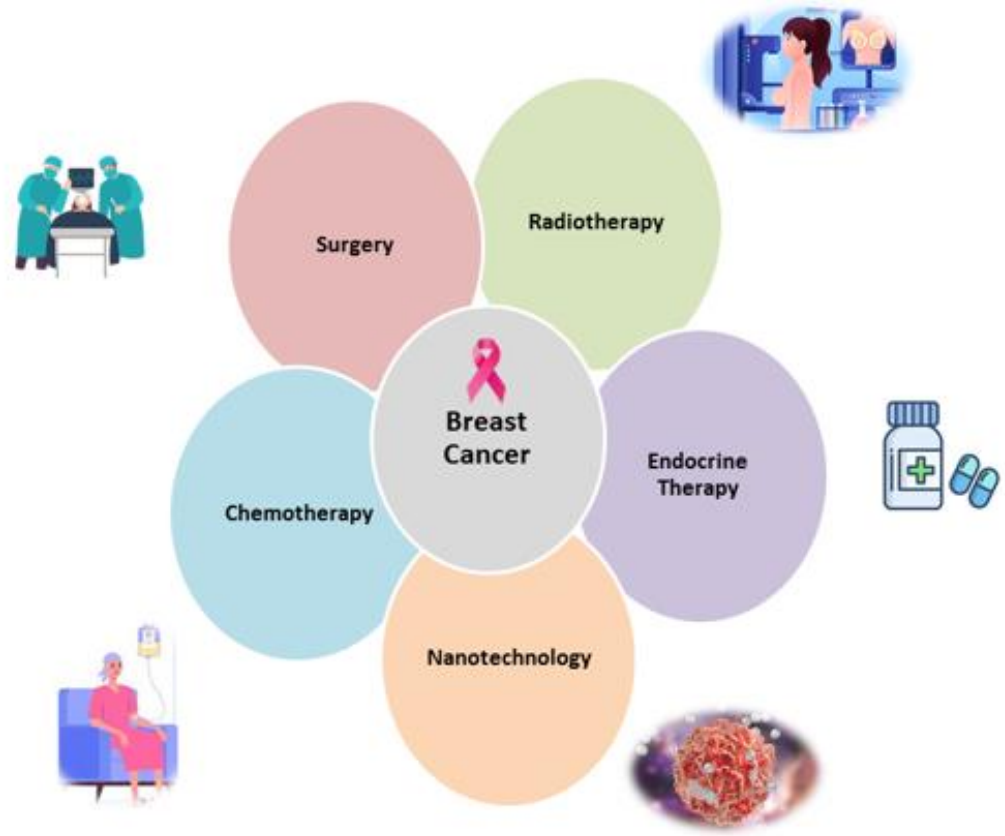

Fig.1: Different methods for treatment of breast cancer.

Caveolae and Caveolin-1:

Caveolae (plasma membrane invaginations in the shape of flasks) are experts in lipid rafts, which can be seen in electron micrographs as plasma membrane invasions measuring 50–100 nm. Adipocytes, endothelial cells, and fibroblasts are examples of fully differentiated mesenchymal cells that contain caveolae (Razani *et al.*, 2002b). Microdomains called caveolae are involved in vesicular trafficking and signal transmission (Galbiati et al. 2001a). Most cell types have caveolae, which are found on the cell membrane. Caveolins are the main protein component of these structures, including Cav-1, Cav-2, and Cav-3. Cav-1 and Cav-2 are found in all human tissues, but Cav-3 is found only in muscles (Qian *et al.*, 2019). The 22-kDa membrane protein caveolin-1, which combines with caveolin-2 to create hetero- and homo-oligomeric complexes, is a vital component of the caveolae's coat structure (Monier *et al.*, 1995; Sargiacomo *et al.*, 1995). Co-expressed with Cav-2 in cells from various tissues, which include endothelium, neural tissues, mesenchyme, as well as some epithelial cells, Cav-1 is a member of a highly conserved gene family. The gene of caveolin-1 has three exons and is translated into the endoplasmic reticulum as either the alpha-isoform, which is a full-length protein with 178 amino acids (aa), or beta-isoform, which loses the first 32 aa (Koike *et al.*, 2010). Compared to luminal cells, myoepithelial cells primarily express caveolin-1 (Jones *et al.*, 2004; Sm *et al.*, 2006). By combining the activities of a variety of signaling molecules, such as glycosyl-phosphatidylinositol-linked proteins, Src-family tyrosine kinases, H-Ras, epidermal growth factor receptor (EGFR) (Couet *et al.*, 1997b), HER2 (Engelman *et al.*, 1998a), and estrogen receptor (ER), caveolae can function as molecular hubs (Lisanti *et al.*, 1994). Caveolin-1's distinctive topology makes this possible. The caveolin-scaffolding domain (CSD) (Couet *et al.*, 1997a), which keeps components in a restrained conformation via a consensus "caveolin-binding motif," is required for interactions with these proteins and confers endogenous

negative control of several kinases (Couet *et al.,* 1997a, b). Caveolae function, which is involved with numerous cellular functions that as vesicular transportation, cholesterol homeostasis, migration of cells, cell cycle, and polarity of cells, is greatly influenced by Cav-1. Through the caveolin-scaffolding domain, this molecule has a direct interaction with pro-proliferative molecules like EGFR, ERBB2, and PI3K and negatively regulates signaling pathways that govern cell proliferation, differentiation, adhesion, apoptosis, and invasion (Liu *et al.*,2002; Williams and Lisanti 2005; Sotgia *et al.,* 2006; Felicetti *et al.,* 2009). Cav-1 has also been linked to tumor development and metastasis (Ting Tse *et al.,* 2012; Patani *et al.,* 2012; Chanvorachote and Chunhacha 2013).

Caveolin-1 As A Negative Regulator For Glucose Metabolism:

Unusual metabolism is one of the characteristics of malignancy (Hanahan and Weinberg 2011). Therefore, a possible cancer treatment method involves focusing on the metabolic variations between healthy cells and cancer cells (Martinez-Outschoorn *et al.,* 2017). In order to meet their bioenergetic needs, cancer cells primarily use glycolytic metabolism, Normal cells, on the other hand, largely utilize mitochondrial oxidative phosphorylation (OXPHOS). The "Warburg" effect has been given to this occurrence. Comparing breast cancer cells to mammary epithelium cells revealed that breast tumor cells also had an increased glycolytic metabolism (Wang *et al.,* 2020). As a result, pharmacological inhibition of breast cancer cells' glycolytic metabolism offers a potential cancer-specific eradication method. Inhibitors of glycolysis are currently being screened with an increasing emphasis on glycolytic pathway targeting. These are some examples: glycolytic metabolism's rate-limiting enzymes and glucose transporters (GLUTs) (Hexokinase 2, pyruvate kinase M2, and phosphofructokinase 1 are a few examples).

Numerous glycolytic preventives have been discovered and shown to be successful in slowing the spread of breast cancer. For instance, the most commonly used glycolytic preventives, 3-bromopyruvate (3-BrPA) and 2-deoxyglucose (2-DG) have demonstrated promising antitumor efficacies in breast cancer (Bost *et al.,* 2016). However, currently, the systemic toxicities and poor selectivity of the existing glycolytic inhibitors have prevented them from producing satisfactory clinical results in clinical trials. Screening for glycolytic inhibitors while concentrating on targets linked to glycolytic metabolism whose expression is not harmful to organisms is one way to address this issue. Cav-1, a plasma membrane component protein, has been linked to the development of malignant tumors and the regulation of metabolism (Wang *et al.,* 2017; Jiao *et al.,* 2019). Additionally, compared to healthy breast epithelial cells, breast cancer cells expressed Cav-1 at a lower level, and its increase may prevent the cancer cells from utilizing glycolysis (Jiao *et al.,* 2019; Wang et al. 2020). When compared to wild-type mice, Cav-1 overexpression in mice via genetic or pharmaceutical methods had minimal negative impacts on the mice's body weight, growth pattern, development, and reproductive functions (Yang *et al.,* 2010; Jiao *et al.,* 2019). These results indicated Cav-1 as a prime candidate for the discovery of glycolytic inhibitors.

Caveolin-1 and Cancer:

The connection between caveolin-1 and cancer is still debated. Because Cav-1 lacks the hallmark characteristics of true tumor suppressor or oncogene genes, its tumor suppressor and oncogenic properties have mostly been deduced from circumstantial evidence. Downregulation is more common in ovarian (Wiechen *et al.,* 2001), colorectal (Bender *et al.,* 2000), and mesenchymal sarcomas (Wiechen et al. 2001). Upregulation, on the other hand, has been linked to the lung (Couet *et al.,* 1997a; Liu *et al.,* 2002), bladder, thyroid (papillary variant), esophageal (Kato *et al.,* 2002), and prostate carcinomas (Yang *et al.,* 1999). On human chromosome 7, the caveolin-1 gene is placed at the D7S522 location in the q31.1 region (Engelman *et al.,* 1998d, e, c, 1999).

This chromosomal region (D7S522/7q31.1) contains the FRA7G fragile site, which is frequently removed from a variety of human tumors, as mammary tumors (Galbiati *et al.,* 2001b). These findings imply that The protein caveolin-1 may have antitumor properties and show the growth-inhibitory protein Cav-1 (Galbiati *et al.,* 2001b). The majority of oncogenically transformed NIH3T3 cells (but not all) and human cancer cells studied thus far exhibit significantly decreased caveolin-1 expression (Sager et al. 1994; Koleske *et al.,* 1995; Lee *et al.,* 1998; Engelman *et al.,* 1998a). Furthermore, a transformed-like phenotype can be induced by antisense suppression of Cav-1 expression (Galbiati *et al.,* 1998).

Two domains make up caveolins; a domain that binds to membranes with three C-terminal cysteines that can be palmitoylated to attach the membrane and a caveolin scaffolding domain with an abundance of aromatic residues (Byrne *et al.,* 2012; Hoop *et al.,* 2012). The CSD directly binds cholesterol, participates in the transport of cholesterol, and offers a scaffold for the caveolar organization of functional proteins to influence signaling (Tagawa *et al.,* 2005; Bosch *et al.,* 2011). By attaching to an aromatic sequence in the interacting partners and keeping them inactive, the caveolin-scaffolding domain functions as a broad-spectrum protein kinase inhibitor. This tonic inhibition is then released upon activation by the necessary stimulus (Couet *et al.,* 1997a, b). Cav-1 interactions with other signaling proteins include adenylyl cyclase (AC), heterotrimeric Gα and Gβγ, Src, PI3 kinase (PI3K), endothelial nitric oxide synthase (eNOS, NOS 3), protein kinase A (PKA), protein kinase C (PKC), and mitogen-activated protein kinase (MAPK, ERK) (Bucci e*t al.,* 2000; Patel *et al.,* 2008). In pancreatic ductal adenocarcinoma and prostate cancer, CSD provides an inhibiting binding location for protein phosphatases 1 and 2A and preserves the importance of Akt activation in cell survival (Li *et al.,* 2003; Okada *et al.,* 2019). We investigated the idea that the scaffolding domain of Cav-1 is crucial in controlling tumor cell migration and proliferation considering earlier research demonstrating the significance of Cav-1 in cancer and cell biology.

Role of Caveolin-1 In Cell Cycle Regulation:

Cav-1 can reduce G0/G1 phase cell cycle arrest and elevate the number of S phase cells, by stimulating the extracellular signal-regulated kinase (ERK) 1/2 pathway and raising the expression of cell cycle-associated proteins (cyclin D1 and β-catenin) in BT474 cells (Wang *et al.,* 2014a). By encouraging cell cycle halting in the G2/M phase, that was achieved by upregulating p27, p21, and cyclin B1 and downregulating cyclin D2, Cav1, on the other hand, Functions as a factor that inhibits cell proliferation in MDA-MB-231 and MCF-7 cells. This antiproliferative effect was boosted by docetaxel (DTX) (Kang *et al.,* 2016). As anchorage-independent development may be stopped by the re-expression of Cav-1 using an inducible system, Cav-1 acts as a transformation inhibitor protein (Engelman *et al.,* 1997). Because Cav-1 (/) fibroblasts are hyperproliferative and Cav-1 re-expression causes their arrest in the G0/G1 phase of the cell cycle, Cav-1 acts as a negative regulator of cell cycle development (Razani *et al.,* 2001). It has been determined that the caveolin-scaffolding domain of Cav-1 (residues 82–101), which also serves as a broad-spectrum kinase inhibitor, is responsible for Cav-1's capacity to cause cell cycle halt (Galbiati *et al.,* 2001b). In fibroblasts, where it typically acts as a transformation suppressor to stop cell cycle development, Cav-1 deficiency is an indicator of oncogenic transformation. The understanding of the tumor microenvironment's growth-promoting characteristics may be significantly affected by these results.

Caveolin-1 Associated With Several Signaling Pathways Related To Breast Cancer:

It is believed that Cav-1 relates to and maintains in a dormant state, the epidermal growth factor (EGF) receptor,

proteins of the growth factor activated Rasp42/44 mitogen-activated protein kinase (MAPK) pathway, ErbB2, in addition proteins involved in pro-survival phosphatidylinositol 3-kinase/Akt pathway. (Razani *et al.,* 2002b). AKT, a homolog of the murine thymoma viral oncogene V-akt, is a critical component of the PI3K/AKT signaling networks. Growth factors, inflammation, DNA damage, and PI3K or phosphoinositide-dependent kinases (PDK) are all known to trigger AKT. Downstream effectors like mTOR, glycogen synthase kinase 3 beta (GSK3), or fork-head box protein O1 are involved in signal transmission. (FOXO1). Numerous cancers, such as lung, ovarian, and pancreatic cancers, have been found to have aberrant overexpression or activation of AKT, which is linked to higher cancer cell survival and proliferation. As a result, AKT blocking might be a crucial strategy for treating and preventing cancer. A particular active v-Akt murine thymoma viral oncogene homolog 1 state that can control pro-survival signaling can be maintained by Cav-1. AKT-phosphatase proteins 1 and 2A (PP1A and PP2A) inhibiting binding to the CSD domain of Cav-1 is likely what facilitates this action (Song et al. 2019). Recombinant Cav-1 expressing metastatic mammary tumor cells demonstrated a substantial decrease in Invasion of Matrigel and significantly decreased activity of MMP2 and MMP9 (Hulit *et al.,* 2000), as well as deregulation (Engelman *et al.* 1998a). The interaction of the HER2 and Cav-1 signaling networks is poorly understood. A CSD-derived 20-amino acid peptide that can stop HER2 autophosphorylation and kinase activity is present in the HER2 kinase domain and contains a Cav-1-binding motif that is like the EGFR (Engelman et al. 1998a). Endocytosed molecules may be regulated to migrate to intracellular compartments for degradation after being internalized by HER2 through the endocytotic pathway, in which caveolae may very well play a role. In caveolae-deficient BC cells, data even indicate that HER2 endocytosis occurs via a Cav-1-dependent pathway: even after ligand activation, HER2 may be maintained on the cell surface. (Sekhar *et al.,* 2013). Therefore, through its downregulation, Cav-1 may help to inhibit the growth and proliferation signals from HER2, serving as a tumor suppressor.

The estrogen signaling pathway has been recognized as a contributing factor to the evolution of breast cancer. Long-term estrogen exposure, as seen in women with early onset of menstruation, delayed onset of menopause, and use of hormone therapies, is strongly linked with a higher chance of getting breast cancer (Clemons and Goss 2001). Increased cell proliferation results from estrogen binding to the estrogen receptor alpha (ER), which modifies the receptor's conformation and activates the ER pathway downstream (Carroll *et al.,* 2006). Cav-1 inhibits the production of its co-activators, that is the co-activator protein for AP1 and ER receptors (CAPER), an ER transcriptional activator and JUN/AP1, in breast cells, acting as a negative regulator of estrogen-stimulated proliferation (G et al. 2008). ER and (CAPER and fork-head box A1 (FOXA1)) co-activator genes were expressed more frequently in Mammary epithelial cells lacking Cav-1, and estrogen hypersensitivity was also present (Mercier et al. 2009b). Studies showed that Cav-1 reduction in stromal cells caused the transforming growth factor beta (TGF beta) pathway to be activated without the need for a ligand and that Cav-1/ stromal cells showed upregulation of 35 transcripts linked to stimulated TGF signaling, such as the TGF target gene CTGF (Pavlides *et al.,* 2010). Reprogramming of the metabolism of CAFs with the activation of glycolysis and autophagy was also demonstrated to be caused by stromal Cav-1 loss (S *et al.,* 2009; Chien *et al.,* 2011; C *et al.,* 2012).

During pregnancy and lactation, the pituitary hormone prolactin closely regulates the growth and differentiation of mammary epithelial cells (Freeman *et al.,* 2000). During pregnancy, prolactin causes the lobuloalveolar growth of the mammary gland and stimulates lactogenesis, or the production of milk, after delivery. It's interesting to note

that prolactin works through the cytokine receptor family member prolactin receptor (Prl-R), which is connected to the kinase Jak-2, to initiate the lactogenic response (Janus kinase 2). The signal transducer and activator of transcription 5 is one of the important signaling molecules triggered by the Prl-R. (STAT5). When STAT5a is phosphorylated, it moves from the cytoplasm to the nucleus where it activates and relates to the promoter of the casein gene to increase milk output (Hennighausen and Robinson 1998; Freeman *et al.,* 2000). Previous research has indicated that Lactation and the expression of Cav-1 are inversely correlated. As an example, in the mature mouse mammary gland, expression of Cav-1 is typically downregulated during late pregnancy and the first few weeks of lactation (Park *et al.,* 2001). It's interesting to note that prolactin seems to be the primary Ras-dependent facilitator of Cav-1 downregulation.

The lobuloalveolar compartment develops more quickly during pregnancy, leading to precocious lactation, and STAT5a is prematurely activated and hyperphosphorylated, according to a study of mammary glands lacking Cav-1 (Park *et al.,* 2002). However, it is still unclear whether these Cav-1 null traits are inherent to the mammary epithelial cells, or whether additional cell types, like adipocytes and stromal cells, play a paracrine role. By stimulating the transcription of the Cav-1 promoter, BRCA1 may increase the amounts of Cav-1 mRNA. Additionally, Cav-1 may be moved from the cytoplasm to the plasma membrane because of BRCA1 translation. Due to the buildup of Cav-1, which is probably controlled by BRCA1, mammalian cells have varying levels of invasiveness and metastatic capacity. In comparison to BRCA1 -/- MEFs cells, which had a higher capacity for invasion and metastasis, BRCA1 +/+ MEFs cells showed decreased invasiveness and metastatic ability. Therefore, the functional relationships between BRCA1 and Cav-1 may be crucial in preventing the growth and spread of tumors (Wang *et al.,* 2008). Cav-1's capacity to inhibit b-catenin/Tcf/Lef-dependent transcription may contribute to its ability to act as a cancer suppressor (Quest *et al.,* 2008). opposition to apoptosis (Krysan *et al.,* 2004b, a). according to this information, it was intriguing to hypothesize that Cav-1 might influence COX-2 expression in addition to survivin via the b-catenin/Tcf/Lef pathway. It was anticipated that by doing this, Cav-1 would lessen the amount of PGE2, a crucial downstream effector connected to COX-2's function as a tumor driver. This assertion is in stark contrast to data from the literature that showed that Cav-1 is incapable of reducing COX-2 activation and, consequently, PGE2 generation in cells. In light of the known relationships between Cav-1, b-catenin, Tcf/Lef, and survivin, and also the relationship between PGE2 and b-catenin/Tcf/Lef, prior research examined whether decreased PGE2 production as a result of survivin expression was influenced by Cav-1 expression. (Liou *et al.*, 2001).

The outcomes obtained here demonstrated that in HEK293T, colon (HT29 (ATCC), DLD-1), and breast (ZR75) tumor cell lines, Cav-1 mediated downregulation of COX-2 entail inhibition of b-catenin/Tcf/Lef dependent transcription. Furthermore, ectopic COX-2 expression or PGE2 supplementation overcame Cav-1 imposed restrictions, such as the downregulation of survivin and reduced cell proliferation. This revealed a constructive feedback loop between COX-2 and survivin involving PGE2 improved transcription of survivin.

Caveolin-1 as Breast Tumor Suppressor:

As it is linked to the formation and progression of breast cancer, Cav-1 is said to have inhibitory effects on the disease (Sotgia *et al.,* 2011; Chiu *et al.,* 2011). Breast stromal fibroblasts exhibit high levels of Cav-1 expression under physiologically normal circumstances (Witkiewicz *et al.* 2009; Patani *et al.,* 2012). Cav-1 expression, on the other hand, is diminished in the stromal fibroblasts of the breast cancer microenvironment and is inversely associated with the malignant potential of tumor cells. Patients with breast cancer who have low or negative stromal

fibroblast Cav-1 expression frequently have poor survival rates, whereas Patients with high stromal Cav-1 expression have a better chance of survival (Witkiewicz *et al.,* 2009; Sotgia *et al.,* 2012). Overall, stromal Cav-1-positive breast cancer patients have an 80% five-year survival rate; stromal Cav-1-negative patients have a 20% five-year survival rate and are more likely to experience early disease recurrence and metastases to lymph nodes (Martinez-Outschoorn *et al.,* 2010). Although the Cav-1 in the stroma has prognostic importance downregulation in breast tumor patients has been documented, the precise mechanism is still unknown (Du *et al.*, 2014).

To fully assess Cav-1's function as a cancer suppressor, more research into the processes involved in the protein's expression is required. The relationships between Cav-1 mRNA, tumor stromal fibroblasts, and tumor cells must also be verified. Fibroblasts, which are important cancer stromal cells, are crucial to tumorigenesis, tumor growth, and spread. They release a variety of chemicals that may block apoptosis, encourage proliferation, and aid in the angiogenesis of tumors (Cirri and Chiarugi 2011; Buckley 2011). Therefore, it is important to comprehend the precise process by which stromal fibroblasts encourage the growth of tumors. Cav-1 downregulation is a possible route for fibroblast oncogenic change. Fibroblasts with reduced expression levels or Cav-1 deletion can create a tumorigenic microenvironment, though the precise molecules involved are still unclear (Wang *et al.,* 2014b). Curiously, researchers have found lower amounts of Cav-1 expression in several human tumor cases (Crisan et al. 2008; Kidd et al. 2009), pointing to a negative regulatory function for Cav-1 in tumor development.

Previous studies indicated that Cav-1 stops the migration and metastases of breast tumor cells (Peng *et al.,* 2005; Orimo *et al.,* 2005; Crisan *et al.,* 2008; Kidd *et al.,* 2009; Jezierska-Drutel *et al.,* 2013). Multifocal dysplastic lesions formed through the complete mammary tree in Cav-1 null mice carrying the MMTV-PyMT transgene, and lung metastases and mammary tumorigenesis were increased (Nagasawa *et al.,* 1996; Lewellis and Knaut 2012). Additionally, compared to their counterparts in normal mammary epithelial cells, human breast tumor cells exhibit substantially lower levels of Cav-1 expression (Engl *et al.,* 2006). Cav-1 is a tumor inhibitor in individuals with breast tumor supported by all the available experimental and clinical data. In 162 cases of breast tumor, Cav-1's mRNA and Protein expression levels were investigated by Sagara et al. (Sagara *et al.,* 2004) who discovered that these levels were inhibited in breast tumor tissue when compared to the matching normal cells. Additionally, in line with other research, it was discovered that decreased Cav-1 significantly P=0.041 correlated with tumor size (Elsheikh *et al.,* 2008; Zuccari *et al.,* 2012). Additionally, Sagara *et al.,* (Sagara e*t al.,* 2004) used real-time polymerase chain reaction to precisely analyze the mRNA levels of CAV1 in 162 breast cancer cases. The decreased Cav-1 mRNA levels have also been found to strongly correlate with growing tumour size P=0.041.

Caveolin-1 Expression In Several Cell Lines:

Pulmonary endothelial cell and mammary gland epithelial cell hyperplasia is a consequence of genetic Cav-1 knockout (Drab *et al.,* 2001; Razani *et al.,* 2001). Additionally, Cav-1 gene deletion causes greater susceptibility to oncogenic and carcinogenic stimuli (Capozza *et al.,* 2003; Cerezo *et al.,* 2009). Cav-1 expression inhibits anchorage-independent development and reduces proliferation in MCF-7 mammary adenocarcinoma cells (Liedtke *et al.*, 2007). In several rodents and breast tumor cell lines of human, primary human cancers, ontogenically transformed NIH3T3 cells, and primary human cancers Cav-1 mRNA and protein are absent or downregulated (Sager *et al.*, 1994; Koleske *et al.,* 1995; Bagnoli *et al.,* 2000; Bender *et al.,* 2000). Protein kinases C alpha (PKC-a) and 3-phosphoinositide dependent protein kinase-1 (PDK1) stimulate the Wnt pathway, cyclin D1, and c-Myc transcription in breast cancer cells, and then

c-Myc suppresses Cav-1 transcription (Zeng *et al.*, 2002). This is supported by the fact that forced expression of canine Cav-1 in the ZR75 cell line decreases COX-2 expression and breaks a feedback loop involving PGE (2) induced signaling events linked to the transcription of survival genes like COX-2 and survivin under the control of b-catenin/Tcf/Lef (Galbiati *et al.,* 2000; Rodriguez *et al.*, 2009), which reduces proliferation and increases apoptosis (Torres *et al.*, 2007).

In MTLn3, a metastatic rat mammary adenocarcinoma cell line, Cav-1 has also been shown to reduce the malignant phenotype by preventing EGF-stimulated lamellipodia extension, inducing a non-motile phenotype, and stopping anchorage-independent growth, which is linked to impaired activation of MAPK/ERK signaling (Zhang *et al.,* 2000). Absent extra genetic or carcinogenic triggers, Cav-1 null mice do not form mammary tumors (Le Lay and Kurzchalia 2005). Even so, ductal hyperplasia, premature lobuloalveolar development, and gestational breastfeeding are caused by Cav-1 deficiency, and they appear to be required for normal mammary development (Lee *et al.*, 2002). Human Cav-1 is ectopically expressed at low levels that inhibit tumor development while also inhibiting metastasis (Sloan *et al.,* 2004). In mammary tumors from MMTV-c-Myc, -Her2, -Src, -Ha-Ras, and p53 null transgenic mice, Cav-1 is also diminished or nonexistent (Engelman *et al.,* 1998b). Therefore, Cav-1 seems to inhibit both growth and change in vitro additionally to the growth of mammary tumors and metastases in vivo (Williams *et al.,* 2004a). Despite these correlations, the underlying mechanisms are still unclear. In MCF7 cells, Cav-1 production reduces the cytoplasmic ER-a pool (Nawaz *et al.,* 1999), whereas Cav-1 haplo-insufficient MCF10A clones show excessive ER-a expression and MAPK activation (Zhang *et al.,* 2005). Methyl-b-cyclodextrin promotes ER-a expression (Zhang et al. 2005) and displaces membranous Cav-1 (Kranenburg *et al.,* 2001).

These results lend credence to the idea that dysregulation of Cav-1 may upregulate Era at an early stage of the molecular etiology of breast cancer (Razandi et al. 2003; Acconcia *et al.,* 2005; Pedram *et al.,* 2007). Canine Cav-1 is ectopically expressed and suppresses E2-induced ERK (MAPK) activation while increasing ER membrane localization (Razandi et al. 2002). Additionally, E2 inhibits the production of Cav-1 and speeds up its breakdown, which may have an impact on ER interactions over a prolonged period and the harmony of nuclear/membranous ER signaling. The oncogenic and invasive characteristics of transformed mammary cell lines are inhibited by forced re-expression of Cav-1 (Le *et al.,* 1996; Zhang *et al.,* 2000; Fiucci *et al.,* 2002). When the metastatic 4T1.2 mammary carcinoma cell line is orthotopically implanted into the mammary gland, Cav-1 expression reduces metastasis to distant organs and slows the development of the main tumor (Sloan *et al.,* 2004).

A second blow from an environmental or genetic insult results in advanced, full-blown tumors in mice with Cav-1 deficiency, but this is not enough to cause cancer growth. For instance, when crossed with the tumor-prone mouse mammary tumor virus-polyoma middle T (MMTV-PyMT) model, Cav-1 (-/-) mice show increased tumor formation in the skin after exposure to the carcinogen 7,12-dimethylbenz (a)anthracene and in the mammary gland (Capozza *et al.,* 2003; Williams *et al.,* 2004b). These findings collectively demonstrate how Cav-1 inhibits tumor growth in the mammary duct. Inactivation of the Cav-1 gene may be a crucial first stage in the development of mammary tumors. Mechanistically, MECs lacking Cav-1 produce and secrete more MMP-2/9 than normal. In line with these results, Cav-1 expression also prevents tumor spread and migration. For instance, it has been demonstrated that expression of Cav-1 in the MTLn3 metastatic cell line inhibits lamellipodia invasion and creation brought on by EGF in culture (Zhang *et al.,* 2000).

Caveolin-1 Mutation:

Cav-1 downregulation contributes to the development of breast tumor. This assumption was also supported by the high prevalence of 7q31 deletions in human cancer (Carver and Schnitzer 2003), a high prevalence of an inactivating Cav-1 mutation in breast cancer (Hayashi *et al.,* 2001; Li *et al.,* 2006), and Cav-1 downregulation in cancer cell lines, which may be related to Cav-1 gene promoter hypermethylation. 7q31 is close to the Cav-1 locus (Sunaga *et al.,* 2004; Chen *et al.*, 2004). More than half of all instances of BC with ER positivity have the Cav-1 (P132L) mutation, This causes a proline to leucine substitution at amino acid position 132 of the transmembrane domain (Li *et al.,* 2003, 2006). This mutation causes ER overexpression and greater sensitivity to estrogen therapy, but it may also be a significant risk factor for the growth of breast carcinoma (Hayashi *et al.,* 2001; Li *et al.,* 2003). These findings might therefore offer a mechanistic explanation for why breast tumor patients with Cav-1 mutations are more likely to experience disease recurrence. Cav-1 (P132L) encourages the expression of ER proteins (as evidenced by Western blotting) and stimulates ER alpha signaling (as shown by gene expression profiling), consistent with the link in human breast cancers between this mutation and ER positivity.

This finding lends further credence to the validity of the model. A dominant negative Cav-1 mutation that causes up to 16% of breast tumors to have a proline to leucine substitution (P132L) was first described by a Japanese team in 2001 (Hayashi *et al.,* 2001; Lee *et al.,* 2002). Previous research looked at Cav-1 variants in samples of human breast cancer and compared them to ERa expression levels. According to prior research, Cav-1 alterations only occur in breast tumors that are positive Era and not Era negative (Li *et al.,* 2006). More precisely, the relative incidence in Era positive breast tumors was close to f35%, with the overall incidence of Cav-1 mutations (P132L and others) in the prior cohort being f19% (Li *et al.,* 2006). Cav-1 mutations and ERa overexpression in breast cancer; their mechanistic interactions can now be explored thanks to these exciting clinical findings.

To investigate the impact of Cav-1 inactivation on ERa signaling, Cav-1 (-/-) null mice were used as a model system because the Cav-1 P132L mutation acts in a dominant negative manner (Lee *et al.,* 2002). By increasing Wnt/h-catenin signaling, Cav-1 deficiency results in the collection of a community of adult mammary stem cells, which may lead to the overexpression of ERa. A proline to leucine substitution at position 132 of the Cav-1 transcript was discovered by Hayashi *et al.,* in 2001. (P132L) (Hayashi *et al.,* 2001). It has been discovered through subsequent research that the Cav-1 misfolding within the Golgi complex is the mechanism by which the P132L mutation has a dominantly negative impact (Lee *et al.,* 2002).

According to the original paper, this mutation was present in 15 of 92 primary breast cancers. A later study found that the P132L mutation was unique to estrogen receptor-positive breast cancers; it was not present in any of the 23 ER-negative tumors. The mutation has been detected in 6 of 32 EsR-positive tumors or 35% of the total (Li *et al.,* 2006). However, using the same technique as detailed in the initial paper, a later study found that none of the 55 breast cancer specimens had the P132L mutation (Chen *et al.,* 2004). Furthermore, no publications from any other study team have shown that this mutation is present in primary breast tumors. To determine whether the mutation could be discovered in a wider collection of primary breast tumor tissues utilizing a conventional direct sequencing approach and a novel sensitive test.

Caveolin-1 as a Therapeutic Agent For Breast Cancer:

Given that Cav-1 is linked to BC recurrence and that tamoxifen resistance emerged in nearly half of the ER-positive patients, the Cav-1 P132L mutation has been proposed as a predictor of subpar in reply to this medication (Mercier *et al.,* 2009a; Babina *et al.,* 2011). The prior research may point to

new therapeutic approaches, angiogenesis inhibitors not included when they are ineffective, and pointing to reducing oxidative stress in tumor fibroblasts with antioxidants and autophagy inhibitors, severing the source of energy for cancer cells (Grépin and Pagès 2010; West and Barnett 2011). One of the most crucial treatments for many cancer types, including those of the breast, is radiation therapy (RT), which aims to control cancer locally at the tumor's location (Di Maggio *et al.,* 2015).

The primary study topics in radiobiology are the radiosensitivity of normal tissues and tumor radio-resistance. High levels of stress are brought on by ionizing radiation (IR), which includes X-rays and high-energy electrons. Many of these stresses rely on the type of cell, its genetic makeup, the dose rate, and the time after irradiation (Hehlgans *et al.,* 2009; Di Maggio *et al.,* 2015). The activation of the DNA repair signaling cascade and to repair of double-strand breaks, homologous recombination and non-homologous end joining are utilized, as well as the maintenance of genomic integrity, are both facilitated by the upregulation of the Cav-1 protein in relation to DNA damaging agents like IR. Since BC comes in a variety of types and subtypes, there is no singular therapy that can be used to treat all patients. The therapeutic options used to treat BC today are distinct.

Prior research outlined the functions of Cav-1 in BC. Cav-1's recently discovered roles in BC's epithelium and tumor stroma suggest that it may be helpful as a diagnostic marker for patient care, guiding clinicians in selecting the best-personalized therapy and maximizing outcomes. Mimetic peptides generated from Cav-1 have tumor suppressor activity that may support current anticancer treatments and halt tumor growth by inhibiting angiogenesis (Gratton *et al.,* 2003). Nitric oxide production is also inhibited by CSD mimetic peptides, and they may also control inflammatory processes in the tumor microenvironment (Bucci *et al.,* 2000). Additionally, HER2 autophosphorylation and kinase activity can be inhibited by CSD compounds. Modulation of the MDR phenotype may also be possible through Cav-1 modification techniques (Cai and Chen 2004). A novel clinical trial for DCIS (Clinical Trials.gov Identifier: NCT01023477) may be relevant given that an autophagy/lysosome inhibitor called chloroquine has the potential to therapeutically restore stromal Cav-1. Therefore, comprehending Cav-1's function in the growth of CAFs might be a crucial new stage in the creation of creative treatment methods that focus on the tumor microenvironment.

Conclusion

Numerous studies have demonstrated that caveolin-1 plays a vital function in inhibiting and suppressing breast cancer progression and metastasis. The loss of stromal caveolin-1 has been strongly linked to early cancer recurrence, metastasis, and drug resistance in breast carcinoma, and it has been discovered as a possible method for treatment. Additionally, caveolin-1 has been shown to inhibit many cancer-associated pathways that promote cancer cell growth, survival, invasion, and migration. While more research is needed in this area, these findings suggest that caveolin-1 modulation may hold great promise as a therapeutic strategy for breast cancer. Overall, manipulating caveolin-1 expression has the potential to become a significant addition to current breast cancer treatment regimens, and its effectiveness may be tested in clinical trials in the future.

List of Abbreviations:

CAF: Cancer-associated fibroblast; TAF: Tumor-associated fibroblast; ECM: Extracellular matrix; BC: Breast cancer; EGFR: Epidermal growth factor receptor; ER: Estrogen receptor; OXPHOS: Oxidative phosphorylation; GLUTs: Glucose transporters; Cav-1: Caveolin-1; PDK: Phosphoinositide-dependent kinase; FOXO1: Fork-head box protein O1.

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