REVIEW ARTICLE

SPARC in Breast Carcinomas: A Critical Review

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ABSTRACT

Breast cancer is the second most common cancer in the world according to World Health Organization statistics. Among Asian countries, Pakistan has the highest incidence of breast cancer. The normal breast development is interplay between various hormones and transcription factors. Estrogen receptor, progesterone receptor and human epidermal growth factor are being utilized for the targeted therapy of breast cancers. However, there is further need of research to improve the treatment strategies in this regard. Secreted Protein Acidic and Rich in Cysteine (SPARC) is a new biomarker and therapeutic target in breast cancer as well as other tumor types. It's a matricellular protein whose main function is to mediate interactions between cells and their extracellular surrounding during morphogenesis, tissue remodeling and angiogenesis. Therefore, SPARC enables tumor cells to interact with stromal cells and the extracellular matrix. Regarding breast carcinoma, SPARC has been identified as an important negative regulator of tumor characteristics associated with poor prognosis.

KEYWORDS: Breast cancer, SPARC, Estrogen receptor, Progesterone receptor, Her2neu receptor, Targeted therapy.

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INTRODUCTION

The breast cancer being most prevalent among the female gender, affects 2.1 million women annually all over the globe. World Health Organization (WHO) statistics show that in year 2018, among all cancers deaths 15% were in women due to breast tumors leading to death of 627,000 patients in the same year due to same reason. Breast cancer may be considered more prevalent in developed countries of the world, yet 50% of cases followed by 58% of deaths take place in underdeveloped part of the world.[1]Less economically developed countries in the world have low breast cancer incidence. South-Eastern Asia has the incidence of breast cancer around 4.17% in new cases however the mortality is 1.61% among women.[2]

Among Asian countries, the breast cancer incidence is highest in Pakistan. During lifetime, Pakistani women are affected by breast cancer in a ratio of 1:9. Appropriate screening practices are not followed in health centers of Pakistan for diagnosis of any cancer and each year the number of breast cancer deaths in women is increasing.[3]

Risk Factors in Breast Cancer

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Diversity of potential risk factors contributing to breast cancer have been known for long now.[4] The risk factors importance is measured by "relative risk" which is defined as; ratio of the breast cancer probability occurring in the exposed group to the probability in a comparable but non exposed groups. Risk factors are further categorized such as ones having relative risk < 4 and others with a relative risk > 4. Risk factors of relative risk < 4 include young age of menarche, family history of breast cancer, old age at the time of first pregnancy, personal history of benign breast lesions, inactivity, diet deficient in vegetables, old age at menopause, use of hormone replacement therapy (HRT), use of oral contraceptives, smoking and increased alcohol uptake, etc. On the other hand, old age, female sex, past history of breast cancer or any other high-risk pathology and previous radiation therapy have relative risk > 4.[5] All of these factors are related to the exposure of estrogen. Other than these the factors such as radiation exposure and genetic mutations are related to a higher risk for breast cancer and not linked to estrogen.[6]

Triple Assessment

The breast cancer diagnosis is carried out by triple assessment. This is based on the detailed clinical examination, accompanied by radiographic evaluation and confirmed by the help of histopathological details. In clinical examination, breasts and axillary lymph nodes are examined by palpation and general physical examination; it is done to clinically assess any other organ involvement. Radiological evaluation is done by breast and regional lymph nodes ultrasound in patients under 40 years and a bilateral mammography for the older age women.[7]It is evident from literature that the number of reported cases increased when mammographic screening was introduced, particularly in younger women. However, < 5% of breast cancers are seen before age 35 and about a quarter before the age of 50 year. Recently, 3D ultrasound, 3D mammography and contrast-enhanced mammography/spectral mammography have been introduced as advanced radiological tools. Not routinely implemented yet can increase diagnostic accuracy in difficult cases.[8]

Pathological diagnosis is most important part of triple assessment; it has diversity in terms of biopsy samples and diagnostic modalities. Simple cytological test like fine needle aspiration cytology (FNAC) or a core needle biopsy is preferred to be obtained under ultrasound or stereotactic guidance. In the candidates of systemic therapy for cancers prior to surgery, a core needle biopsy is very guiding for the diagnosis of invasive breast carcinoma followed by biological markers assessment. In mastectomy specimens a surgical clip or thread to mark the margins of surgical specimen helps pathologist to assess the exact site.[9]

Pathological diagnosis is deficient without tumor–node–metastases (TNM) staging system recommended by World Health Organization. Histological grade, type, immunohistochemical (IHC) evaluation of estrogen receptor (ER) and progesterone receptor (PR) status (by H-score or Allred score), IHC of human epidermal growth factor 2 receptor (HER2) protein/gene expression are the mandatory components of a pathological report. If HER2 status by IHC gives an equivocal result, it is confirmed by fluorescence in situ hybridization (FISH).[10]

Breast Morphogenesis

Not formed at birth completely, mammary gland develops in early years of puberty followed by enlarging and branching of primitive ductal structures. The origination of terminal ductal lobular units (TDLUs) and its continuous complexity with successive menstrual cycles, pregnancy and lactation takes place under the influence of multiple pioneer factors and coregulators of estrogen receptors (ER) (Fig.1).[11]

Most of the human breast tumors develop from TDLUs having typical morphological features of luminal epithelial cells. Estrogen hormone and various transcription factors play their role in the mammary glands morphogenesis. In breast 15–30% of normal luminal epithelial cells express a nuclear transcription factor estrogen receptor α (ERα), responsible for the proliferation and growth of luminal epithelial cells. More than 70% of the breast cancers positive for prototypic predictive markers i.e. estrogen receptor (ER) and

progesterone receptor (PR) are likely to respond to targeted endocrine therapy.[12]

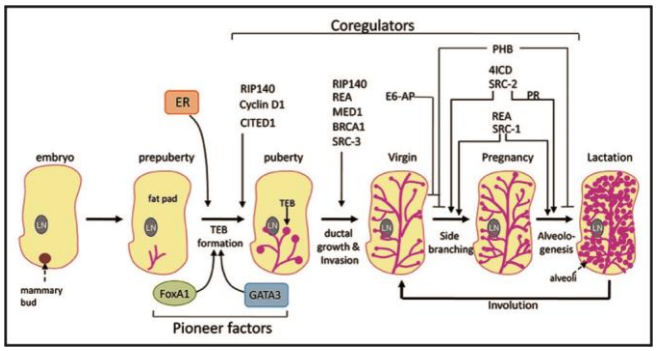

Fig.1: Pioneer factors and coregulator of estrogen receptors in mammary gland morphogenesis.[11]

The arrows pointing downward (↓) show the defects in development at various mammary gland stages owing to coregulator expression loss. However, the sign of inhibition (⊥) points to the suppression of coregulators during mammary gland development. [ER, estrogen receptor; TEB, terminal end buds; LN, lymph node].

Secreted Protein Acidic and Rich in Cysteine

A matricellular glycoprotein "Secreted Protein Acidic and Rich in Cysteine" (SPARC) is also famous as osteonectin, ONT, ON, OI17 or BM-40. The genetic location in human chromosomal region is shown in the **Fig.2**. Having molecular size of 25.5 Kb, SPARC has three specific domains, formed by 286 amino acid sub-units.[13]It has a molecular weight of about 32 kDa and prior to the secretion of mature SPARC, a 17 amino acids peptide is removed. SPARC mediate intercellular and intracellular interactions. It also harmonizes cell cycle, angiogenesis and promotion of change to cell shape.[14]

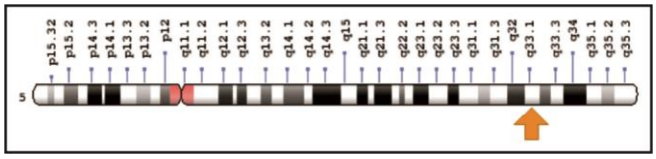

Fig.2: Chromosomal location of SPARC.[13]

The yellow arrows points at cytogenetic Location: 5q33.1, which is the long (q) arm of chromosome 5 at position 33.1.

SPARC Ultrastructure

The structure of the SPARC has 3 biological domains. Acidic N-terminal (NT) domain is the first one followed by domain named as folli stattin (FS)-like, and a Ca2-binding extracellular (EC) domain (**Fig.3**). A 52 amino acids (Ala1-Glu52) NT domain has a loose helical structure.[15] Rest of the 85 amino acids are spanned by FS-like domain consisting of cysteine residues inhibiting the endothelial cell migration. The 149 amino acids EC domain of C-terminal (Cys138–Ile286) has two EF-hand motifs not only has high affinity binding for calcium but also has anti-angiogenic features.[14]

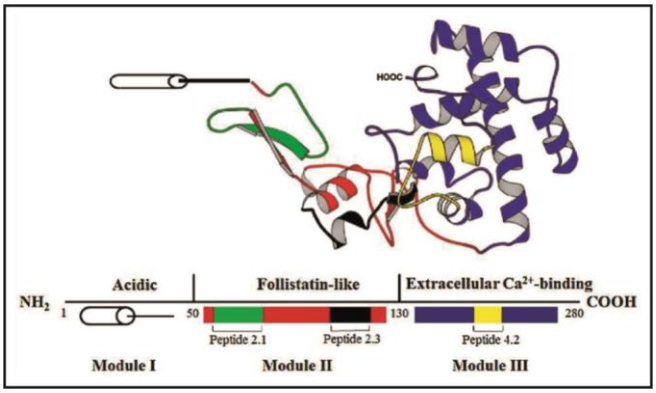

Fig.3: Structure of human SPARC protein.[15]

Extracellular Matrix in Breast

The extracellular matrix (ECM) comprises of basement membrane (BM) surrounding the glands in breast; collaborating with two most essential components, i.e. myoepithelium and luminal epithelium. Composed of type IV collagen, laminin LM-332 and LM-111, entactin, proteoglycans and epiligrin; BM maintains the epithelial cells polarity. A mélange of ECM, key enzymes in carbohydrate and lipid metabolism, TGF-β, Wnt and JAK-STAT signaling and lactogenic hormones are required for mammary glnad epithelial cells development.[16,17]

SPARC Modulates ECM

Riley and Bradshaw[18] in a recent study have discussed diverse mechanisms through which SPARC modulates the assembly and arrangement of collagens and basal lamina; their alteration is noticed in SPARC-null mice. An effective

arrangement of fibronectin (Fn) matrix is mandatory for ECM maturation. For an essential Fn-induced integrin linked kinase (ILK) activation followed by intracellular signaling cascades, SPARC is essential which in turn mediates cellular contractile components. Reduced ILK-dependent cell-contractile signaling and Fn-induced ILK activation is noticed in cells without SPARC. Fibrillar collagen and mitochondrial functions are also affected by SPARC in the ECM.[19]

SPARC and Cell Adhesion

Cellular anti-adhesion process is essential for cells especially during morphogenesis. Anchorage-dependent cells are incompatible without cell adhesion. Malignant tumor cells detach in the initial step of tumor invasion in nearby tissues and later a distant metastasis takes place, this is due to a change in tumor cell adherence. SPARC has been considered to have an "anti-adhesive" property due to the fact that cell attachment is opposed by it.[20] SPARC is released whenever there is an injury. It induces dropping of actin stress fibers and focal adhesion plaque is alteredby decreasing type IV collagen levels in the basement membrane; this leads to the speedy transition of cells to intermediate state of adhesiveness.[21]

SPARC and Cell Migration

The intermediate state of adhesion in the cells followed by an injury for instance, promotes cell motility. There is also an increased expression of matricellular proteins during wear and tear, proposing that cell migration might be promoted due to modulation of the intermediate adhesive state of cells. The chemotaxis of endothelial cell in response to fibroblast growth factor-2 (FGF-2) is inhibited by SPARC.[22]

Role in Cell Survival and Apoptosis

The cell survival and cell death equilibrium is disturbed by dysregulation of cellular activities. This in turn can initiate the cancer development, its further progression and can reducethe response of radio-chemotherapy in tumor. Several researches have supported the affected cell growth and apoptosis in response to SPARC over expression.[23,24] Multiple growth factors like VEGF, PDGF and TGF are controlled by SPARC etc. It not only inhibits proliferation of endothelial cells triggered by VEGF and FGF-2 but also with holds the PDGF activity in stromal cells.[25] There is an evidence that TGF-β and SPARC in a reciprocal connection can stimulate to adjust cellular functions. Not only this but TGF-β & SPARC can inhibit various physiological processes like cell cycle progression and cell proliferation in different cancer cells.[26]

SPARC in Carcinogenesis

SPARC is emerging diagnostic and prognostic biomarker in other cancers in which there is involvement of growth factors, cell surface receptors, proteases and ECM components.[27] Depending upon the domains of SPARC there is a variable effect in terms growth and progression of tumor. SPARC N-terminus domain is documented to suppress the tumor growth and in the contrary the tumor growth is accelerated by follistatin-like (FS) domain.[15] SPARC is thought to mediate the interaction of cancer cells of ECM and stromal cells. As a factor to interact tissue morphogenesis, angiogenesis, growth factors, component of the ECM and cell adhesion, SPARC is associated to advanced tumor growth and poor survival patients suffering from cancers like tumors of colorectal, pancreatic and prostate.[28,29]

SPARC in Cancer Development

There is an observation in a study regarding up regulated pattern of SPARC in adjacent stromal cells while its down regulated pattern in cancer cell types in pancreatic cancers; which makes its role disputed in cancer progression.[30] However, according to another study a positive association of elevated SPARC levels and more aggressive tumors was noticed.[31]There are researches that suggest SPARC tumor suppressor role as in colorectal, breast, lung, ovarian and pancreatic cancers. In the same way the SPARC controls cell proliferation, angiogenesis and adhesion, negatively but its expression is increased in Grades II-IV gliomas. These conflicting roles of SPARC may be due to differences in several proteolytic molecules

including elastases, cathepsins, MMPs and serine proteases.[32]

SPARC and Tumor Growth

Tumor advancement takes place by the release of cytokines and metalloproteases due in response to SPARC secretion.[33] SPARC modulate collagen deposition and fibrilogenesis when lung cancer cells progressed faster.[34]

Response to Chemotherapy and Radiation

An albumin-binding protein, SPARC is helpful in mediating intra-tumoral build-up of drugs bound to albumin i.e. nab-paclitaxel. Nab-paclitaxel, a targeted therapy may enhance the efficacy of drug in the tumor microenvoirnment on interaction with SPARC.[35] SPARC expression is increased in triple-negative tumors in comparison to other breast cancer molecular subtypes. Hence in triple-negative breast cancers, SPARC shows highest expression rate. Interestingly higher pathological complete response (pCR) rate is achieved when SPARC expression is increased. By definition pCR is "absence of any invasive cancer in the breast and in lymph nodes". Increased chances of pathological complete remission in response to chemotherapy is achieved when primary tumor has high SPARC expression.[36]

Bone Metastasis

SPARC as a chemotactic factor might promote cell migration towards bone in breast and prostate tumors.[36,37] A study has also documented that secondary tumor sites SPARC expression is increased than that of the primary tumors.[38]

SPARC in Epithelial-Mesenchymal Transition

In embryogenesis the pivotal role of mesenchymal-epithelial transition (MET) and epithelial-mesenchymal transition (EMT) are recognized earlier. EMT includes gene regression in epithelial cells such as E-cadherin yet obtaining some new characteristics like cell adhesion loss and cell mobility promotion; similar changes are observed in the mesenchymal cells. The crucial role of EMT in cancer developmental programs during cancer invasion and metastasis is astonishing; this can be observed when EMT in primary tumor cells moderate ovarian cancer metastasis.[39]

In EMT, SPARC follows two signal pathways; Wnt signal pathway and TGF signal pathway. Increased expression of Snail was noticed due to SPARC overexpression in primary human melanocytes through Wnt signaling. Particular EMT changes were seen due to reduction of epithelial E-cadherin.[40]

SPARC and Pro-apoptosis

A pro-apoptotic activity of the N-terminus of SPARC was noticed in colorectal cancer. In apoptosis Bcl2 an anti-apoptotic member of the intrinsic/ mitochondrial pathway, interacts with caspase 8, and inhibit the apoptosis pathway of tumor cells. Caspase 8 is targeted by the N-terminus of SPARC; preventing its interaction with Bcl2, SPARC activates the extrinsic pathway of apoptosis; later the intrinsic pathway is subsequently promoted.[41]

SPARC expression is also though to promote autophagy followed by upregulation of cathepsin B and later apoptosis mediated through mitochondria. The apoptotic cell death begins when mitochondrial release of cytochrome c due to cathepsin B and caspase-3, takes place.[41]

Role of SPARC in Breast Cancers

SPARC is not expressed in luminal A subtype of breast cancers however, basal, HER2þ and luminal B breast cancer types express SPARC.[42]Overall survival and disease free life expectancy is poor in breast cancer cases with high SPARC expression.[43] When there is a loss of ER, PR and HER2 expression in breast cancer, that molecular type is termed as triple-negative breast cancer (TNBC) (**Table-1)**.

Accounting for 10-17% of all breast carcinomas, it is the most feared of subtype with high recurrence rate and worst prognosis.[44]In comparison to hormone positive breast cancers, these are generally larger in size with higher histological grade at the time of presentation. The biomarkers for TNBC prognosis are currently undetermined which make TNBC more challenging in terms of oncology. Though unrelated to TNBC, SPARC expression is related with high grade, metastasis and tumor growth.[45]

Table-1: Molecular classification of breast cancers.

	Luminal A	*Luminal B*	*Her-2/neu*	*Basal-Like*
Gene expression Pattern	Expression (LMW) cytokeratins, and high expression of HR's and associated genes	Expression (LMW) cytokeratins, and moderate to weak expression of HR's and associated genes	**High expression of Her-2/neu.** Low expression of ER and associated genes	High expression of basal epithelial genes, basal cytokeratins. **Low expression of ER and Her-2/neu** associated genes.
Clinical	**~50%** of invasive breast cancer	~20% of invasive breast cancers	~15% of invasive breast cancers	~15% of invasive breast cancers
ER/RP status	**ER/PR positive**	ER/PR positive	ER/PR negative	Most ER/PR negative
Her-2/neu status	Her-2/neu negative	Her-2/neu expression variable (+/-)	Her-2/neu positive (by definition)	Her-2/neu negative ("triple negative")
Biological features		High proliferation than luminal A	High proliferation	High proliferation

SPARC mRNA expression was assessed by Azim et al.[46] in accordance with the molecular subtypes of breast cancer and its association in silicon response. Higher pathological complete response (pCR) after chemotherapy was obtained in triple-negative molecular subgroup of patients with breast cancer, when SPARC expression was used as an indicator.

SPARC as Breast Cancer Therapy

Nab-paclitaxel, a promising targeted response could be utilized after SPARC expression. Increased SPARC levels in tumor might accumulate albumin within the tumor site, pertaining to SPARC-albumin high affinity bonding.[47] When pancreatic cancer shows high SPARC expression it is associated with a bad prognosis.[48] The role of SPARC in breast cancer is still controversial. On one hand where studies show that among all breast cancer molecular subtypes, TNBC has worst prognosis due to higher SPARC expression.[49]On the other hand Linder et al.[50] have shown its contradictory utility.

Higher SPARC expression breast cancers could be treated with nab-paclitaxel. There are multiple reasons to favor it some of these can be that the drug might be brought to tumor in a targeted fashion and it has the capacity to compile within the tissue. This compilation improves effectiveness and gives better tolerance for the drug. Not to forget the lesser side-effects as compared to other chemotherapeutic drugs.[51] In a study where solvent-based taxane and nab paclitaxel were considered, the later promised not only a prolonged metastatic-free survival for patients but a better therapeutic response as well. Now nab-paclitaxel is endorsed as second-line therapy in advanced breast cancer cases.[36]

Role of SPARC in Bone Metastasis

Breast cancer metastasis to bone is not only a favored site but also bone metastasis in breast cancer patients is a death warrant. Before secondary out growth, the osteotropic malignant cells quiescent for a longer time, skeletal metastases may develop even ten years later to the primary tumor surgical removal.[52] Multiple organs, particularly bone marrow is predicted to be the most frequent site of distant metastasis and the frequency is as high as 70% for advanced breast cancers to have metastasis in the bone. Osteocytes are the cells of mesodermal lineages. Due to its origin from bone marrow, the mesenchymal stem cells also called as bone marrow stromal fibroblasts. During metastasis in the bone microenvironment these cells have a potential tendency to express SPARC and have a pro-tumorigenic role.[53]

CONCLUSION

Breast carcinomas being divergent in heterogeneity, have a different response to the targeted therapies independent of hormonal status. There is a dire need to forecast clinical behavior and the patient's response to recent treatment strategies at a newer molecular level akin to hormonal status for the promising curative response. There is also a need to assess the immunohistochemical status of SPARC along with the hormone status (ER/PR) and Her2neu scores in patients with various grades and stages of breast carcinoma. SPARC is predicted to evolve as a promising IHC marker be holding future refulgence in breast cancer diagnosis, prognosis and treatment

guide for patients in resource constrained countries like Pakistan.

LIMITATIONS OF STUDY

This is a simple narrative review; a systematic review with critical analysis using recommended guidelines may give more conclusive picture of utility of SPARC in breast cancers.

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CONFLICT OF INETEREST

None to declare.

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None to disclose.

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Author's Contribution

WAM: Design of study, acquisition of published data.

SK: Conception, design of published data and article drafting.

NN: Conception of study, critical revision for intellectual content, final approval of the manuscript.

AHN: Critical revision for intellectual content andfinal approval of the manuscript.