Journal of Pharmaceutical Research International

33(56A): 82-99, 2021; Article no.JPRI.76975
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Therapeutic Targets In Breast Cancer Signaling: A Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i56A33889

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/76975

Review Article

Received 20 September 2021
Accepted 29 November 2021
Published 13 December 2021

ABSTRACT

For women, the most dominant type of cancer is breast cancer and perhaps one of the most recognizedreasons of death. This is a disorder of many distinct traits, many of which are known as positive hormone receptor, human epidermal receptor-2 (HER2+), and three negative breast cancers (TNBC). Drugs that directly target and kill tumors constitute a rapidly-growing form of molecular therapy for cancer patients. Analysis reveals that stable breast tissue cells exhibit receptors which aren't usually present. As a result, it is imperative to cognize the molecular roots of breast cancer and the myriad compromised pathology-related processes and pathways to ensure

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progresses in early diagnosis and prevention. This study demonstrates essential cellular pathways relevant for breast cancer including improvements in cell proliferation, apoptosis, and hormone balances in breast tissues. On the basis of these notions, we consider how breast cancer is associated to the creation of potentially therapeutic interventions and predictive biomarkers.

Keywords: Breast cancer; tumor; apoptosis; cell proliferation.

1. INTRODUCTION

Cancer of the breast is the most prevalent form of cancers in females across the world [1], and it is still the leading cause of death [2]. If we talk about prevalence of breast cancer then in Britain 1 out of 12 females are diagnosed with breast cancer [1]. Breast cancer is very common type of cancer in women and 18% cancers are breast cancer of all types of cancer diagnosed in women [1]. In 2021 the incident of breast cancer is going to increase 85 per 100,000 cases [1]. Breast cancer is considered to be the most pronounced and heterogeneous disease affecting both chromosomal and non-chromosomal causes [3]. The genes that target estrogen receptor (ER) and HER2 crosstalk between ER and other signaling networks as well as epigenetic pathways have been proposed to be implicated in hormone tolerance to endocrine therapy [4,5]. With the new advances in molecular biology and immunotherapy, very precise personalized treatments can be adapted to different categories of breast cancers [6,7]. Therapies targeted for breast cancer comprises of substances or drugs which impede with the biochemistry of cells unsettling the growth of cancerous cells [8]. Women's breast cells might overexpress receptors that triggers them to proliferate, metastasize, etc. [9]. It's a heterogeneous disorder, having multiple risk factors such as diet, size, and family background [10]. Breast cancer is categorized according to a specific place of tumor development and gene expression profiling [11]. While alterations in a few primary genes such as BRCA1 and BRCA2 are related with high cancer risk, majority of cancer cases are caused by genetic traits with low penetrance [12]. To recognize the genetic origins of breast cancer is important because it aids in the detection and prevention of malignant growths [13]. In this study, we outline important cellular mechanisms which have been substantially linked to breast cancer, guiding to modifications in cell proliferation, apoptosis, and hormone balances of breast tissues cells [14,15]. We address some possible indications that can detect breast cancer. There were 13.8 lac new cancer cases in 2008 (23% of total) and 458,400 (14% of total) cancer deaths that year [1]. Around 60% of mortalities from breast cancer are prevalent in technologically advanced nations, predominantly Western and Northern Europe, North America, Australia and New Zealand [16]. According to the American Cancer Society, in 2008 out of 182,500 (approx.) American women who are diagnosed with cancer 40,500 died [1,17]. This is why there are various kinds of breast cancer [18]. There are several pre-test considerations of patients into account [19,20]. It has been shown that positive prognosis exists if receptors are high. Centered on the genetic pattern, breast cancer was classified into three types [21]. In the first group were ER or PR positive tumors and in the second group were positive for HER2 with or without ER and PR positivity [22-24]. TNBC is diagnosed because you cannot find an expression of the genes ER/PR and HER-2 [25,11]. Receptor signaling pathways play a critical role in the growth and development of breast cancer, inhibition of these receptors is main therapeutic strategy of breast cancer treatment [26].

2. TYPES OF BREAST CANCER

There are mainly 3 subtypes conditional on the absence or presence of molecular markers for estrogen or progesterone receptors and human epidermal growth factor 2 (ERBB2; previously HER2): hormone receptor positive/ERBB2 negative (70% of patients), ERBB2 positive (15- 20%), and triple-negative (tumors lacking all 3 standard molecular markers; 15%) [1,27]. At the time of diagnosis more than 90% of breast cancer are non-metastatic [28] . For metastatic individuals, the clinical targets would be to cure the illness and avoid recurrence that's why triple- negative breast cancer has much inferior prognosis in contrast to other two forms of breast cancer because of its 5-year survival rate of 55 percent [28] as shown in Fig. 1.

Epidemiology of Molecular Types of Breast Cancer

HER2-positive

It is known that 20% of the aggressive breast cancers in the united states are her2 + [29]. Her2

+ cancers have the worst prognosis because they respond poorly to hormone therapy and her2 + cancers have greater chance of recurrence [30]. The breast cancer has so many copies of her2 gene, gene which activates the her2 proteins, which can be located on the cancer cells [31]. While in a normal function her2 receptors controls the growth, division and repair of healthy breast cell while in proliferated state the cell division is rapid and uncontrolled due to the excess absorption of substance known as "human epidermal growth factor 2" energizing cell growth [32]. HER2+ breast cancer has same symptoms as that of the other kinds of cancer including protuberance in the breast; breast shape change, pain, engorgement and unusual discharge [33]. Treatment options for HER2+ breast cancer may include combination of surgical procedure, exposure to radiation, chemotherapy and/or administration of targeted therapy such as the immune monoclonal antibody, trastuzumab depending on its stage [34,35].

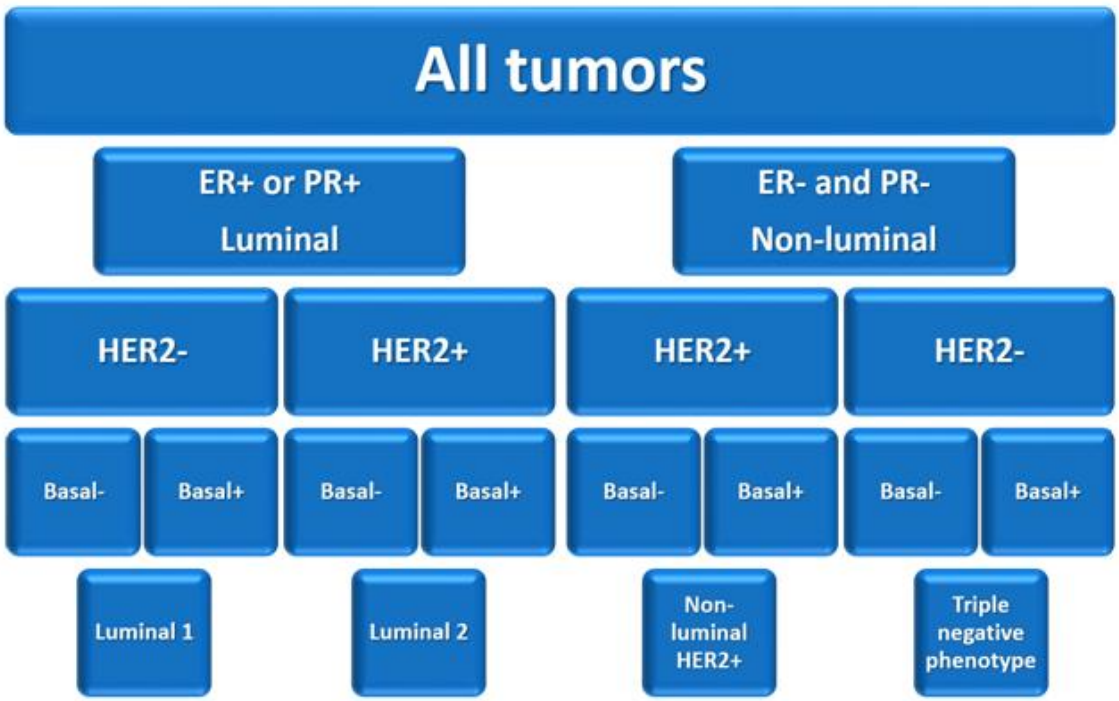

Fig. 1. Ihc based breast cancer subtype classification. Two major subtypes are the luminal (er+ or pr+) and non-luminal tumors (er- and pr-). These are further sub-classified into luminal 1 (her2-), luminal 2 (her2+), non-luminal her2+ and triple-negative phenotype (tnp) [1]

Table 1. Types of Breast cancer [1-4]

Type of breast cancer	ER status	PR status	HER2 status	Target therapy	Occurrence (%)
Luminal A	+	+	-	• Hormone therapy • Chemotherapy	68%
Luminal b	+	-	+	• Chemotherapy • Hormone therapy • Her2 inhibitors	10%
HER2 positive	-	+	+	• Chemotherapy • Her2 inhibitors	4%
Triple negative or basal like	-	-	-	• Chemotherapy	10%
Others	unknown	unknown	unknown	multiple	8%

Luminal A

Luminal A is the predominant subtype for each race and era. These tumors are normally +ive and slow-growing estrogen receptor (ER) and progesterone receptor (PR). Treatment normally requires hormonal therapy [36-38].

Luminal B

Luminal B comprises of the tumors that are estrogen receptor +ive, progesterone and HER2 +. The growth of these tumors is rapid in comparison with Luminal A type. This type of tumor may benefits from chemotherapy and hormonal therapy and treatment targeting the HER2 receptor [39].

Triple –Negative

Cells of this form of cancer have no estrogen, progesterone or HER2 receptors, this form is commonly aggressive and normally starts in the lymph nodes of breast [40]. Strong breast cells include estrogen and progesterone hormone receptors. They also contain HER2 receptors that promote normal cell development. ER-, HER2- breast cancer cannot be controlled with hormone treatment or HER2 blocking drugs [41]. Fortunately, other medicines, such as chemotherapy, radiation therapy and non-HER2, can be used to combat triple negative breast cancer [42] as shown in Table 1.

Therapeutic targets

Systemic treatment for no metastatic breast cancer is focused on subtype: hormone-positive tumor patients undergo endocrine therapy, and a few receive even chemotherapy; ERBB2-positive tumor patients receive ERBB2-oriented antibody therapy paired with chemotherapy, and chemotherapy is provided to patients with triple-negative tumors [28] as shown in Table 2.

Signaling Pathways (Molecular/ Intrinsic) involved in breast cancer development

Important similarities exist between natural growth and molecular cancer progression [43]. Human normal development is closely regulated by complex signal pathway allowing cells to interact with one another and the factors around them [44]. Various of these similar signaling channels are not surprisingly deregulated or discovered by cancer cells and CSCS [45]. Essentially, cancer is triggered by genetic and epigenetic modifications, which enable cells to escape the pathways that govern the proliferation, survival and migration of cells [45]. All of these shifts map signals regulating cell proliferation and division, cell mortality, cell differentiation and destiny and cell motility [45]. Initiating proto-oncogenic mutations can cause these pathways to be hyperactivated, whereas inactivating tumor suppressors gene destroys essential negative signal regulators [45] the emphasis is on the prevalent signaling mechanisms controlling the natural growth of mammary glands and stem cell functions of breast cancer, namely the signals from the oestrogen receptor (er), her2 and canonical wnt. [46].

Cyclin dependent kinases (CDKs)

Classical division of mammalian cell characterized them into 4 different phases namely G1, S, G2 and M [47,48]. The ordered progression of these phases are strictly regulated at ‘checkpoints’ by the interaction of several cyclins and CDKs. [49,50] (Fig. 1). Belonging to a well preserved family of serine/threonine protein kinases approximately 12 distinct genetic loci are identified to code for the CDKs [51,52]. The family comprises of three cyclins CDKs (CDK2, CDK4, CDK6), a single mitotic CDK (CDK1, known as CDC2 formerly), and several regulatory CDKs such as CDK7, a part of CDK activating complex, and transcriptional CDKs (CDK8, CDK9) [53,54]. Unlike CDKs acting as regulatory subunits of the CDK-cyclin holoenzyme, cyclins are extremely assorted family of protein further divided into four classes (A-, B-, D-, E-type cyclins) [55]. Regardless of the large number of CKDs and cyclins only few have been intensely involved in pathogenesis of breast cancer [56,57]. There are numerous evidence proving that dysregulated cyclins D1:CDK4/6 complex have pivotal role in both initiation and progression of several cancers including breast cancer [58]. Dysregulation of the cyclin D1:CDK4/6 axis is regarded as an early step in breast cancer pathogenesis [59,60] as shown in Fig. 2.

Her2 signaling

Human epidermal growth factor receptors (EGFRs or HERs) 1 to 4 are a class of tyrosine kinase receptors that are found in normal tissue also in wide variety of cancer types [61,62]. The receptor-2 human epidermal growth factor (or

her2/neu, c-erbb2) is an egfr collaborator [63,64]. Like other receptors, her 2 is a tyrosine kinase receptor consisting of a ligand-binding extracellular domain, a transmembrane domain, an intracellular domain [65,66]. The active ingredient makes her2 a mainconstituent for constructing dimers with other molecules and provides her2 with an ability to influence several cellular functions through different Pathways [67,68]. The phosphorylation of tyrosine residues within the her2 intracellular domain is induced by the binding ligand and subsequent dimerization, which leads to the activation of a number of downstream signaling pathways, including mapk and pi3k. [69,70]. These signals are heavily related to breast tumorigenesis [69,71] (Fig. 3).

Table 2. Therapeutic targets of breast cancer [5]

Target gene	Mutation	Drug type	Example
HER2/ERBB2	Amplification/Mutation	HER 2 inhibitor	Hyaluronidase, Trastuzumab, Lapatinib, Neratinib, fam-trastuzumab deruxtecan
ER	Amplification	ER inhibitor	Tamoxifen, Clomifene, Raloxifene, Fulvestrant, Anastrozole
EGFR	Amplification/mutation	ER downregulator	Faslodex
PI3K-K	Amplification/Mutation	mTOR inhibitor	Sirolimus,
AKT1/2/3	Amplification		Everolimus,
PTEN	Mutation/deletion		Temsirolimus
Mtor	Amplification		
KRAS	Amplification/Mutation	BRAF, MEK inhibitor	Dabrafenib and Trametinib,
BRAF	Amplification/Mutation		Vemurafenib and Cobimetinib,
NF1	Mutation		Encorafenib and Binimetinib
CDKNIB	Alteration	CDK4 inhibitor	Abemaciclib
CCCND1	Amplification		Palbociclib, Ribociclib
BRCA1/2	Mutation/deletion	PARP inhibitor	Olaparib, Rucaparib, Niraparib, Talazoparib

Table 3. Organization of MAPK pathways. The MAPK core consists of three kinases (MAPKKK, MAPKK, and MAPK), which form a signal transduction cascade that receives input from G-proteins and produces different biological outputs [6,7]

	ERK	JNK	P38
G protein	RAS	RAC/RHO/RAP	
MAPKKK	BRAF	MEKK1/2	MEKK3/4
		MLK1/2	ASK1
		Tpl-2, TAO1/2	MCK3
			DLK
			TAK
			TAO1/2
MAPKK	MEK1/2	MKK4/7	MKK3/6
MAPK	ER1/2	JNK1,2,2	P38alpha/beta/gamma
OUTPUT	Proliferation, differentiation and survival	Proliferation, cell death, differentiation, inflammation	

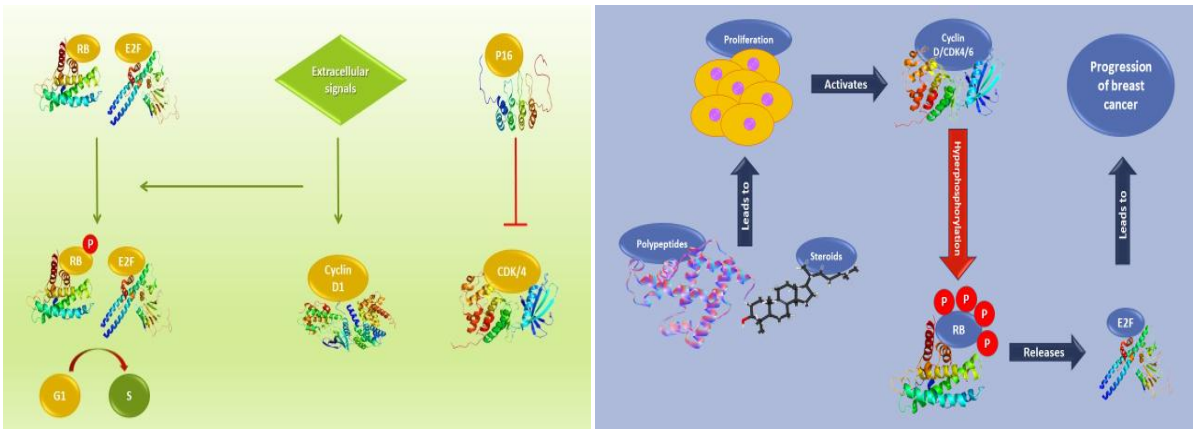

Fig. 2. The cyclin D/cyclin-dependent kinase (CDK)4/6/retinoblastoma (Rb) Pathway. In the context of breast cancer, both steroid and peptide growth factors drive proliferation through cyclin D/CDK4/6 activation. This results in the hyper-phosporylation of pRb as G1 progresses. When retinoblastoma protein (pRb) is hyper-phosphorylated, the transcription factor E2F is released and the cell cycle progresses through S phase. Small molecule kinase inhibitors of CDK4/6 aim to block the hyper-phosphorylation of pRb inducing a G1 arrest and preventing proliferation. ER estrogen receptor [2]

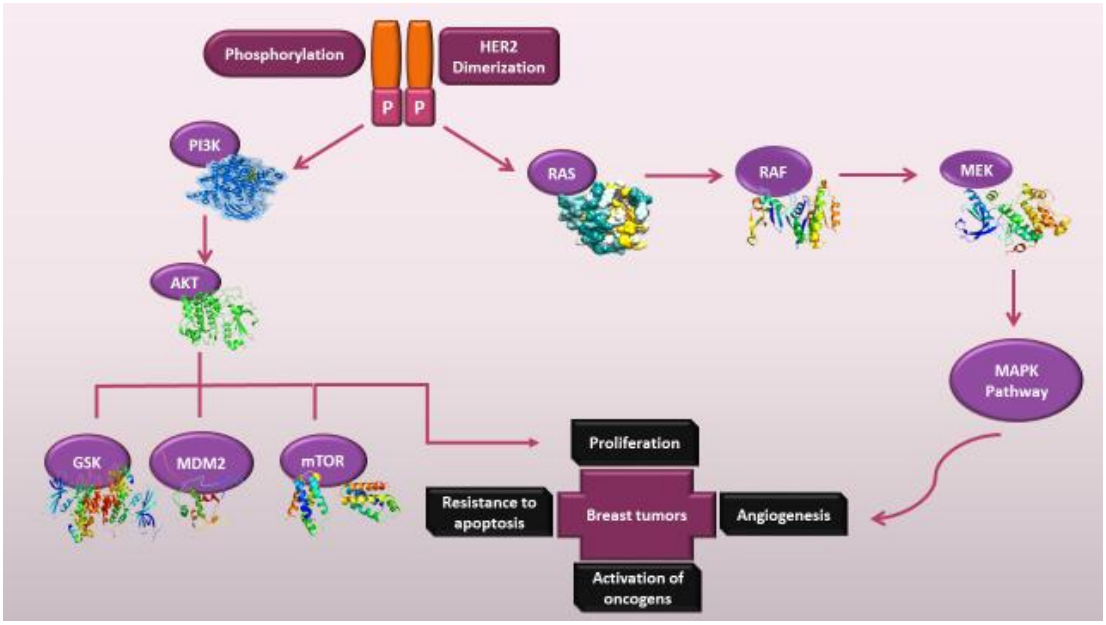

Fig. 3. The HER2 Signaling pathway. HER2 as well as the other members of the EGFR family are receptor tyrosine kinases which are located on the cell membrane and responds to a wide variety of ligands. Phosphorylation of the tyrosine kinase domain in the cytoplasm initiates downstream oncogenic signaling pathways such as PI3K/AKT pathway and Ras/MAPK pathway [2]

MAPK pathway

Three kinases are considered as important regulators in MAPK signaling cascade, with the strongest upstream (MAPKKK) which is reactive to different extra- and intracellular signals, and with simple phosphorylation activation of the middle kinase (MAPKK) [72,73]. MAPKKs are exclusively phosphorylated and activate MAPK, normally using several substrates that execute cell fate decisions that are adequate for the input signal, including development, proliferation, differentiation, motility, stress response, survival and apoptosis [74,75]. Today, 4 distinct MAPK

mammalian cascades were defined according to the components of their MAPK: extracellular signal-regulated kinase 1 and 2 (ERK1/2), c-Jun N-terminal kinase (JNK), p38 and ERK5 [76,77] (Table 3).

There are three main pathways to MAP kinase in human tissues, but the ERK-1 and -2 pathways are the most significant in termsof metastatic breast cancer progression and pathogenesis [78,79]. The main regulators for ERK-1 and -2 are peptide growth factors that function via tyrosine kinase containing receptors [80,81]. Estradiol, progesterone and testosterone can be non- canonicalto activate MAP kinase via membrane- associated receptors and to various other ligands working through heterotrimeric G protein receptors [82,83]. Latest findings indicate that breast cancers also involve an increased proportion of cells when MAP kinase is activated. MAP kinase pathways will execute cross-talk results on the basis of ER and cell cycle mediated transcription in estrogen receptors positive for the breast tumor [84]. Estradiol promotes cell proliferation by different signaling pathways involving the signal transduction activation of MAP kinase through activation of non-transcriptional factor which are important in pathogenesis of cancer cell along with elevation of growth factor, this leads to MAPK signaling cascade activation. Progesterone and androgen are main growth hormones which are responsible for stimulation of MAP kinase which in turn cause cancer progression and pathogenesis [73] Fig. 4.

RAS signaling

The RAS proteins belong to superfamily of low-sub-atomic weight GTP restricting proteins [85]. Cell development is controlled by RAS family & actin cytoskeleton is controlled by RHO family [86]. Transmembrane receptors play and important role in signal transduction of cancer cell progression, for this purpose RAS G-proteins are important mediators [87]. There are 4 highly homologous isoforms of RAS-G proteins; NRAS, HRAS and two alternative variants of KRAS termed as KRAS4A and KRAS4B. NRAS encodes for neuroblastoma RAS viral oncogene homolog, HRAS encodes for Harvey rat sarcoma viral oncogene homolog while KRAS encodes for kristen rat sarcoma viral oncogene [87]. On the basis of upstream receptors RAS proteins play and important role as binary switches which causes activation of GTP through binding of GDP on it [85,86,87]. Following the activation of receptor tyrosine kinases, for example, the epidermal growth factor receptor (EGFR), the auto phosphorylated receptor is bounded to the SH2 DOMAIN of growth factor-receptor-bound protein 2 (GRB2) [88]. Modulation between ON and OFF state of coupled proteins conversion of GDP to GTP or GTP to GDP takes place through enzymes. Various extracellular and intracellular signals are responsible for proper functioning of RAS proteins, in which multiplicity of GTPase and GAPs are of great importance [89,90]. EGFR & ERBB2 are stimulated by their overexpression in various kinds of cancers; including breast, ovarian & stomach carcinomas. Extracellular space is required for truncated receptors in EGFR & this transformed receptor is detected to be overexpressed in glioblastomas & in many other tumors [85]. Among all receptors, G-protein coupled receptors are main for activation of RAS protein [91]. By the autocrine creation of EGF- like factors EGFR-family tyrosine kinases are activated, for example, changing development factor-a (TGF-an) in tumors [92]. Numerous other receptors are responsible for improper functioning of RAS protein, they inactivate RAS through various signal transductions signaling pathway which leads to progression and pathogenesis of metastatic breast cancer [91]. (Fig. 5).

Wnt signaling

Wnt family plays an important role in apoptosis, cell death, signal transduction and cellular pathways, they can decide the fate of a cell by affecting its morphology [93]. 19 wnt genes which are available in spliced isoforms are termed as main encoding genes for biological cellular functions [94,95]. Studies have shown that stem cells can be auto-renewed by Wnt signaling in specific tissues [96]. The genes of Wnt were recognized as cancer genes that depicts pivotal role in mouse model in tumorigenesis of mammary glands, so they cause breast cancer in a broad range of different tissues of human [97]. This shows mutation or dysregulation in Wnt signaling leads to breast cancer [98]. In mammals 19 Wnt genes are present, they encode for cysteine-rich secretory glycoproteins, mammary gland of human & mice also expresses a maximum of seven types of Wnt gene mutation is breast cancer [99,100]. 7 transmembrane domains are present on frizzled receptors, on this receptor wnt proteins bind which leads to initiation of signaling pathway [94,95,101].

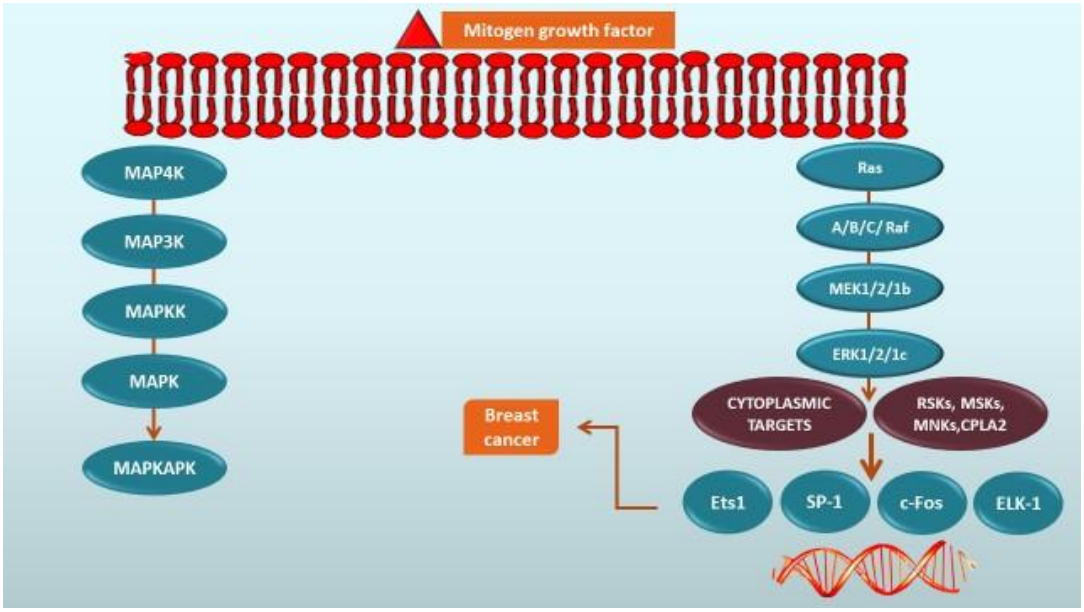

Fig. 4. The MAPK cascades. MAPKs are present in the cytoplasm which can be translocated into the nucleus, where they catalyse the phosphorylation of lots of cytosolic proteins along witj numerous nuclear transcription factors [3]

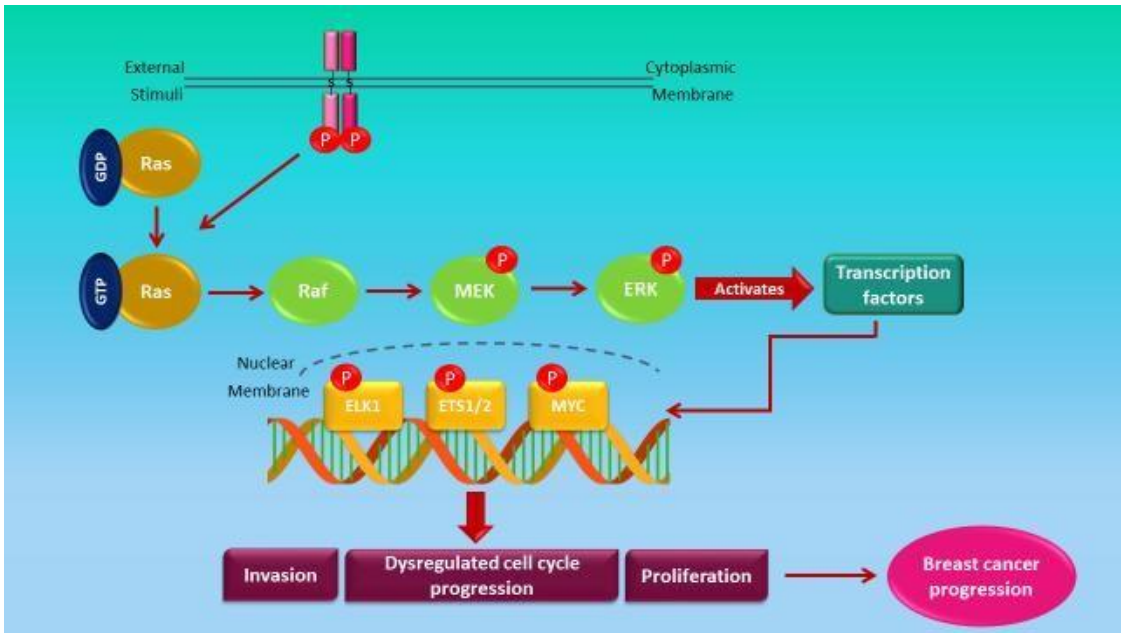

Fig. 5. The Ras/MAPK signaling pathway. External stimuli including ligand-activation of receptor tyrosine kinases, among others, initiate the activation of Ras, a small GTPase, through membrane-associated signaling complexes. Ras facilitates the heterodimerization and activation of Raf intracellular kinases, which starts a kinase cascade through MEK and ERK, resulting in the activation of transcription factors that drive genomic signature programs of dysregulated cell cycle progression, proliferation, invasion, and survival. Negative regulation of the pathway is accomplished through the action of DUSP family phosphatases on ERK, the hydrolysis of Ras-associated GTP by NF1, and the negative feedback actions of ERK on both MEK and Raf signaling complexes, among others [4]

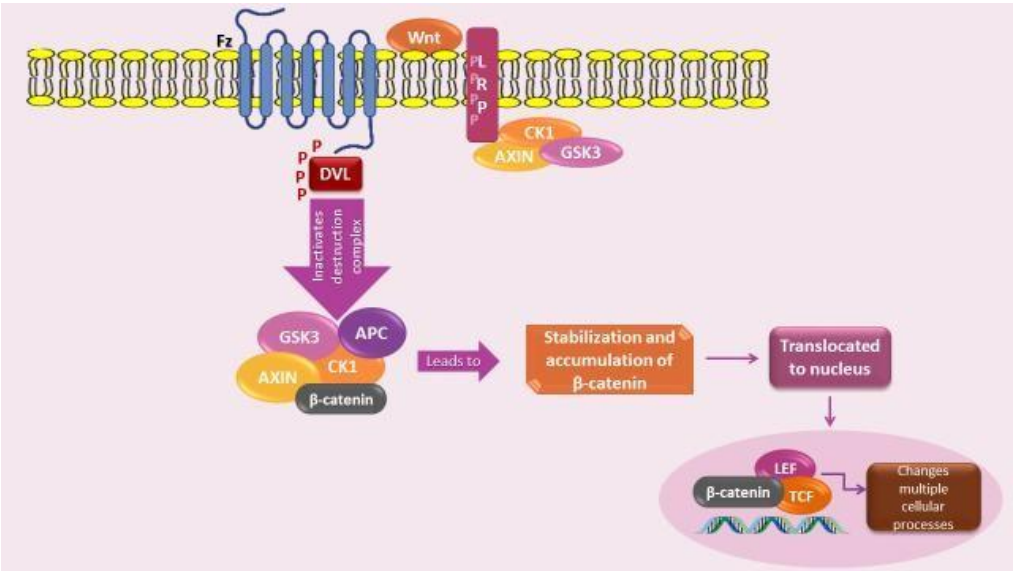

Fig. 6. The Wnt signaling pathway. canonical Wnt signaling is activated as secreted Wnt ligands bind to the seven-pass transmembrane receptor Frizzled (Fzd) and the single-pass low-density lipoprotein receptor-related protein (LRP) (light blue). LRP is then phosphorylated, which leads to the recruitment and polymerization of Dishevelled (Dvl) proteins (red) at the plasma membrane. The Dvl polymer (active) is now able to inactivate the destruction complex; that consists of AXIN, adenomatous polyposis coli (APC), and GSK3β, which leads to the stabilization and cytoplasmic accumulation of β-catenin (orange) which then translocates to the nucleus. Once it reaches the nucleus it is imported, once inside β-catenin forms acomplex with T-cell factor (TCF) and lymphoid enhancer factor (LEF) (purple), acting as a transcriptional switch, that changes multiple cellular processes [5]

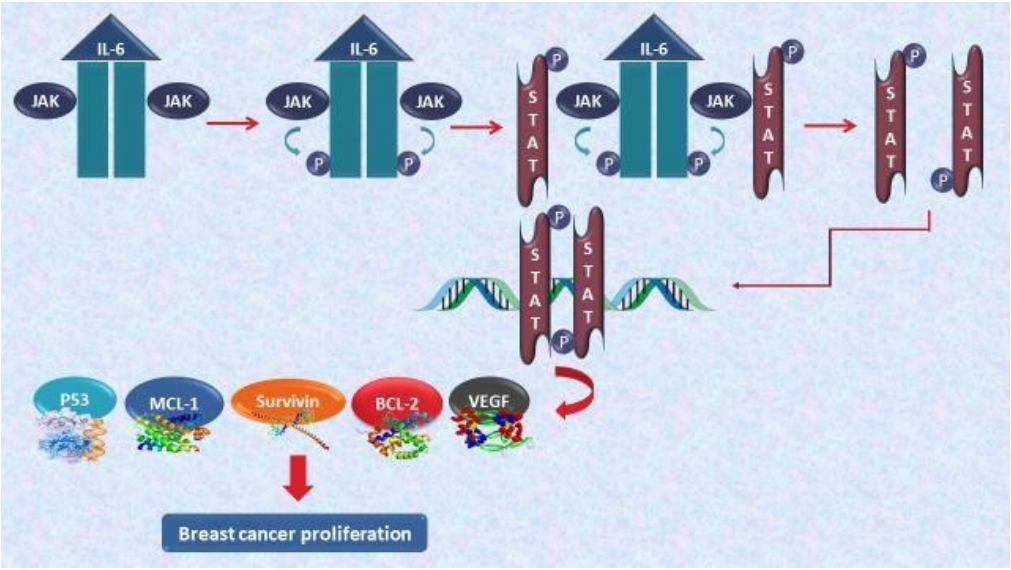

Fig. 7. The JAK/STAT pathway. After the cytokine binds to the receptor, JAK adds a phosphate to (phosphorylates) the receptor. This attracts the STAT proteins, which are also phosphorylated and bind to each other, forming a pair (dimer). The dimer moves into the nucleus, binds to the DNA, and causes transcription of genes. Enzymes that add phosphate groups are called protein kinases [6]

In human beings approximately 10 frizzled receptors have been identified to take part in signaling cascade [102]. Wnt signaling pathways also present alternative to non-canonical, which lacks α-catenin. For this pathway cell surface receptors are consists of two proteins: the Frizzled family protein that is seven trans-membrane domain protein & LRP5 or LRP6 those are LDL receptor-related proteins [103]. Due to their structural resemblance, a large number of Wnt proteins have the same pathway for signaling & are practically completed in trial tests [104,105]. This mutual pathway includes α-catenin a cytoplasmic protein as an intermediate in important signaling & is called as the α-catenin process [106]. Homo and hetero-oligomers are formed by frizzled receptors which are cell specific and signal specific in their expression. Other mechanism of action involved association of frizzled receptors with other co-receptors [107]. When Wnt protein is absent low level degradation is responsible for maintenance of beta-catenin signaling pool. Glycogen synthase kinase 3 beta (GSK3b) and serine/threonine kinase 1 (CK1) are responsible for phosphorylation of beta-catenin [108]. A complex consists of adenomatous polyposis coli (APC) protein, diversin and axin is main place for phosphorylation of beta-catenin [109]. GBP/Frat-1 is recruited through to dishevelled proteins (Dsh) because degradation of Beta- catenin is prevented upon receipt of wnt signal [104,105]. This leads to displacement of GSK3b from destruction complex [107]. Wnt signaling is mediated by assistance of low density lipoprotein receptor related protein family (LRP5/6) [104,110]. Dsh comes in contact with frodo and beta- arrestin, while effect of Dsh is effected by Dapper because it is antagonist of Dsh [111] (Fig. 6).

A, wnt1/3 binds the g-protein coupled receptor fzd and the tyrosine kinase receptors lrp5/6 to start initiation of signaling pathway [112]. The subsequent signaling complex elevates β-catenin translocation to the core & along these lines drives development period of melanoma, whereby cells separate & multiply on the surface. B, an expansion in wnt5a enacts the non- canonical wnt signaling pathway through fzd and the tyrosine kinase ror2 [104,110]. Downstream effectors, for example, arf6, akt, jnk and pkc drive a change to the vertical development stage, whereby melanoma attack through the dermis and metastasize c. In breast cancer cells, on the other hand, wnt5a signaling activates camkii to promote -catenin corruption, preventing the translation of qualities that promote metastasis and attack [111].

Jak STAT pathway

STATs are proteins in nature that were found in 1988 [113]. IFNs type I's transcription is initiated by them interferon (IFN)-stimulated response elements are bound to it that is a sequence of DNA [114]. In 1992 three labs separately found JAKs, so that they authored the JAKs pathway [115]. The JAK is a word which originates from deceptive god of Romans that concludes two spaces; it has kinase like space & a synergist field [113]. Type I-and II receptors are closely related to JAKs. The receptor dimerization is caused by a ligand known as cytokine & JAKs are initiated [116]. Trans-phosphorylation takes place when tyrosine residues attaches to JAKs and as a result activates it, STATs docking sites are created for recruitment of inactive cytoplasmic translation factors [117]. In the cell biology Phosphorylation is the most widely recognized alteration, they have a significant role in signaling pathways by its controlling action. In the cytoplasm unphosphorylated (OFF) STATs are present. When JAKs are activated they phosphorylates STATs (ON) and STATs dimers, by this docking sites are abandon on receptors. That's why nucleus is translocated & they activate or suppress gene transcription by binding to specific DNA sequence [115]. Serine phosphorylation is independent [118]. Transcriptional potency is enhanced by phosphorylation of serine of STAT, though serine phosphorylation of STAT3 has been accounted in a negative way. P38, Erk and JNK are involved in serine phosphorylation of STATs [119]. The JAK-STAT pathway additionally encourages different cell reactions to assorted types of cell stretch [120].

JAK1, JAK2, JAK3 and TYK2 are four main members of JAKs family (Stark *et al*., 1998). Every JAK part comprises of a few distinctive fields which are following: N-terminal FERM domain which is named after the discovery of a protein containing this domain (band 4.1, Ezrin, Radixin and Moesin) [121]. 3 sub-domains F1, F2 and F3 are present in FERM domain, which are basically like CoA binding, pleckstrin homology-phosphotyrosine restricting spaces and Ubiquitin [122]. Protein-protein communications are its responsibility, like on its membrane scaffold &adoptor interaction [123].

The SH2 (Src homology 2) contain around 100 residues in its domain for binding of tyrosine.

Dimerization and activation of STATs is done by SH2 domain [124]. On account of homology to Protein Central pseudo kinase domain is named; catalytic function is absent in them, but they perform regulatory function [125]. On C-terminus PTK domain is located. It comprises roughly 250– 300 residues and an ATP-restricting site comparing a synergist domain. On special downstream substrates it is responsible for phosphorylation of tyrosine residues [126]. Seven STATs members are included in humans' STAT family: STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B and STAT6 [127]. They have exciting homology in these regions: Unique N-terminus region is involved in STAT activation e.g. dephosphorylation of the STAT interactions or STAT, like formation of tetramer [128]. In protein-protein interactions and nuclear export coiled-coiled domain plays an important role. AS-type immunoglobulin fold is present on DNA binding domain and is also found in p53. Sequence-specific binding is assisted by this [129]. TTCN3–4GAAA sequence is recognized in target genes on the promoter region [130].Trans-Activation Domain is abbreviation of C-terminus and very conserved residues of tyrosine are present here [131]. In recruitment of special proteins many discovered varieties are included, like histone deacetylases, DNA polymerase II, etc. [129]. JAKs are activated in response to cytokine binding, and the intracellular region of the receptor is phosphorylated to serve as a docking site for STATs to be recruited & phosphorylated [132]. Through SH2 domain homo and hetero dimerization starts to takes place. StIP protein (STAT Interacting Protein) is related to JAK- STAT pathway. It assists phosphorylation of unphosphorylated STATs. In the nucleus in impor tin α-5 dependent manner phosphorylated STATs are translocated through Ran nuclear import pathway. Dimerized STATs bind to complex DNA sequences at the end of their transition to control transcription of their own target genes. [133]. Anyhow great knowledge is provided about the process of STAT phosphorylation, dephosphorylation of STAT in the nucleus is not completely defined [134-138] (Fig. 7).

3. CONCLUSION

Not only are these pathways involved in hormone signaling to cancer cells, but these pathways also control cellular roles that impacts the onset and progression of cancer of breast. Signaling pathways are critical for mammary growth, and variations within pi3k pathway are more prevalent in many diseases, such as parkinson's, diabetes type ii, and various forms of cancer. As the multiple dysregulations in key nodes of the multiple pathway are identified as having links with different diseases, identifying particular alterations and knowing their functional significance will permit for more precise selection of medication, having least side effects. It is seen that the MAPK pathway have pivotal part in progression of breast cancer through inducing cell propagation or leading to further pathways.The movement of cell for the interaction within the extracellular world is carried out by JAK-STAT signalling mechanism/pathway. Dysregulation of Wnt signalling can contribute to development of cancer as it governs cellular differentiation and proliferation. Several facets of regulation of these pathways are still under study, particularly regarding the cross talking of these pathways, their effect on former pathways, feedback, tumor microenvironment interactions, cellular metabolism, risk factors, and reaction to drug therapy. Conversely, both of these mechanisms are seen to be in a coordination acting as a network, and a number of potential interventions need to be considered. In this sense, an increasingly thorough analysis of these pathways facilitates the generation of important and transformative knowledge on the molecular basis for gene expression regulation in normal as well as cancerous cells, as well as the nature of cellular contact. Understanding breast cancer progression and incorporating molecular-based methods for quality improvement in diagnostics, prognostics, and care of breast cancer patients necessitates identifying the spectrum of mutations that exist throughout the major signaling pathways, as well as how they interact throughout pathways. In this era of pandemic it has become mandatory to understand all factors which take parts in pathogenesis of breast cancer because cancer patients are more vulnerable to covid-19. So in future our strategy will be simultaneous treatment of breast cancer and covid-19. For this purpose, we will use two in 1 drugs which will show anti-viral and anti-cancer drugs so that we can improve mortality rate by clinical management strategies. This can be done by better understanding of all signaling pathways which are responsible for progression and pathogenesis of breast cancer.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/76975