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PATHWAYS INVOLVED IN BREAST CANCER: A REVIEW

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ABSTRACT

Cancer can be thought of as a disease that affects cell communication. Cancer is caused by genetic and epigenetic changes that allow cells to overproliferate and bypass survival and migratory pathways. Breast cancer is the most frequent cancer among women all over the world. The process of cell transduction is crucial in the formation and progression of cancer. Tumor cell proliferation, advancement, and survival are aided by changes in multiple cell signalling pathways. Various pathways are there which are involved in various cellular processes. Aberrant regulation of these pathways leads to cancer. This review looks at several of the cell signalling pathways like MAPK pathway, PI3K/AKT/mTOR pathway, NF-kB pathway, JAK-STAT Signaling Pathway, Hedgehog Signaling Pathway, Notch Signaling Pathway, Wnt Signaling Pathway, and their links to cancer, focusing on how abnormal signalling in these pathways can lead to breast cancer. Targeting various molecular events of these pathways provide treatment strategy for breast cancer.

KEYWORDS: Breast Cancer, Signaling pathway, Epidermal Growth Factor Receptor.

INTRODUCTION

Cancer refers to a vast category of diseases that includes about 100 separate and distinct diseases.[1,2] Cancer is defined as an abnormal development of cells that multiply uncontrollably, producing a tumour, are immortal, and, in some situations, tend to metastasize.[2] Men are more likely to develop lung, prostate, colorectal, stomach, and liver cancers, while women are more likely to develop breast, colorectal, lung, cervical, and thyroid cancers.[3]

In a healthy body, the trillions of cells that make up a healthy body develop and divide as the body need them to function on a regular basis. Cells have a fairly particular life cycle in normal conditions, multiplying and dying off in ways that are defined by the type of cell. As old and damaged cells die, new cells created via a precise life cycle take their place. In the case of cancer, this mechanism is interrupted, resulting in aberrant cell proliferation and the formation of tumors.[1] This ordered process, however, is disrupted when cancer develops. Old or damaged cells survive when they should die, and new cells form when they are not needed as cells become increasingly abnormal. These additional cells can divide indefinitely, leading to tumour formation.[4]

Breast cancer is the most common malignancy in women globally, and it is defined by the uncontrolled growth of abnormal cells in the breast's milk production glands or the tubes (ducts) that supply milk to the nipples. It is a malignant tumour that begins in both male and female breast tissue. Males have breast tissues, which are made up of fat, fibrous tissues, fine channels, and glandular elements or lobules, just like females. The ducts are where the majority of breast cancers start (ductal cancer). A small percentage begin in the sacs or lobules (lobuler cancers). Breast cancer has the potential to spread to lymph glands as well as other regions of the body, including the bones and liver.[5] It can be cured in 70-80% of people with early stage, non-metastatic cancer. With current therapy, advanced breast cancer with distant organ metastases is considered incurable.[6]

Types of breast cancer

There are several types of breast cancer, and they are divided into two main categories “Invasive” and “Noninvasive” or In Situ. Noninvasive cancers do not spread from the original tissue but the invasive type spreads from the breast ducts or glands to other parts of the breast.

These two categories are used to describe the most common types of breast cancer, which include.

Ductal carcinoma in situ (DCIS): The cancer cells in DCIS are restricted to the breast ducts and do not spread to the surrounding tissue.

Lobular carcinoma in situ (LCIS): LCIS is a type of breast cancer that develops in the milk-producing glands.

This kind of breast cancer is like DCIS and does not spread to the surrounding tissue.

Invasive ductal carcinoma (IDC): Breast cancer of this type is the most frequent. This kind of breast cancer starts in the breast's milk ducts and subsequently spreads to adjacent tissues.

Invasive lobular carcinoma (ICL): This kind of breast cancer begins in the breast lobules and can spread to surrounding tissues.

Other, less common types of breast cancer include.

Peget disease of the nipple: This type of breast cancer starts in the nipple ducts, but as it progresses, it affects the skin and areola of the nipple.

Phyllodes tumor: This extremely rare kind of breast cancer develops in the breast's connective tissue. The majority of these tumours are harmless, but a few are malignant.

Angiosarcoma: This type of cancer develops in the breast blood vessels or lymph vessels.

Inflammatory breast cancer (IBC): It's an uncommon cancer that grows quickly and aggressively. The cells penetrate the skin and lymph vessels of the breast in this malignancy. It frequently results in no discernible tumour or lump within the breast that can be felt and identified. When the lymph arteries are clogged by breast cancer cells, however, symptoms arise.

Triple-negative breast cancer (TNBC): Another rare kind of breast cancer is TNBC. TNBC lacks three of the most frequent types of receptors that are known to fuel most breast cancer growth: oestrogen, progesterone, and the HER-2/neu gene. As a result, TNBC is resistant to standard treatments such as hormone therapy, and medicines that target oestrogen, progesterone, or HER2 are unsuccessful. TNBC, on the other hand, may react to chemotherapy even better in the early stages than many other cancers.[7,8]

Metastatic breast cancer: Breast cancer is also known as Stage 4 Breast cancer. Breast cancer that has progressed to other regions of the body, most commonly the lungs, liver, bones, or brain.[7]

Various pathways involved in breast cancer

There are numerous mechanisms that lead to cellular division and proliferation. Any interruption in these pathways leads to the development of cancer, which is a slow and complicated process. Breast cancer involves a number of interconnected signalling pathways that influence biological responses such as cell survival, proliferation, migration, differentiation, and apoptosis. The EGFR (Epidermal Growth Factor Receptor) family of receptor tyrosine kinases are important regulators of normal cellular growth as well as crucial participants in the development of malignancies, including breast cancer. Understanding these signalling pathways aids in the understanding of breast cancer pathophysiology and the targeting of these pathways to combat breast cancer formation, progression, and metastasis.

MAP Kinase pathway

MAKs are serine-threonine kinases that regulate intracellular signalling. The multifunctional Mitogen-Activated Protein Kinase (MAPK) signalling system is made up of many pathways that regulate a variety of cellular functions including gene transcription, metabolism, motility, cell proliferation, apoptosis, synaptic plasticity, and long-term memory. The final MAPK components linked with the three primary signalling pathways activate these various downstream effectors:

- Extracellular-Signal-Regulated Kinase (ERK) Pathway
- c-Jun N-terminal Kinase (JNK) Pathway
- p38 Pathway

A three-tiered kinase cascade consists of a MAP Kinase Kinase Kinase (MAPKKK, MAP3K, MEKK or MKKK), a MAP Kinase Kinase (MAPKK, MAP2K, MEK or MKK), and the MAPK in each MAPK pathway. The ultrasensitive switch-like reactions to stimuli are mediated by this three-tier module. The Mitogen-Activated Protein Kinase (MAPK) signalling toolkit includes these cascade protein kinases as well as other functional components as receptors, transducers, scaffolding protein, and target protein.[9] Breast tumours usually have an increased number of cells with the activated version of MAP Kinase, according to recent research. Activated MAP Kinase is a comprehensive indicator of various biological mechanisms that control breast cancer progression. MAP Kinase is a critical molecule in regulating breast cancer growth and apoptosis for these reasons.[10]

The Epidermal Growth Factor Receptor (EGFR) is an ErbB family transmembrane receptor tyrosine kinase that is excessively activated in a variety of malignancies, including breast cancer. The ligand binding to the extracellular domain activates EGFR, which then undergoes autophosphorylation at the tyrosine kinase domain, which activates several downstream signalling pathways, including components of the Ras/Raf/MAPK/ERK, PI3K/AKT, Signal Transducer and Activator of Transcription (STAT), and Protein Kinase C pathways. Cell proliferation, differentiation, apoptosis, invasion, and angiogenesis are all linked to abnormal EGFR regulation, which finally leads to carcinogenesis.

The Ras/Raf/MEK/ERK pathway: The RAS GTPase proteins are transformed from the inactive GDP-bound state to the active GTP-bound state in this pathway, which is triggered by ligand-induced activation of

receptor tyrosine kinase. Through contact with their RAS binding domain, activated RAS proteins send signals to downstream effectors, including RAF family protein kinases.[11] Raf stimulates MEK1 and MEK2 in the activation loop by phosphorylating serines 218 and 222. ERK1 and 2 are phosphorylated at particular T and Y residues by activated MEK. Many cytoplasmic and nuclear targets, such as kinases, phosphatases, transcription factors, and cytoskeletal proteins, are phosphorylated by active ERKs. ERK signalling regulates processes like proliferation, differentiation, survival, migration, angiogenesis, and chromatin modification, depending on the cell type. Activated ERK can translocate to the nucleus and phosphorylate other transcription factors such as Elk-1, CREB, Fos, and globin transcription factor 1 (Gata-1) that bind to promoters of many genes, including growth factor and cytokine genes, and play a key role in promoting cell growth and preventing apoptosis.

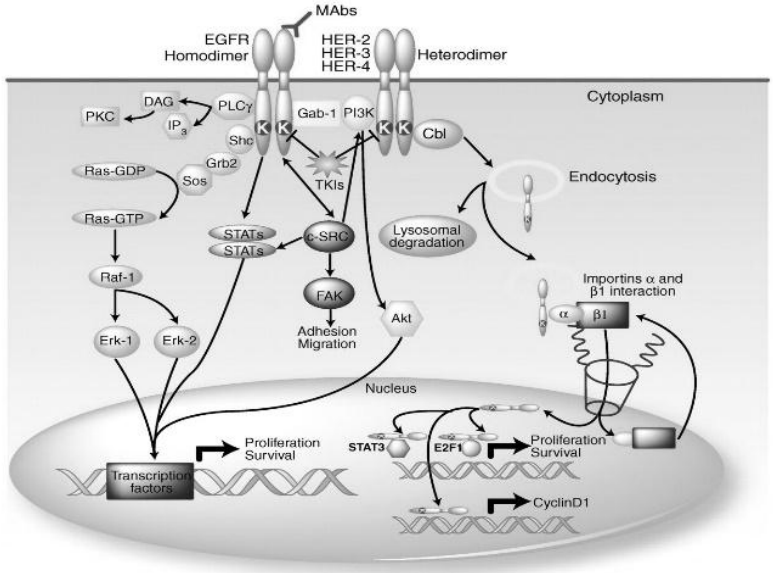

Fig: Schematic diagram of EGFR Signaling Pathway in breast cancer.

EGFR activation causes receptor dimerization, which stimulates the Ras/Raf/MEK/MAPK/ERK and PI3K/AKT pathways, two critical breast cancer survival pathways.

Abnormal cellular proliferation and differentiation can lead to cancer if this pathway is not properly regulated. Apoptosis regulation that is abnormal is linked to breast cancer.

Hyperactivation of Ras, which in turn mobilises the Raf/MEK/ERK cascades, can be caused by aberrant overexpression or mutational activation of receptor tyrosine kinases (e.g., EGFR and HER2), which is observed in 5% of breast tumours. The low prevalence of activating ras mutations in breast cancer has led to the assumption that Ras does not have a significant pathogenetic function in this malignancy. However, multiple Ras-signaling growth factor receptors are overexpressed in breast cancer, suggesting that Ras may be activated in some breast malignancies via upstream processes.[12,13]

The JNK pathway: One of the key signalling cassettes of the MAPK signalling route is the c-Jun N-terminal Kinase (JNK) pathway. It regulates a variety of cellular functions, including proliferation, embryonic development, and apoptosis.[14] The JNK pathway is a "death" signalling mechanism in general.

Environmental stressors (ionising radiation, heat, oxidative stress, and DNA damage) as well as inflammatory cytokines and growth hormones activate the JNK module.[14] Jnk1, Jnk2, and Jnk3 are the three genes that make up the family. The Rho family GTPases Cdc42 and Rac are frequently involved in signalling to the JNK module. Those receptors, or receptor-independent stress-induced membranal alterations, send signals to adaptor proteins, which can activate kinases in the MAP4K and, in some cases, MAP3K tiers of the JNK cascade on their own. Following that, the active MAP3Ks relay the signals to MAPKK kinases, primarily MKK4 and MKK7. The primary JNK kinases (MKK4, MKK7), like the other MAPKKs, are activated by phosphorylation of the Ser-Xaa-Ala-Xaa-Ser/Thr motif (Ser 198, Thr 202 in MKK7), and can then relay the signal to the JNK level. JNKs, like the other MAPKs, translocate into the nucleus shortly after being activated.[14] The transcription factor c-Jun, which is phosphorylated at serines 63 and 73 and increases AP-1 transcriptional activity, is a prominent JNK substrate. ATF-2, NF-ATc1, Elk 1, HSF-1, and STAT3 are among the transcription factors that JNKs can phosphorylate.

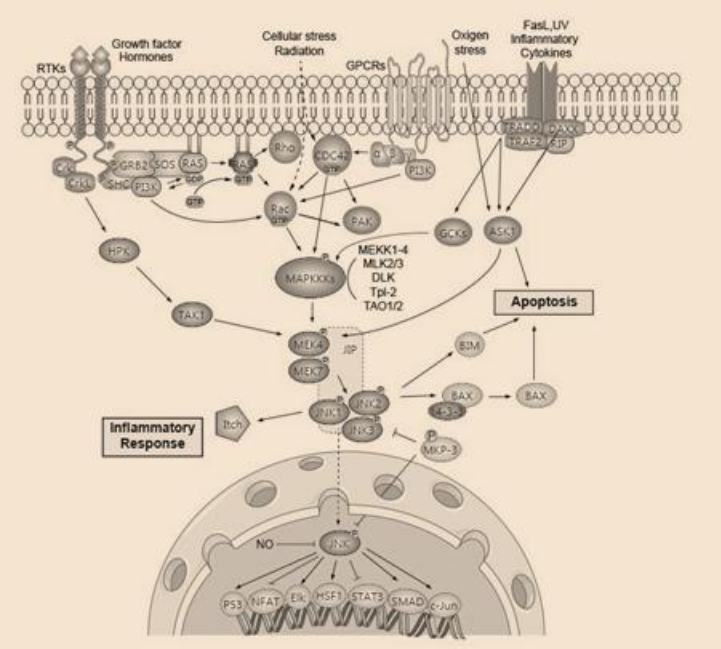

Fig. JNK Signaling Pathway.

JNK binds to and phosphorylates p53 in response to UVB exposure, oxidative stress, and DNA damage. This can result in an increase in p53 transcriptional activity and p53 stability, depending on the phosphorylation location. Ras-induced cancer has been linked to JNK activity and c-Jun phosphorylation, and Ras and c-Jun work together in cellular transformation. Ras causes c-Jun to be phosphorylated on the same locations as JNK, and c-Jun-deficient genetic alterations that inactivate the JNK pathway can cause breast cancer. Breast cancer is linked to loss-of-function mutations in the JNK signalling pathway (e.g., MAP3K1, MAP2K4, and MAP2K7).[15] JNK deficiency's ability to disrupt normal mammary gland development could be important to breast cancer. The role of JNK in breast cancer, however, is unknown.[16]

P38 pathway

The mitogen-activated protein kinase (MAPK) signalling system's p38 pathway is the third key signalling cassette. Environmental stressors and inflammatory cytokines, like the JNK pathway, greatly increase p38 signalling. Inflammation, apoptosis, cell differentiation, and cell cycle regulation are all aided by its activation.[13] MKK3 and MKK6 are the major MAPKKs for p38 modules, but MEK4 can also activate p38 in some cases. MLK2 and MLK3 are MAPKKKs, as are MEKKs, ASKs, TAK1, and TAO1 and TAO2.

The signals are sent by the induction of a complex network of signalling molecules, which frequently culminates in the activation of small GTPases like Rac and CDC42, or via adaptor protein connections. These two processes then activate protein kinases in the p38 cascade, either at the MAP4K or directly at the MAP3K tiers. This vast number of MAP3K tier kinases send signals to a considerably smaller number of MAPKKs, phosphorylating them on Ser and Thr residues in their activation loops using the classic Ser-Xaa-Ala-Xaa-Ser/Thr pattern. MKK6 and MKK3 are the two most important MAPKKs in the p38 cascade. The p38 kinases in the next layer of the cascade are all activated by phosphorylation of the Tyr and Thr residues in the Thr-Gly-Tyr motif in their activation loop.[17]

P38 proteins can move from the cytosol to the nucleus once activated, where they phosphorylate serine/threonine residues in their many substrates.[13] Activated p38 phosphorylate regulatory molecules like PLA2, heat shock proteins, the transcription factors ATF2, ELK1, CHOP, MEF2C, and others.[17]

In breast cancer, p38 activity is increased. In a mouse model of breast cancer, p38 deletion hindered the DNA damage response and increased replicative stress, DNA damage, and chromosome instability, indicating that p38 is necessary for tumour progression (CIN). P38 deletion also lowers tumour volume in a breast cancer model.[18]

PI3K/AKT/mTOR pathway

In response to external signals, the PI3K-AKT System is an intracellular signal transduction pathway that promotes metabolism, proliferation, cell survival, growth, and angiogenesis. This is accomplished by phosphorylating a variety of downstream substrates with serine and/or threonine. Phosphatidylinositol 3-kinase (PI3K) and AKT/Protein Kinase B are two key proteins involved.

PI3K is a kinase that can phosphorylate the 3position hydroxyl group of phosphatidylinositol's inositol ring. PI3K is normally activated by being directly stimulated by the regulatory subunit linked to the active receptor or indirectly via adaptor molecules such as the insulin

receptor substrate (IRS) proteins. A GTP-binding RAS protein can also activate PI3K.

PIP3 phospholipids are docking phospholipids that bind particular domains to facilitate protein recruitment to the plasma membrane and subsequent signalling cascade activation. The 3-position phosphate group of PIP3 can bind to both PDK1 and AKT protein, allowing PDK1 to access and phosphorylate T308 in the "activation loop," resulting in partial PKB/Akt activation. Then, either through mTORC2 or DNA-PK, phosphorylation of Akt at S473 in the carboxy-terminal hydrophobic domain stimulates full AKT activity. AKT regulates cell growth, proliferation, motility, adhesion, neovascularization, and cell death via phosphorylating or suppressing a wide range of proteins involved in cell growth, proliferation, motility, adhesion, neovascularization, and cell death.

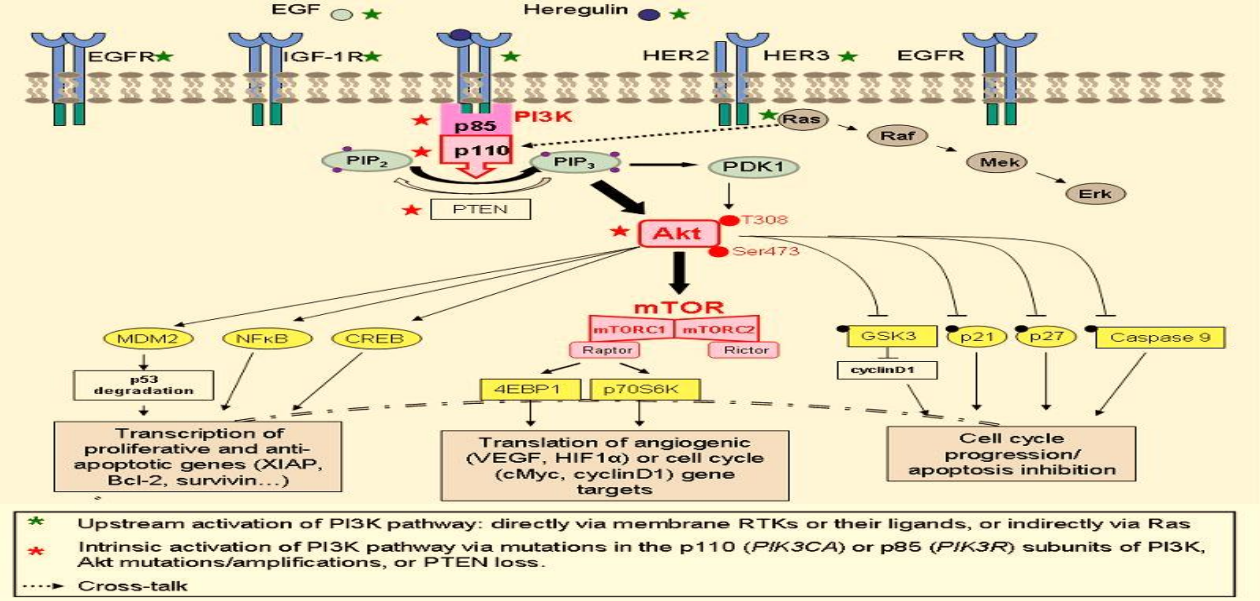

Fig: PI3K/AKT/mTOR Signaling Pathway.

The PI3K/AKT/mTOR pathway is activated by mutations at multiple locations, which contributes to the development of many human malignancies, including breast cancer. Germline and somatic mutations, amplifications, rearrangements, methylation, overexpression, and abnormal splicing are all genomic aberrations that affect the PI3K pathway. In malignancies, activating mutations in PI3K, encoded by PIK3CA and PIK3R1, and AKT1, as well as inactivating mutations in PTEN, LKB1, and TSC2, have been reported.[19,20,21]

NF-kB pathway

NF-kB is a short name of Nuclear Factor kappa-light-chain-enhancer of activated B cells.[22,23]

The canonical and noncanonical routes are the two most well-known NF-kB pathways. Pro-inflammatory cytokines including TNF and IL-1, T- and B-cell mitogens, bacterial liposaccharide (LPS), viral proteins, and physical and chemical stress all activate the classical NF-kB pathway. The activation of TGF-activated kinase 1 (TAK1) is the first step in the classical pathway, which then activates a trimeric IkB Kinase (IKK) complex composed of regulatory (NF-KB essential modulator (NEMO or IKK)) and catalytic (IKK and IKK) subunits.[23] The activated IKK complex catalyses IkB phosphorylation (at Ser32 and Ser36 of IkBa), polyubiquitination, and subsequent breakdown by the 26S proteasome, followed by nuclear translocation of NF-KB, primarily the p50/p65 heterodimer.[22] After binding to the B site, the heterodimer activates a number of genes involved in inflammatory and immunological responses, including cytokines, chemokines, inflammatory mediators, adhesion molecules, and apoptosis inhibitors.

The noncanonical pathway, in contrast to the canonical system, reacts to a small number of receptors, including the lymphotoxin- receptor (LTR), B-cell activating factor belonging to the TNF family receptor (BAFFR), CD40, and receptor activator for NF-KB (RANK). These receptors activate the kinase NF-KB-inducing kinase (NIK), which then phosphorylates and activates IKK, after attaching to its specific ligand. Following proteasomal breakdown of the C terminal IB-like structure of p100, activated IKK phosphorylates the p100/RelB heterodimer at the carboxyterminal serine residues of p100, culminating in p100 processing and nuclear translocation of p52/RelB. After binding to the particular B enhancer, the activated p52/RelB heterodimer promotes transcription of its target genes, which are involved in a variety of biological functions.[22,23]

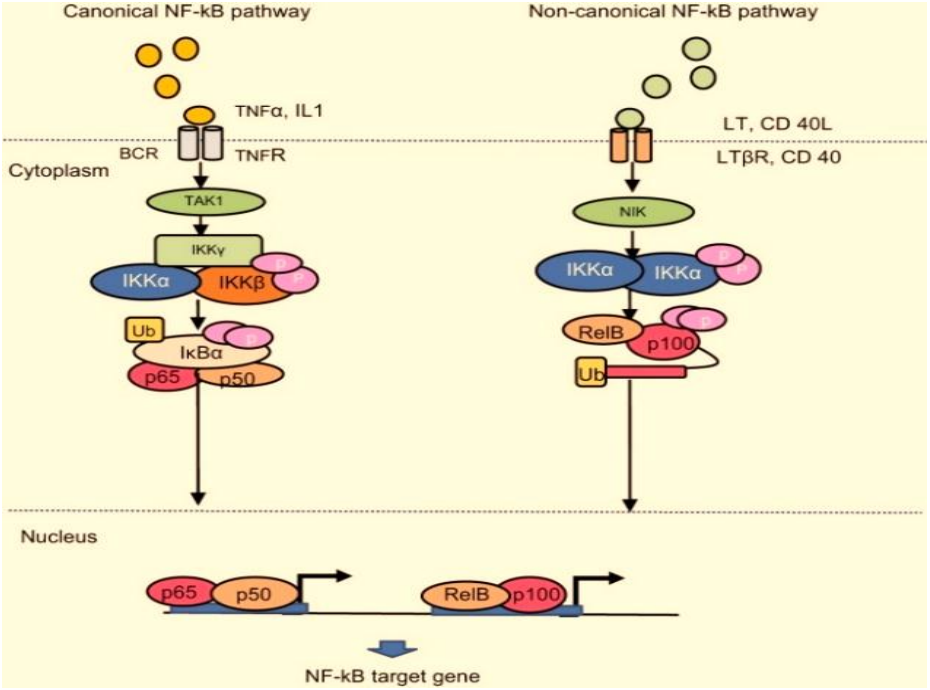

Fig: NF-kB Signaling Pathway.

In breast cancer, the NFB pathway is frequently changed, boosting tumour cell proliferation and survival.[24] Oncogenesis, cell survival, proliferation, angiogenesis, metastasis, and chemo- and radio-resistance have all been linked to constitutive activation of NFB in breast cancer. Although NFB is necessary for proper mammary gland morphogenesis, breast malignancies have been linked to inappropriate constitutive expression of NFB subunits (such as c-Rel, p65, and p50). Excessive innate immune activation and aberrant cell proliferation are two factors that promote tumour development and progression.[24,25]

JAK-STAT Signaling Pathway

Extracellular chemical signals are sent to the nucleus via the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway, which results in DNA transcription and expression of genes involved in immunity, proliferation, differentiation, apoptosis, and oncogenesis. Many cytokines use this route to mediate signal transduction.

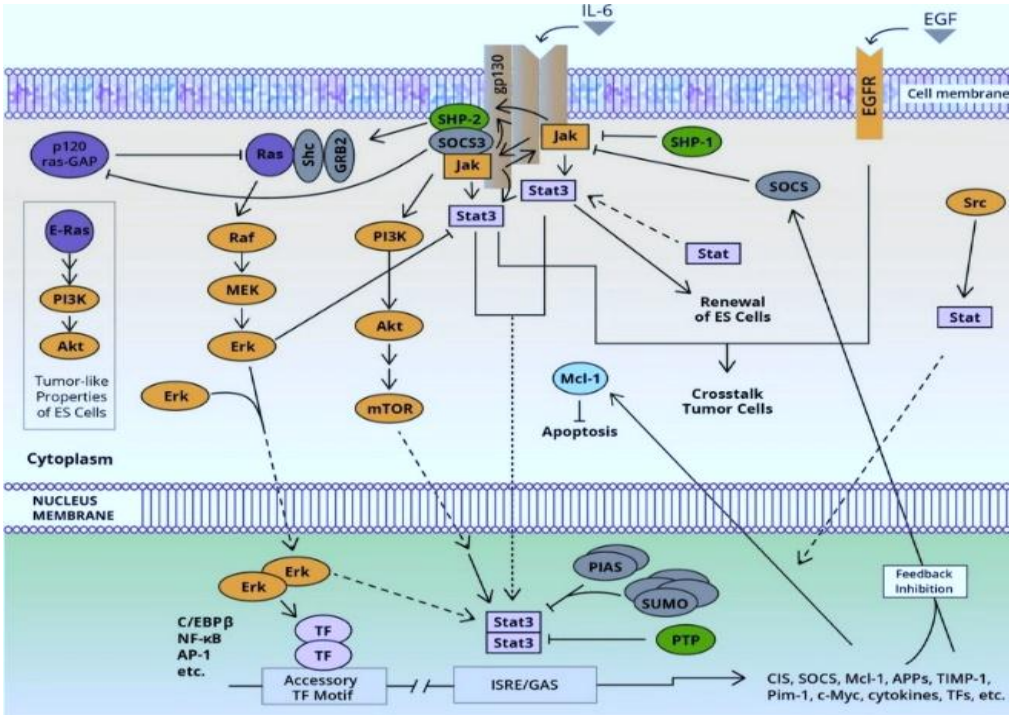

Fig: JAK-STAT Signaling Pathway.

Ligand interaction appears to increase receptor dimerization, which brings their JAKs closer together. JAKs then phosphorylate and activate one another (transphosphorylation). Following that, the active kinases phosphorylate specific tyrosine residues on the receptor. This enhances direct interaction between the receptor and one or more members of the STAT family of cytoplasmic proteins. The JAKs phosphorylate (and so activate) the STATs after they attach at the receptor surface. STATs that have been activated translocate to the nucleus and influence the production of IFN and other cytokine-sensitive genes directly. The JAK-STAT cascade thus provides a direct pathway for extracellular signals to be translated into transcriptional responses.[26,27,28]

JAKs usually engage with tyrosine receptors and then go into a dormant state until ligand binding occurs. Genetic mutations or polymorphisms that cause aberrant activation of the JAK-STAT system results in chronic activation of JAKs in the absence of cytokine signalling, which can lead to carcinogenesis or carcinogenic activity.[28,29]

Hedgehog Signaling Pathway

Hedgehog (Hh) signalling is important for embryonic development, tissue regeneration and repair, and stem cell renewal. By binding to the twelve-transmembrane (TM) receptors Patched1 and/or Patched2 (PTCH1 and PTCH2), the Hh protein family initiates a signalling cascade that results in the degradation of the seven-TM protein Smoothened (SMO).[30] The suppressor of fused (SUFU)-glioma-associated oncogene homologue (GLI) complex is then dissociated by SMO. This causes the transcription factors GLI1 and GLI2 to translocate to the nucleus, where they stimulate gene transcription. GLI1, GLI2, PTCH1, CCND1, IGF2, MYCN, and BCL2 are all Hh target genes that are stimulated by activated GLI proteins.[30,31,32] Hh ligands activate GLI-dependent transcription, which is referred to as "canonical" Hh signaling.[30] The existence of an intact primary cilium is also required for proper Hh signaling.[32] When a Hh ligand binds to PTCH1 in the main cilium, it inhibits and internalises the protein, resulting in the accumulation of SMO in the ciliary membrane and the activation of GLI2 and GLI3. The signalling cascade is stopped when the primary cilium is disrupted.[30,32]

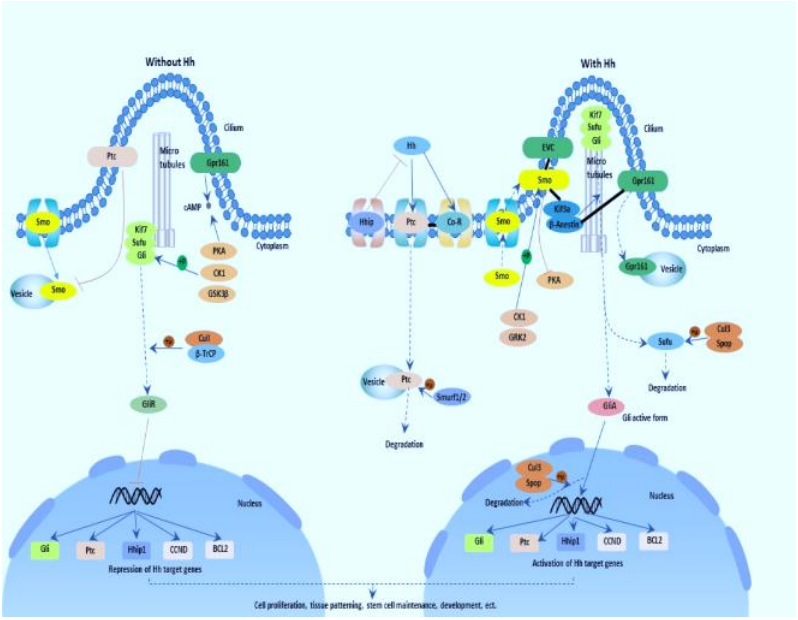

Fig: Hedgehog Signaling Pathway.

During embryonic development, the mammary gland develops, expands during puberty, and differentiates during lactation. At different developmental stages, the components of the Hh pathway are expressed differently in breast tissue.[30]

Hh-mediated malignancy has been linked to two primary pathways. Constitutive Hh signalling activation is caused by either ligand-independent mutations of Hh pathway components or ligand-dependent Hh overexpression.[33] Many cancer types have been linked to the canonical Hh pathway, which has been involved in carcinogenesis and progression. Basal cell carcinoma (BCC) and Shh-type medulloblastoma growth are driven by ligand-independent constitutive activation of GLIs (as a result of PTCH1 loss-of-function mutations or SMO gain-of-function mutations).[30,33]

Notch Signaling Pathway

In all metazoans, the Notch system controls cell proliferation, cell fate, differentiation, and cell death.[34,35]

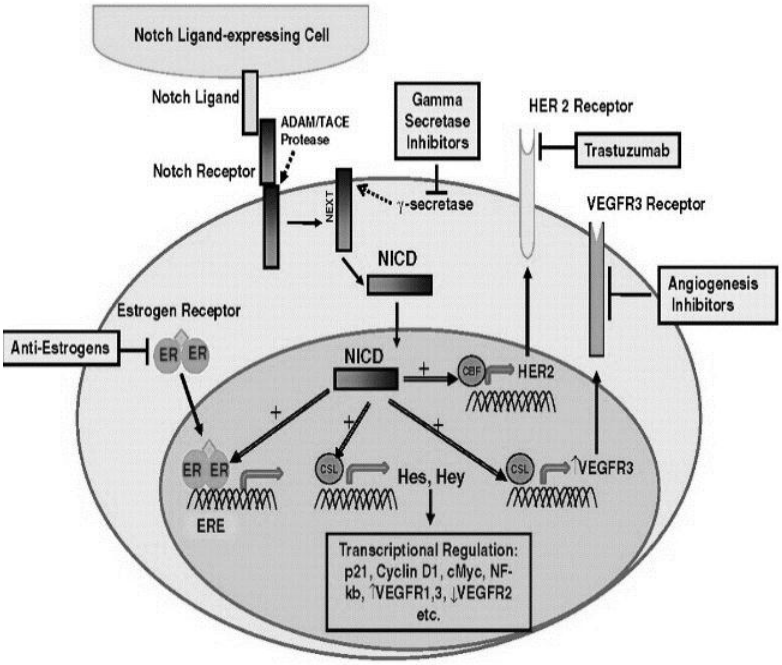

Fig: The Notch Signaling Pathway

The basic signalling pathway for all four Notch receptors is activated by the binding of Notch ligand on one cell to the extracellular domain of a Notch receptor on an adjacent cell. The Notch ligand–receptor complex is then cleaved in a number of places. The cleavage is initiated by the ADAM/TACE family of proteases and occurs at an extracellular location (S2), approximately 12 amino acids outside the transmembrane domain, between Ala (1710) and Val (1711) residues. The NEXT (notch extracellular truncation) product is then cleaved by the -secretase complex, which is made up of two essential proteins called presenilin and nicastrin. -Secretase cleaves NEXT, releasing NICD, which translocates into the nucleus and binds with CSL, a constitutive transcriptional repressor [CBF-1 (C-promoter binding factor 1), Suppressor of Hairless and Lag-1]. After binding to Notch, CSL acts as a transcriptional activator, inducing transcription of downstream targets such as many Hairy/Enhancer of Split associated genes (Hes, Hey), pT, and Notch1 itself, in collaboration with co-factors such as mastermind-like (MAML) proteins. Cell-cycle regulators (p21 and cyclin D1), transcription factors (c-Myc, NF-Kb2), growth factor receptors (HER2), and regulators of angiogenesis and apoptosis are among the transcriptional targets. The activation of notch signalling is suppressed when receptor and ligand are present on the same cell (i.e., interactions are in cis).[34,35]

Many breast cancer cell lines have abnormal expression of Notch ligands, receptors, and target genes. The Notch signalling system has been found to promote an aggressive phenotype partially through NF-B, whereas Notch signalling deactivation abolishes this aggressive phenotype. Furthermore, active NF-B upregulates Jagged-1 in TNBC tumour cells, which increases Notch signalling in CSCs.[36]

The Wnt Signaling Pathway

"Wingless-related integration site" is what Wnt stands for. During embryonic development, Wnts are released factors that govern cell growth, motility, and differentiation.

The Wnt signalling system is an old and evolutionarily conserved pathway that controls important elements of embryonic development such as cell fate determination, cell migration, cell polarity, neural patterning, and organogenesis.

The Wnt/β-catenin signaling cascade: By interacting to the Frizzled (Fz)/low density lipoprotein (LDL) receptor-related protein (LRP) complex at the cell surface, Wnt proteins produced from or displayed on the surface of signalling cells act on target cells. Dishevelled (Dsh), glycogen synthase kinase-3 (GSK-3), Axin, Adenomatous Polyposis Coli (APC), and the transcriptional regulator, -catenin, are all transduced by these receptors. After phosphorylation, -catenin is ubiquitinated by -trcp and then destroyed by the proteasome. Continuous proteasome-mediated degradation, which is controlled by a complex involving GSK-3/APC/Axin, keeps cytoplasmic -catenin levels low. When Wnt signals are received, the degradation pathway is blocked, and -catenin accumulates in the cytoplasm and nucleus. Nuclear -catenin regulates transcription by interacting with transcription factors like lymphoid enhancer-binding factor 1/T cell-specific transcription factor (LEF/TCF).

The Wnt-PCP signaling cascade: On a cellular level, this route controls cell polarity by affecting the cytoskeletal architecture.

The Wnt-Ca2+ signaling cascade: Wnt 5a and Wnt 11 activate the Wnt/Ca2+ pathway, which involves an increase in intracellular Ca2+ and activation of Ca2+-sensitive signalling components like calmodulin-dependent kinase, calcineurin phosphatase, and the transcription factor NF-AT.[37,38]

During embryogenesis, postnatal development, and pregnancy with adult mammary glands harbouring Wnt-responsive stem cell populations, Wnt signalling is required for proper breast stem cell activity and mammary gland development. Abnormal Wnt signalling in breast cancer stem cells (BCSCs) has been identified as a crucial event in breast carcinogenesis. In TNBC cells and CSCs, Wnt/-catenin signalling has been linked to carcinogenesis by modulating critical tumor-associated features such as motility, stemness, proliferation, and chemoresistance.[39]

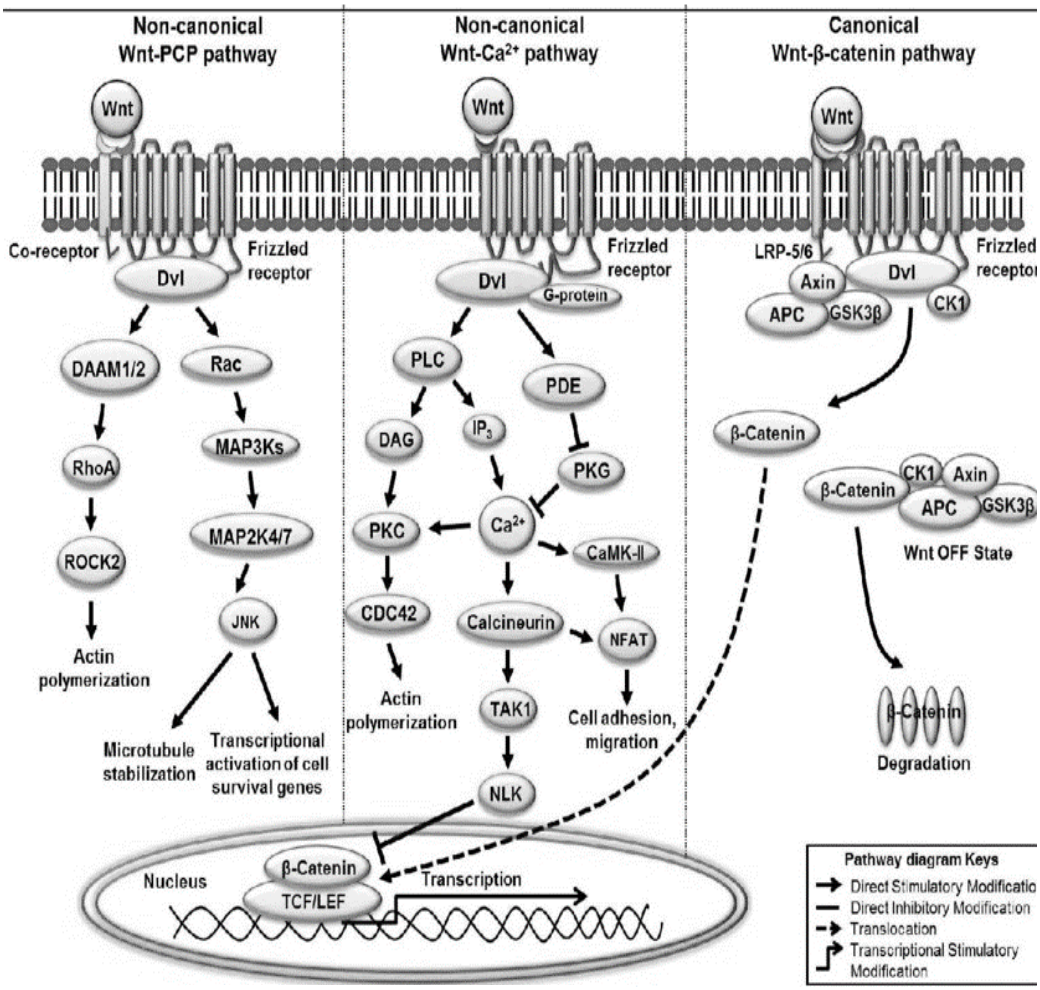

Fig: Canonical and non-canonical Wnt Signaling Pathway.

CONCLUSION AND FUTURE PROSPECTS

The continual progress in understanding the altered molecular events in cancer cells has resulted in a flood of new targets and medicines for clinical testing. The targeting of the ER and HER2 pathways offers hope for identifying those most likely to benefit from a targeted treatment that might operate as a single agent while also improving the efficacy of already available chemotherapeutics. Various targets will almost certainly need to be targeted for maximum therapeutic benefit due to the redundancy of biological pathways and the multiple concurrent abnormalities in cancer cells. Furthermore, several of the medicines have yet to well-defined, verified, and recognisable targets in individual patients. This stymies the best development of these drugs, as patient selection is crucial for identifying activity of a drug that only acts in tumours with specific biologic properties. Clinical trial designers will need to find and refine biologic assays that can quantify the impact of these medicines on the targeted pathways as a result of therapy. New agent trials in the neoadjuvant environment may be one strategy to validate therapeutic targets, with the possibility of acquiring repeated biopsies for suspected drug activity biomarkers and correlating with response. However, better response and/or biologic end points in the neoadjuvant setting have not been established to predict survival benefit in the adjuvant setting definitively. It's possible that single-

agent testing of these drugs in refractory populations isn't the best way to find clinical benefit, and that rational testing of combinations with chemotherapy, endocrine therapy, and radiation therapy is required to take advantage of the potential synergies of these approaches. Furthermore, the known "cross-talk" between some of these pathways can propose rational combinations for testing in order to enhance the inhibition of abnormal cellular signalling.

Conflicts of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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