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REVIEW ARTICLE

# Tumor microenvironment pathways: Cross regulation in breast cancer metastasis

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Wnt

**Abstract** The tumor microenvironment (TME) is heterogeneous and contains a multiple cell population with surrounded immune cells, which plays a major role in regulating metastasis. The multifunctional pathways, Hedgehog (Hh), Wnt, Notch, and NF-kB, cross-regulates metastasis in breast cancer. This review presents substantial evidence for cross-regulation of TME components and signaling pathways, which makes breast TME more heterogeneous and complex, promoting breast cancer progression and metastasis as a highly aggressive form. We discoursed the importance of stromal and immune cells as well as their crosstalk in bridging the metastasis. We also discussed the role of Hh and Notch pathways in the intervention between breast cancer cells and macrophages to support TME; Notch signaling in the bidirectional communication between cancer cells and components of TME; Wnt signal pathway in controlling the factors responsible for EMT and NF-κB pathway in the regulation of genes controlling the inflammatory response. We also present the role of exosomes and their miRNAs in the cross-regulation of TME cells as well as pathways in the reprogramming of breast TME to support metastasis. Finally, we examined and discussed the targeted small molecule inhibitors and natural compounds targeting developmental pathways and proposed small molecule natural compounds as potential therapeutics of TME based on the multitargeting ability. In conclusion, the understanding of the molecular basis of the cross-regulation of TME pathways and their inhibitors helps identify molecular targets for rational drug discovery to treat breast cancers.



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## Breast cancer

Breast cancer (BC) is one of the most common deadliest malignancies affecting women worldwide. It accounts for 30% of total cancer incidences and half a million deaths in the last two decades. The subpopulation of BCs with characteristic self-renewal capacity and differentiation is responsible for tumorigenicity and high metastatic and cancer recurrence.[1] Currently, BCs are being treated by surgical, chemo, and radiation therapy, but most BC patients remain incurable and lead to high mortality in women.[2] The progression and development of the metastatic stage are one of the major death-related causes of BCs. In addition, dysregulated signaling pathways also responsible for excessive cell proliferation and survival. The major signaling pathways which dysregulated are the Hedgehog pathway (Hh), Notch, Wnt, and NF-kB.[3] These pathways play a central role in the proliferation, differentiation, as well as evasion of apoptosis. Recent studies have shown the importance of these pathways in the breast tumor microenvironment (TME). The breast TME has high inflammation reinforced by the infiltrated immune cells, growth factors (GFs) and cytokines. Breast tumors along with immune infiltration shows different patterns based on the presence of ER. Regulatory T-cells with negative immune feature associated with both ER-positive and ER-negative breast tumors and confess an immunosuppressive environment.[4] This characteristic feature has an importance in the immune TME of breast cancer.

## Tumor microenvironment

The tumor microenvironment (TME) contains multiple cell populations, such as the tumor cells, surrounded by immune cells and stromal cells, which play a critical role in promoting tumor growth and progression.[1] The TME is continuously changing during the progression of tumor growth. The subtypes of breast tumors differ in the TME. The stroma consists of different connective tissues, which acts as a framework for tissues and many organs.[1] Among all, fibroblasts are important in synthesizing extracellular matrix. The primary tumor mass surrounding the TME encompasses the metastatic destination, which resembles a similar network of communication. The connection between cells of TME acts as a signaling bridge, which activates angiogenesis, migration, cell adhesion, and invasiveness.[5] The cell population of TME, which are non-malignant, but resides in the extracellular matrix (ECM) and constituents of matrices, are cancer-associated fibroblasts (CAFs), tumor-associated endothelial cells (TAEs), and tumor-associated osteoblasts and osteoclasts (TAOs). The cancer cell behavior is influenced by stromal cells through the secretion of ECM proteins, growth factors, cytokines, and chemokines. Stromal cells influence cancer cells by secreting various proteins via activating autocrine and paracrine loops. The stromal cell interaction and underlying genomic instability in cancer cells govern the tumor cell morphology, growth, and metastasis. Within the breast TME, the stromal cells with alterations in the molecular and aberrant signaling pathways have prognostic significance in the clinical setting.[6]

Intratumoral hypoxia increases the risk of metastasis and drug resistance by promoting neovascularization. It also influences metastasis and drug resistance by recruiting stromal cells, remodeling ECM, forming premetastatic niche, inducing cell migration and local invasion, and maintaining the cancer stem cell phenotype in breast TME.[7] Inflamed TME promotes metastasis of breast cancer cells to bone or lung, or the brain depends on their interaction with TME cells. It also induces cancer cell proliferation, angiogenesis, invasion of apoptosis, and suppression of antitumor immunity. Additionally, TME frequently imparts a niche for the stay and interaction of cancer cells with surrounding stromal and immune cells. The cancer cells and stromal cells' interactions predispose breast cancer metastasis by remodeling TME cellular components, ECM, and neovascularization. TME promotes metastasis and drug resistance by inducing epithelial cell transition to stem cells.[8] TME induces oncogenic metabolic reprogramming, including increased glycolytic activity, TCA cycle, glutaminolysis, and biosynthesis of fatty acids that influence breast cancer progression.[9] TME also actively contribute drug resistance and heterogeneity by providing an environment for the interaction of breast cancer cells with surrounding stromal cells. Theses interactions tightly regulate vital steps of invasiveness by various signaling pathways. Recent studies explored significant alterations in gene expression in TME cells, which helps cancer progression by promoting cancer hallmarks.[10] In addition to stromal cells, major immune cells infiltrate into TME and associate with the negative prognosis of BCs. They include tumor-associated macrophages (TAMs), tumor-associated neutrophils (TANs), tumor-associated dendritic cells (TADCs), myeloid-derived suppressor cells (MDSCs), and regulatory T-cells (Tregs). The stromal and immune cells with unique functions shape breast TME (Fig. 1).

## Tumor-associated macrophages

A subclass of myeloid cells differentiates into TAMs by the tumors within TME. The TAMs mediate different opposing function based on tumor-derived cytokines.[11] They include M1 (classically activated) as well as M2 (alternatively activated) macrophages. M1 macrophages activate the target genes associated with anti-tumor immune response,[12] while M2macrophages mediate an anti-inflammatory activity in response to cytokines.[13] The TAMs are major mediators of the TME remodeling.

## Cancer-associated fibroblasts

Fibroblasts are phenotypically similar to mesenchymal cells, form a tumor stroma. They play an important role in the secretion and remodeling of ECM.[14] CAF's are the specialized group of fibroblasts, which promotes the growth and invasion of tumor cells by providing unique TME.[15,16]

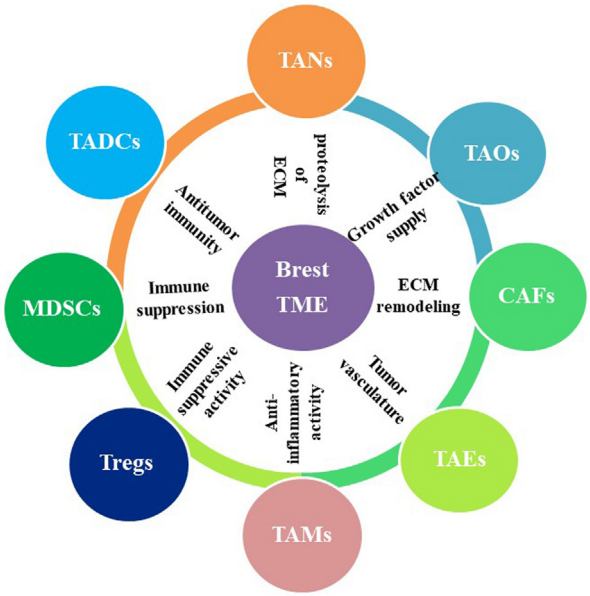


**Figure 1** Role of major stromal and immune cells in shaping breast tumor microenvironment. Cancer associated fibroblasts (CAFs) promotes the growth and invasion of breast tumor cells by enhancing ECM remodeling in TME. Tumor associated osteoclasts and osteoblasts (TAOs) increase the metastatic behavior by supplying growth factors and cytokines. Tumor associated endothelial cells (TAEs) promotes invasion, metastasis and drug resistance by forming vasculature. Tumor associated macrophages (TAMs) activates the target genes associated with anti-tumor immune response and anti-inflammatory activity in response to cytokines. T-regulatory cells (Tregs) diminish T-cell immunity to tumour-associated antigens by expressing high levels of immune checkpoint molecules. Myeloid derived suppressive cells (MDSCs) induce infiltration and secretion of IL-6, which in turn trigger metastasis. Tumor associated neutrophils (TANs) promotes tumor growth, invasion and metastasis via proteolysis of ECM. Dendritic cells (DCs) recognize critical mediators of TME and promotes anti-tumor immunity.

The CAFs maintain the integrity of ECM and promotes the remodeling of ECM by secreting many proteases.[17] The activated fibroblasts, which are stimulated by inflammatory condition, also promotes wound healing.

## Tumor-associated endothelial cells

Proangiogenic behavior of tumor-associated endothelial cells (TAEs) is highly influenced by the hedgehog pathway, where the ligand of Hh encourages migration, invasion, and proliferation of endothelial cells. It is believed that the nuclear translocation of Gli facilitates through the activation of integrin in the presence of Hh ligands.[18] The expression of MMP9 and Osteopontin, in ECs causes the phosphorylation of focal adhesion kinases.[19] The TAEs are mostly responsible for tumor cell invasion, metastasis, stem cell maintenance, promotion of neutrophil infiltration, and drug resistance.[20] Together, TAEs assist cancer progression and metastasis in the TME.

## Tumor-associated osteoblasts and osteoclasts

The cancer-associated osteoblasts and osteoclasts (TOAs) are the centerpiece of the metastatic bone microenvironment (BME). Bone is made of mineralized matrices, and mineralized tissues promote the development of bone metastasis.[21] Mineralized bone matrices contain many GFs such as IGF's, TGFβ, and FGF-1 etc.[21] The most abundant GF stored in bone is IGF-1, which stimulates cell growth of breast cancer. Overexpression of IGF-1 increases the bone metastasis and reduces the apoptotic breast cancer cells.[22] The IGF-1 is released from bone as a result of osteoclastic bone resorption, which plays an important role in the proliferation and inhibition of apoptosis in metastatic breast cancer cells. TGFβ is also stored in bone in large amounts and released during osteoclastic bone resorption. A subpopulation of TAOs is edified via crosstalk with BCs by secreting inflammatory cytokines in the bone TME.[23] The BME has a unique biological feature, through which cancer cells circulate and proliferate.

## Myeloid-derived suppressor cells

Myeloid-derived suppressor cells (MDSCs) are specialized immune cells characterized by the presence of high CD33 and CD14 and low HLA-DR in tumors. In TME, breast cancer cells induce MDSCs for infiltration and secretion of IL-6, which triggers metastasis in BCs.[24] These cells are formed in the bone marrow and then move to tumor tissues. They have an important role in tumor progression by suppressing anti-tumor immunity.[25] These myeloid-derived suppressor cells form a differentiation pattern, which results in the rapid differentiation of TAMs. Mostly in relation to these cells in peripheral lymphoid organs, these cells suppress the T-cell in a non-specific manner.[26] They are major tumor favoring and immune suppressor cells, promotes tumor metastasis.

## Tumor-associated neutrophils

Neutrophils are major kinds of myeloid cells derived as white cells and circulating in the human blood.[27] The N1 neutrophils counteract the cancer cells by cytotoxicity, tumor rejection, and anti-tumor immunity. Recent studies reported that N1 neutrophils are polarized to N2 or Tumor-associated neutrophils (TANs) in the TMEby TGF-β and IFN-β. The N2 neutrophils are harmful to the host but beneficial for tumor growth, invasion, and metastasis via ECM proteolysis.[28] Furthermore, ROS and proteinases released by neutrophils impact regulation of cancer cell proliferation, angiogenesis, and metastasis.[29] Neutrophils significantly influence the TME by releasing cytokines and chemokines, which promotes recruitment and activation of inflammatory cells.

## Tumor-associated dendritic cells (TADCs)

Dendritic cells (DCs) are compelling antigen-presenting cells, recognized as critical mediators of anti-tumor immunity. The prostaglandin E2 and β-catenin mediates the

impairment of the function of tumor-associated DCs.[30] Recently, regulatory DCs with immune suppressive activity are reported in TME by MDSCs.[31] The TADCs interfere with the activation of NK-cell pathways or receptors that control NK-cells' activation and reduce anti-tumor activity.[32] Thus, identification of TME mediated immune cells together with stromal cells, represent key questions for the design of effective therapies of breast cancers.

## Regulatory T-cells

The regulatory T cells (Tregs) are essential for the maintenance of T-cell tolerance to self-antigens. High infiltration into tumors is frequently associated with poor prognosis. The Tregs have distinct characteristics, including high expression of chemokine receptor (CCR4) and CTLA-4 in breast cancers.[33,34] A subsets of Tregs with high expression of immune checkpoint molecules support tumor progression.[35] They diminish T-cell immunity to tumor-associated antigens.[36] TME promotes differentiation and proliferation of Tregs as well as secretion of immunosuppressive signals for the recruitment of immunosuppressive cells.[37] CAFs increase the ability of regulatory T cells to inhibit the proliferation of T effector cells.[38] However, the proliferation of Tregs is distinctly inhibited by CDK4/6 inhibitors.[39] These distinct characters offer an opportunity for the design of targeted immunotherapies.

## Crosstalk between TME cells

### Crosstalk between cancer cells and stromal cells

The TME promotes the progression as well as metastasis of tumor cells by acquiring specific crosstalk between stromal and cancer cells. For example, under hormonal influence, stromal cells promote tumor progression by releasing chemokines and cytokines.[40] Cancer cells co-opt with reactive stromal cells by releasing pro-tumorigenic factors, which recruit other pro-tumorigenic cells for architecting TME. The interaction of stromal cells and TAMs promotes metastasis via the IL-33-ST2-dependent pathway.[41] The crosstalking of cancer cells with ECM and stromal as well as immune cells, promote the polarization of monocytes into TAM. CAFs recruit granulocytes to tumors by releasing chemokines CSF1,[42] suggesting that crosstalk between cancer cells and stromal cells mediates the tumor progression by signaling molecules.

### Crosstalk between cancer cells and immune cells

The role of tumor-associated immune cells in the remodeling of TME is countless. TAMs are abundantly rich in TME communicate with tumor cells and stromal cells through complex signaling mediated by chemokines, cytokines, GFs, and proteases.[43] The TAMs also have cross-talk with immune cells and tumor cells to induce epithelial to mesenchymal transition (EMT) via JAK2/STAT3/miR-506-3p/FoxQ1 axis.[44] TAMs communicate with tumor cells for the formation of vasculature by secreting IL-1$\alpha$ and activating NF-kB.[45] TAMs mediate tumor-induced angiogenesis, a critical metastasis phenomenon by cross-talking innate immunity and humoral response cells with cancer cells in the TME.[46] The crosstalk of TAMs with tumor cells promotes metastasis by increasing migration of tumor cells,[47] suggesting that TAMs are the major mediators of crosstalk between BCs and immune cells in promoting metastasis.

### Exosome mediated crosstalk between TME cells

Exosomes are nanovesicles recognized recently as mediators of intercellular crosstalk. CAFs have dynamic crosstalk with tumor-associated immune cells, TAEs via exosomal proteins, and activates the CSC within TME.[48] CAFs communicate with cancer cells by transmitting exosomal microRNAs, lncRNAs, and proteins. CAFs induce stemness and drug resistance by delivering lncRNA H19 containing exosomes[49] indicating that key tumor-associated stromal cells contribute to tumor progression by modulating TME.

Tumor cells cross-talk with TAEs for the formation of new blood vessels by secreting VEGF-enriched exosomes.[50] Cancer cells disseminate through the pro-metastatic crosstalk with endothelial cells by providing exosomal miRNAs.[51] The crosstalk of cancer cells with surrounding TME cells activates oncogenic signaling and abnormal expression of angiogenesis-associated genes via tumor-derived exosomal lncRNAs.[52] Tumor cells interact with TAEs to regulate angiogenesis via derived exosomal microRNA-194.[53] Cancer-derived exosome-mediated crosstalk of stem cells with immune cells and blocks their anti-cancer activity by promoting transform them into suppressor cells via transferring miRNAs.[54] Exosome mediated cross-talk induces tumor phenotypes in mesenchymal stem cells by activating glycolysis.[55] Even, exosomes derived from M2 -macrophage induces migration and invasion of cancer cells. Exosomes enriched with lncRNAs from CAFs reinforcing their crosstalk with tumor cells.[56] These studies propose that blocking the interaction of exosomes and the components of TME has potential in therapeutic approaches.

### Multifunctional pathways of TME

The highly conserved ancient and multifunctional developmental signaling pathways, including Hh, Notch, and WNT, as well as NF-kB pathways, are hyperactive in TME and regulate the basic cellular mechanisms such as proliferation, differentiation, and survival and trigger most of the critical cell fate decisions (Table 1).

### Hedgehog signaling pathway

The Hh pathway plays a significant role in tissue regeneration, self-renewal, and embryonic development. The Hh protein family comprises Sonic hedgehog (Shh), Desert hedgehog (Dhh), and Indian hedgehog (Ihh). The Ihh is

**Table 1** Summary of biological functions and target activity of developmental pathways.

| Developmental pathway | Biological function | Target of activity |
|---|---|---|
| Hedgehog pathway | • Tissue regeneration and embryonic development | • Activates fibroblasts |
| | • Ihh promotes differentiation of bone | • Regulates TGF-β and PDGF |
| | • Dhh mediates differentiation of gonads | • Regulates normal growth and tissue repair |
| | • Shh inferior survival of TNBC | • Intervenes TAMs with BCs |
| | • Gli 1 involve in transcriptional activation of genes | • Stimulate generation of proliferative and pro-survival molecules |
| | • Gli-3 associate with transcriptional repression of genes | • Regulates self-renewal capacity |
| | • Gli-2 control both transcriptional activation and repression | • Promotes tumor initiation and metastasis |
| Notch pathway | • Normal embryo development | • γ-secretase activates transcription of Notch genes |
| | • Transformation of normal cells into cancerous cells | • Notch ligands promotes pathological angiogenesis |
| | • Jogged correlates with mortality of BCs | • Regulates stem cell phenotype |
| | • Differentiation of breast epithelial cells during normal development | • Promotes metastasis |
| Wnt pathway | • Governs cellular and developmental processes | • Activates EMT pathway |
| | • Directs tissue homeostasis and stem cell proliferation | • Mediates the progression of BCs |
| | • Stimulates intracellular signal transduction | • Mediates lung and brain secondary metastases |
| | • Implicated in breast tumorigenesis | • Promotes metastasis |
| | • Essential for normal breast stem cell function | • Control stem cell like features in breast cancer cells |
| NF-kB pathway | • Cytokine production | • Oncogenic mechanism enhances tumor progression and metastasis |
| | • Mediates inflammatory response | • Protective mechanism destroys transformed cells |
| | • Regulates immune response | • Activates cytokine genes |
| | • Required for normal mammary gland morphogenesis | • Modulates cell cycle and apoptosis |

primarily involved in the differentiation of bone, Dhh intricates in the differentiation of gonads, and Shh is broadly expressed and best studied in the Hh pathway.[3,57] These proteins activate the signaling cascade that binds to the 12-pass transmembrane (TM) receptorsPatched1 and 2 (PTCH1/PTCH2). These receptors differ in amino acid composition in the human population. In the cell membrane, SMO activates the TFs of Gli via Intraflagellar transport proteins (IFT). These proteins are important for the functioning of cilia.[58] The Gli- TFs are the zinc finger family members, consisting of Gli-1,-2, and -3. Gli-1 plays a role in gene activation, whereas Gli-3 is repressive, and Gli-2 plays a role in both activation and repression. Hh pathway also intervene between breast cancer and macrophages that support the TME.[59,60]

For tumor initiation and metastasis, the tumors supplant many signaling pathways, which participate in normal growth and tissue repair. The mammalian embryos involve many signaling pathways in development, regulating cell proliferation, growth, vascularization, and tissue patterning.[61] The range of Hh signaling in TME is extensive. The TME contains non-tumor cells, which are important for the promotion of cancers.[62,63] Shh pathway directly targets fibroblasts.[64] Further, sustained synthesis of Shh leads to genetic instability and accumulation of mutations. Hh signaling regulates several proteins such as TGF-β and PDGF,[65,66] which activate fibroblasts to produce proliferative and pro-survival molecules.

## Notch signaling pathway

Notch signaling, a highly conserved pathway, is important for the development of the normal embryo as well as tissue homeostasis.[67] It is related to diverse types of cancer. The Notch receptor is cleaved into two fragments and is placed in the plasma membrane, which is linked to a heterodimer of the N- and C-terminal fragments. After binding with the ligand, the receptor is a cleavage in two steps, one is mediated by ϒ-secretase complex, which releases the active intracellular domain, and the mastermind mediates the other step like protein, which activates the transcription of the Notch target gene. Notch signaling acts as a promising target for BC treatment. High levels of Jagged and Notch correlates with the mortality of BCs.[68,69]

Notch signaling was recognized as an important pathway in BCs development by a series of experiments. The first indication was on the study of mouse mammary tumor virus

(MMTV).[70,71] The MMTV activates protooncogenes by flanking, which causes the malignant transformation of the mammary gland that results in truncated Notch 4 proteins. Cancer progression and metastasis depend on bidirectional communication between cancer cells and the environment, thus forming TME.[72,73] The role of this pathway in cancer acts as a tumor-suppressive pathway. Notch signaling in TME expresses various ligands and receptors that induce between sending a signal and receiving a signal. Notch signaling in TME is involved in pro and anti-tumor effects.

## Wnt signaling

Wnt signaling is a regulatory pathway that governs the cellular and developmental process. The research on the Wnt pathway has established gene products of wingless in drosophila.[74] Wnt pathway consists of a hydrophobic and cysteine family -rich glycolipoprotein, which directs the tissue homeostasis and stem cell proliferation. Humans contain 19 genes that encode Wnt, which connects to receptors and stimulate the intracellular signal transduction pathway.[75,76] This pathway is either canonical, which depends on β-catenin, and non-canonical, which is independent of β-catenin.

The canonical pathway is triggered by the interaction of the frizzled receptor (Fz) with Lipoprotein receptor protein ($LRP_5$). When Wnt bounds this receptor, the receptor complex stimulates the canonical pathway.[77] When this pathway gets activated, Fz gets to interact with a cytoplasmic protein called Dishevelled (Dsh), which acts as an upstream regulator of β-catenin.[78,79] The non-canonical pathway utilizes downstream signaling, which evokes the response in transcription. This pathway activates the $Ca^{2+}$ signaling cascade. Binding of Fz to Wnt ligand causes the activation of membrane-bound phospholipase C[80,] indicating that the pathway results in cancer progression and neurodegenerative diseases.

EMT is an essential process in which the epithelial cells lose their contact and acquire properties that resemble mesenchymal cells. The TME also assists in metastasis of cancer, which induces EMT.[81,82] The GFs of TME is also responsible for Wnt signal activation. Platelet-derived growth factor (PDGF) is one of the growth factors that activate Wnt signaling, Phosphorylation of P68 led by PDGF promotes β-catenin signaling. VEGF is another GF, which stabilizes β-catenin levels in endothelial cells. $PGE_2$, which is secreted by TAEs of TME.[83,84] The regulation of Wnt signaling is associate with aggressive and hyperproliferative behavior of BCs. The knowledge expanded in the recent past provides an opportunity for the rational design of novel BC therapeutics.

## NF-κB signaling pathway

The nuclear factor kappa-light chain enhancer of activated B cells (NF-κB) involve in the cytokine production. It mostly regulates immune response, which is linked to cancer, inflammation etc.[85] NF-κB is a superfamily of transcription factors (TFs) discovered in 1986includesRelA (p65), C-Rel,RelB,NF-κB1 (p50)and NF-κB (p52).[86,87] The N terminal region contain Rel, which is responsible for the binding of specific DNA, while the C-terminal is responsible for binding with other TFs.[88,89] NF-κB is present in the cytoplasm as inactive form by complexing with inhibitor subunits $I_κB$-α,-β and-ϒ.[90,91] The dissociation of inhibitory subunits ($I_kBs$) results in the activation and rapid translocation of KF-kB to the nucleus.

Increased expression of NF-κB genes results in tumor progression and metastasis.[92,93] The role of NF-κB in tumor growth with reference to TME is very complex because of different functions.[94,95] Human breast cancers form the nuclear accumulation in classic form KF-kB dimer $p^{50}/p^{65}$. The activated NF-κB dimer increases the proliferation of cancer cells and decreases apoptosis.[96] Stimulation of NF-κB in solid tumors results in the loss of mutations, which results in inflammatory TME.[97,98] The chronic inflammation develops many other changes in the cellular environment such as metabolic changes, DNA damage etc.[99] The inflammation response involved in the release of cytokines and activation of the canonical NF-κB signaling pathway. However, the activated pathway destroys transformed cells.[100,101] This is mostly owing to the protective mechanism against cancer cells. In breast cancer, leukocytes infiltrating tumors in the stroma may lead to cancer progression and result in the increase of malignancies in breast epithelial cells involving NF-kB signaling.[102,103] Activation of this pathway regulates the expression of various cytokine genes.[104,105] NF-κB is a major player of chronic disease, which includes cancer. Therefore, it can be used to predict the prognosis of breast cancers.

## Cross regulation of TME signaling pathways

The TME is the birthplace for the activation of various developmental pathways and is prompted by crosstalk's mediated by signaling (Fig. 2). The Hh pathway is required for embryonic development as well as in the formation of different tumors.[106,107] NF-κB recognized as the TF in response to inflammation results in the overexpression of Shh in cancer. Out of three ligands in Hh, Shh plays an important role.[108,109] The Shh is function through two transmembrane proteins, such as SMO, patched, and TFs related to the Gli family. Cancer development and the chronic inflammation association is recognized for many years. Different cytokines, i.e., TNF-α and IL-1, majorly contribute to the inflammatory response. The Shh pathway, which is induced by NF-κB, increases proliferation of cancer cells in a ligand dependent manner.[110]

The intracellular pathways mediated Raf/MK/ERK associate with Gli 1/2 proteins and regulated the transcription of Jagged 2, a Notch ligand, indicating a link between Hh and Notch signaling.[111] Hes1, a Notch target protein, promptly binds to Gli1 promoter and suppresses its transcription triggering the low activity of Hh.[112] Besides, expression of Jagged 1 has a promising association with Notch and WNT pathways.[113,114] Lately, Notch 2 was recognized as the target of the WNT/β-catenin pathway.[115] Unexpectedly, Notch 1 has suppressive activity on WNT/β-catenin target genes.[116] Wnt and Hh pathways regulate

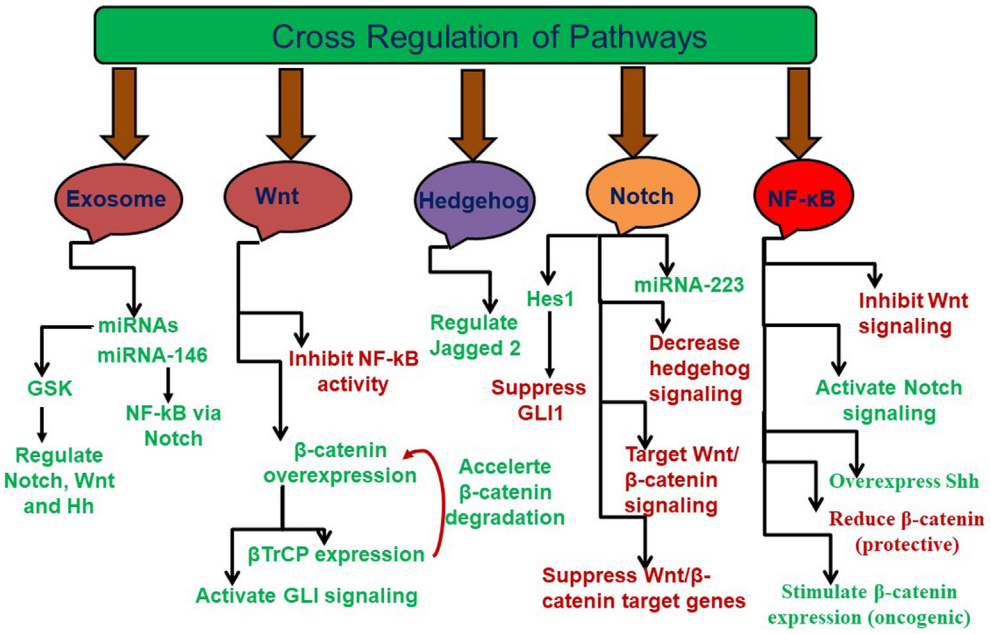


**Figure 2** Cross regulation of TME pathways. NF-kB signaling inhibits Wnt signaling, activate Notch signaling, overexpress Shh, reduces β-catenin activity in protective mechanism and stimulates β-catenin expression in oncogenic mechanism. Notch signaling pathway decreases Hh signaling, targets Wnt/β-catenin signaling, suppresses Wnt/β-catenin target genes and activates exosomal miRNA-223. Hes 1, a Notch protein suppresses GLI1 expression. Hh pathway regulates Jagged 2. Wnt pathway inhibits NF-kB activity, overexpress β-catenin, activates βTrCP expression and activates GLI1 via β-catenin. Exosomal miRNAs regulates Notch, Wnt and Hh signaling via GSK. Exosomal miRNA-146 activates NF-kB signaling via Notch.

among each other that affect their outcome, which results in the TFs. The activation of Hh signaling is a key step for tumorigenicity in breast cancer cells. There is existence for the positive results between the Hh and Wnt, which are present in the epithelial transformation, where there is an activation of Gli expression throughout the signaling. One side β-catenin enhances directly with the luciferase activity and results in the induction of post transcription, which stabilizes Gli mRNA, which upregulates the CRD-BP (coding region determinant-binding protein).[117] On the other hand, induction of Gli through activation of Wnt2b, Wnt 4, Wnt7b, which triggers the Wnt pathway that promotes the β-catenin.

In relation to Hh, Notch signaling is also involved in the differentiation of multiple tissues. Notch pathway also increases the survival and self-renewal capacity of hematopoietic progenitors that controls the regulation of T-cell expansion.[118] Hh and Notch pathways play similar roles during the development of T-cell. Both Hh and Notch pathways maintain the balance of intracellular levels through the integration of other signaling pathways.[119] Hh signaling results in the formation of tumor growth and cancer stem cells.

β-catenin interacts and is inhibited by NF-κB that functions in the breast cancer cells. β-catenin results in the formation of the complex with RelA and p50 that decreases NF-κB binding to DNA and increases transactivation activity and targets the gene expression. β-catenin activation is inhibited by the expression of NF-κB target genes.[120] Many studies have revealed the negative regulation of NF-κB that has stimulatory effects of β-catenin. Activation of the Wnt pathway results in the overexpression of β-catenin that increase βTrCP expression. βTrCP induction by β-catenin accelerates the degradation of β-catenin that serves as negative feedback.[121,122]

Activation of NF-κB is controlled via κB kinase, which forms a complex with two inhibitory subunits IKK1 and IKK2, and regulatory protein such as IKK3. The NF-κB signaling includes cytokines.[123,124] Notch and NF-κB pathways are triggered by the ligation of notch receptors, leading to the proteolytic cleavage of Notch intracellular domain, subsequent translocation into the nucleus binds to the DNA —binding protein.[125] NF-κB is a putative target gene of activated Notch-1.[126] Notch and Wnt pathways closely relate to cells' differentiation. Activation of the notch pathway inhibits the specific markers results in the influence on β-catenin translocation.[127,128] Activation of notch signaling in the differentiated cells indicates upregulated markers and activates the canonical pathway. These findings suggest that cross-regulation of developmental pathways initiates a prometastatic phenotype in TME.

Exosomal and non-exosomal miRNAs significantly affect the cross regulation of signaling pathways by transporting oncogenic miRNAs between different cells of TME. miRNAs crosstalk with Wnt, TG-F-β, and Notch signaling pathways and control stem cell phenotype.[129] The regulatory crosstalk of miRNAs with Wnt/β-catenin, Notch, and Hedgehog signaling pathways control cancer stem cell

reprogramming.[130] Further, miR-146 regulates NF-κB via the Notch-mediated signaling pathway of immunity and cancer.[131] Coregulatory signals of Notch and NF-kB promotes miR-223 dependent suppression of cancer cells.[132] GSK-3 regulates Wnt, Hh, and Notch signaling crosstalk via miRNAs.[133] Taken together, exosomes mediate cross-regulation of pathways involved in TME.

## Inhibitors of TME pathways

Targeting TME is an attractive strategy for the treatment of metastatic BCs. Small molecules and natural products, which are potentially important in targeting either components or signaling pathways of TME, can overcome the immune escape and drug resistance. The small molecule, cyclopamine was first described as the hedgehog pathway inhibitor.[134] It is a steroid alkaloid produced by corn lilies, which has teratogenic and anti-tumor activities (Fig. 3). Cyclopamine breast cancer by directly binding to the hydrophobic core of the SMO.[135,136] It suppresses the proliferation of MCF-7 and MDA-MB231 cells[137] and reduces invasiveness.[138] Cyclopamine sensitizes the BC cells to Paclitaxel, EGFR inhibitors, and tamoxifen.[139] Cyclopamine inhibits estrogen-receptor (ER) positive as well as ER-negative tumorigenic BCs at higher doses.[140] Co-delivery with BSA nanoparticles reverses Dox resistance by down-regulating P-glycoprotein.[141]

SMO antagonists inhibits breast cancer growth and drug resistance (Fig. 4). Sonidegib, which is antagonistic of SMO[118] is also well studied in clinical trials against different cancers.[142] Vismodegib is a synthetic SMO inhibitor.[143] It is under clinical trial for TNBC.[144] The SMO inhibitor Vismodegib directly binds to the SMO[145,] which results in the inhibition of cancer cell progression.[146] Hh pathway mediates

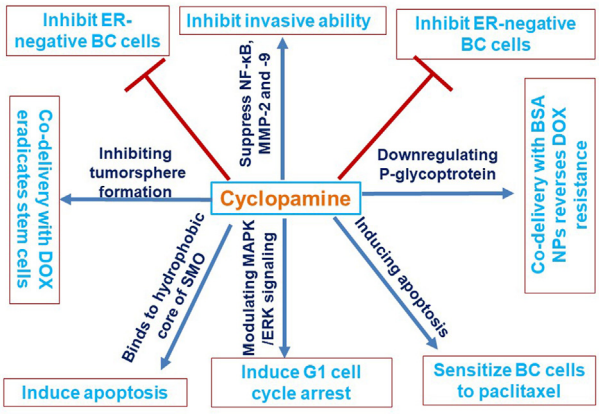


**Figure 3** Cyclopamine inhibits breast cancer by different mechanisms. Cyclopamine inhibits invasive ability of breast cancer cells by suppressing NF-kB, MMP-2 and MMP-9. It inhibits growth of ER-positive and -negative breast cancer cells by inducing cytotoxicity. It induces cell cycle arrest by modulating MAPK/ERK signaling, and apoptosis by binding to hydrophobic core of SMO and sensitizes breast cancer cells to paclitaxel. Co-delivery of cyclopamine with BSA nanoparticles reverses doxorubicin resistance in breast cancer and co-delivery with doxorubicin eradicates stem cells.

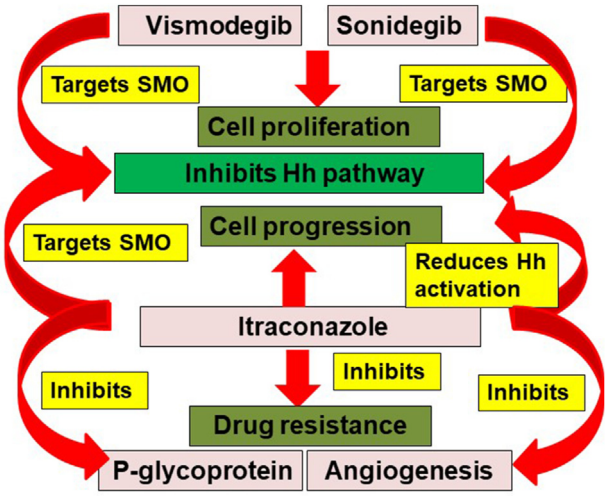


**Figure 4** SMO inhibitors targets breast cancer progression. Vismodegib and Sonidegib inhibits breast cancer cell proliferation by targeting SMO. Itraconazole inhibits Hh pathway by targeting SMO and inhibits cell proliferation by reducing Hh activation. It reduces drug resistance by inhibiting P-glycoprotein and angiogenesis.

self-renewal of stem cells; therefore, the rationale of inhibiting the Hh pathway leads to the dismissal of cancer stem cells and prevent the recurrence. Itraconazole is an antifungal triazole compound, which inhibits the Hh pathway by acting on SMO.[147,148] However, its inhibitory effect on Hh signaling appears to be different.[149] It binds to SMO at a distinct site, which is different from other SMP inhibitors. When administered into mice, the drug suppresses the growth of medulloblastoma and reduces Hh activation markers.[118,150] Itraconazole reduces drug resistance by inhibiting P-glycoprotein and angiogenesis.[151,152] Some of the small molecule SMO inhibitors that target Hh signaling are approved by the FDA to treat cancers.

The small molecule inhibitors inhibit breast cancer by targeting different developmental pathways (Fig. 5). XAV 939 inhibits Wnt pathway by blocking degradation of Axin 1 and IWR-1 inhibit the Wnt pathway by stimulating the degradation of β-catenin via stabilizing Axin1.[153] However, small molecule Dishevelled inhibitors NSC668036 and FJ9 bind to the frizzled receptors on C-terminal inhibit the Wnt pathway.[154,155] Wnt pathway is closely related to the other pathways, such as Notch. The gamma-secretase inhibitors (GSI) indirectly target Wnt pathways in CD44+ cancer stem cells (Fig. 6).[156] As Notch signaling is associated with breast cancer progression, it is recognized as a promising therapeutic target.[157,158] MRK-003 is s new generation GSI inhibits tumor-initiating cells transplanted mouse model.[159] BMS-906024 is the only GSI that equipotent in inhibiting all the four NOTCH isoforms, which is under clinical trial for breast cancer.[160] Therefore, small molecule inhibitors that are blocking Wnt and Notch pathways could be implicated in targeting breast cancer stem cells.

The target-specific anti-cancer agents are failed to accomplish the anticipated results; therefore, new multi-targeted natural products have become significant. Mounting evidence has established that several natural

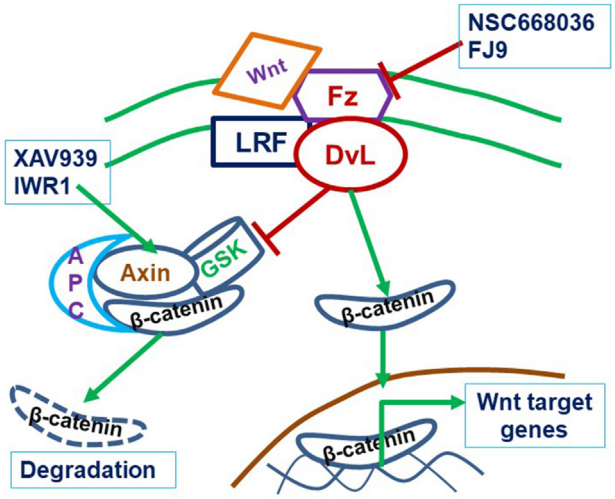


**Figure 5** Small molecules inhibit Wnt pathway. Small molecules inhibit breast cancer growth by targeting Wnt pathway via promoting degradation of β-catenin. IWR1 inhibits Wnt pathway by stimulating the degradation of β-catenin via activating Axin 1 and XAV939 inhibits Wnt pathway by blocking the degradation of Axin 1. NSC668036 and FJ9 inhibits Wnt signaling pathway by targeting Dishevelled via binding with Fizzled receptor.

small molecules could inhibit developmental pathways.[161,162] Genistein (Gn) is an isoflavone present in soy, and other plants are reported to have activity against breast and prostate cancers (Fig. 7).[163] It affects many signaling pathways, which suppress tumor growth. Gn shows the reduction in SMO and Gli expression, which

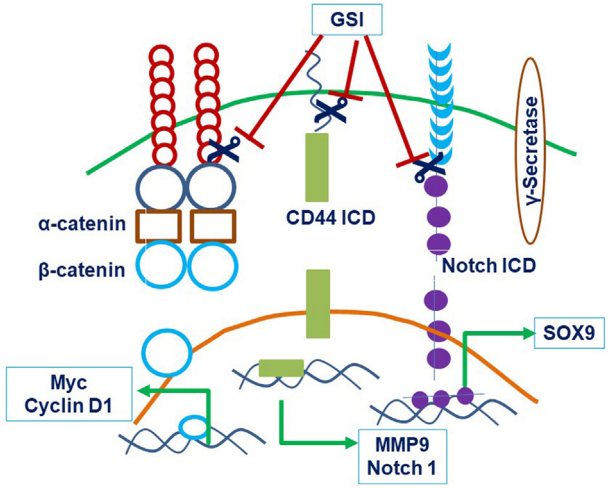


**Figure 6** Gamma-secretase inhibitors inhibit Wnt and Notch pathways. Gamma-secretase inhibitors (GSIs) reduce breast cancer progression by targeting Wnt and Notch pathways. GSIs inhibits Notch signaling by preventing the release of Notch ICD via blocking the cleavage of Notch, and Wnt pathway by preventing the release of β-catenin via blocking the cleavage of E-cadherin and CD44 signaling by preventing the release of CD44 ICD via blocking the cleave of CD44 through targeting gamma-secretase.

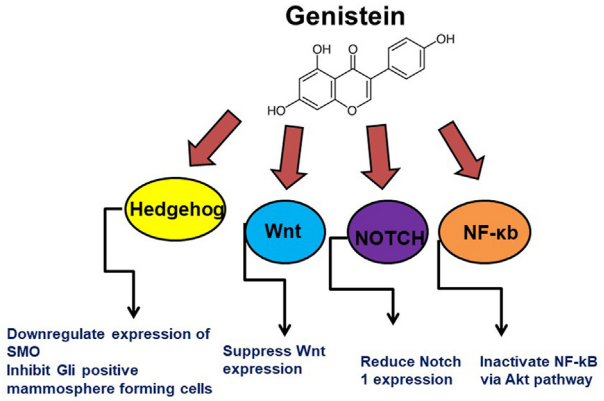


**Figure 7** Genistein inhibits breast cancer stem cells by targeting developmental pathways. Natural compound genistein suppresses breast cancer growth by targeting Hh pathway via reducing SMO and GLI1 expression, inactivates NF-kB pathway via targeting Akt, and Notch signaling by reducing the expression of Notch 1 expression and Wnt pathway by blocking Wnt expression.

results in the reduction of cancer stem cells.[164] It also inactivates NF-kB via the Akt pathway.[165] Gn inhibits expression of Notch 1[166] and Wnt.[167]

Curcumin has biological activity against inflammation, ischemia, and cancer (Fig. 8).[168,169] Hh is also affected by curcumin.[170] Wnt/β catenin, Notch and MAPK are also the targets of curcumin.[171] Curcumin induced GSK-3β causes downregulation of nuclear β-catenin.[172] It downregulates the expression of SMO and Gli-1 in breast cancer stem cells.[18] It also inhibits oncogenic NF-kB activity.[173] The Hh pathway stimulation by overexpression of Gli-1 increases cancer stem cell markers such as CD44, CD24, BMI-1 etc. and suppresses the effect of curcumin.[174] It is under clinical trial for breast cancer along with radiation treatment and chemotherapy.

Green tea, a widely consumed beverages, contains EGCG, reported preventing many cancers including breast

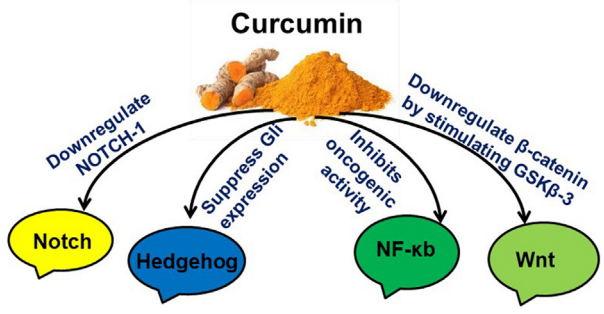


**Figure 8** Curcumin inhibits breast cancer stem cells by targeting developmental pathways. The natural compound curcumin inhibits breast cancer growth by targeting Notch pathway via downregulating Notch 1, Hh pathway via suppressing GLI expression, NF-kB pathway via inhibiting oncogenic activity and prevents Wnt signaling by downregulating β-catenin via stimulating GSKβ-3.

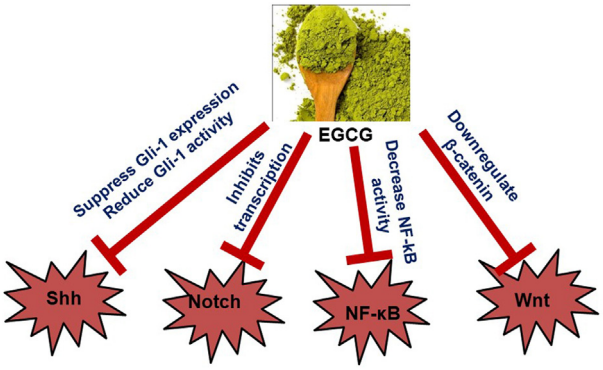


**Figure 9** EGCG inhibits breast cancer stem cells by targeting developmental pathways. The natural compound epigallocatechin gallate (EGCG) targets Shh signaling by suppressing GLI1 expression and GLI1 activity, Notch pathway by inhibiting Notch 1 transcription, NF-kB pathway by inhibiting its activity and Wnt signaling by downregulating β-catenin.

cancer (Fig. 9).[175] It mostly inhibits the Shh pathway by suppressing Gli-1 mRNA expression and downregulation of Gli-1 activity,[176] Wnt pathway by downregulating the expression of β-catenin,[177] decreased activation of NF-κB[178] and transcriptional levels of Notch.[179] The Hedgehog pathway cross talks with the Notch, Wnt, and NF-kB can be implicated for therapeutic interventions in breast cancers.

## Conclusion

The ancient developmental pathways are important for tumor progression. Cross regulation is reported to involve many cellular mechanisms, especially in the development and maintenance of cancer stem cell phenotype and metastasis. The hedgehog pathway is a predominant regulator of the paracrine network in TME; therefore, its inhibitors target both tumor cells as well as other supporting cells. Notch signaling also plays a role in oncogenic solid tumors like breast cancer, especially in tumor angiogenesis; therefore, it is a viable target for breast cancer treatment. Wnt signaling promotes tumor stem cells, provides a large platform for rational drug discovery. NF-κB is a key regulator of inflammatory pathways prevalent in TME and mediates chemo-radio resistance, also the principal target of breast cancers. Because target-specific anti-cancer agents fail to present anticipated results, multi-targeted natural products like curcumin, genistein, and EGCGs are significant in targeting TME to develop therapeutics for breast cancers.

## Author contributions

Prof. RamaRao Malla has substantial contributions to the conception and design of the work as well as drafting a part, interpretation of data and revising it critically for important intellectual content. Ms.P.Kiran has contributed to drafting the part of the manuscript. Final approval of the version to be published; AN.

## Conflict of interests

The authors declared that there is no conflict of interest.

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