Review of literature

2.1. Molecular basis of breast cancer

Development of cancer is a multi-step process that occurs as a result of many genetic, molecular and cellular changes over time. The persistent ambiguity with regard to the time of origin, specific etiology involved, and the molecular mechanisms responsible for cancer initiation and progression, have made it almost impossible to eradicate cancer [1]. The development of breast cancer is dictated by endocrine conditions, controlled by the ovary and its function [1]. In spite of the profound uncertainties regarding the origin of cancer, several studies have revealed numerous threat causes associated with breast cancer, with specific acknowledgement of the hereditary history of cancer, previous history of breast diseases, mutation susceptibility to BRCA1 and BRCA2 genes, exposure to radiations, food habits, socioeconomic status, hormonal and reproductive issues [2-5]. The elucidation of hormonal factors mainly focuses on the level of estrogen, though in practice, the molecular mechanism underlying the role of estrogen in breast cancer is poorly understood [1,6]. Estrogen is accredited with the induction of breast cancer mainly by receptor-mediated pathway or by CytP450 mediated metabolism or by DNA repair mechanism [1,6]. The breast cancer initiation starts with uncontrolled proliferation of cells and the genetic amendments include stimulation of proto-oncogenes, de-regulation of DNA repair and tumor suppressor genes [7,8]. During this process, susceptible cells are expected to gain graded mutations in genes that regulate proliferation i.e. tumor suppressor and proto-oncogenes. In general, the rate of mutation is slow in humans, but exposure to various environmental mutagens like chemical mutagens, radiation, and tumor viruses critically increases the rate of mutation and concomitantly, boosts the prospect of emerging cancer. Each time a new mutation occurs in the cells, they gain an extra benefit, which leads to uncontrolled expansion, by facilitating changes in normal processes like cell cycle deregulation, inhibition of apoptosis and enhancing metastasis properties [7]. Proto-oncogenes are mutated to oncogenes, resulting in excessive production of growth factors, unrestricted stimulation of the transitional pathways, overflow of the replication signals and elevated levels of transcription factors leading to cell growth [7]. In human cancer, RAS is the most frequently mutated oncogene, which encodes a GTP-binding protein RAS, that wheels a number of key signaling pathways, responsible for cell division. In normal cells, this same RAS is momentarily stimulated and recruits Raf, which triggers the MAPK pathway to communicate growth-promoting signals with the nucleus. It is the

permanent activation of the mutant RAS protein in cancers, which leads to the non-stop stimulation of cells, which gives it a wholly different dimension. Other oncogenes frequently mutated in cancer are SIS, HST-1, INT-2, TGFα, ERB-B1, ERB-B2, PDGF-R, KIT, K-RAS, H-RAS, N-RAS, ABL, BRAF, β-catenin, C-MYC, N-MYC, L-MYC, Cyclin D and E, and CDK4 [7,9,10]. Tumor suppressor genes are responsible for encoding proteins that inhibit cell proliferation, regulating cell cycle progression and growth signaling pathways (*e.g.* APC or PTEN), besides; controlling checkpoints and promoting apoptosis. The example of few tumor suppressor genes are TP53, PTEN, RB, BRCA1, BRCA2, CDKN2A, CDH1, MEN1, NF1, SMAD4, APC, TSC1, TSC2, VHL, WT1 [7]. Growth factors stimulate proliferation by different receptor-mediated signaling pathways which include binding of the growth factors to membrane-bound receptors and activating different transduction signals in the inner membrane. The latter leads to activation of targets like transcription factors, genes either in nucleus or cytosol, finally stimulating cell cycle progression and cell division. But in cancer, cells produce their own internal signals stimulating uncontrolled proliferation which is not influenced by environmental factors [7,11-14].

2.2. Hormone-dependent Breast cancer

Breast is a hormone-dependent organ and its development is influenced by complex hormonal interactions [1,15,16]. Breast cancer includes several different types of neoplasm in the breast tissue of both men and women, the most common is the adenocarcinoma of the breast cells [17-21]. The growth of breast cancer is regulated by steroid and peptide hormone receptors [22-24]. They express hormone receptors and proliferate after hormone stimulation and hence called hormone-dependent breast cancers [17,25]. The steroid hormones involved in breast cancer are estrogen (ER) and progesterone (PR) whereas Human Epidermal Growth Factor Receptor 2 (HER2) is a peptide hormone, which also plays a significant role in breast cancer along with other types of cancers like ovary, bladder, lung, head & neck [26,27]. About 80% of all breast cancers are ER-positive i.e. express the estrogen receptor. Amongst these, about 65% of the cells express the progesterone receptor i.e. these cells are both ER and PR positive. A smaller percentage of these cells can also express the Human Epidermal Growth Factor Receptor 2 (HER2). The rest 20% of the cancer cells are called triple-negative breast cancers as they do not express either of the three hormone receptors and they are

the most aggressive among all cell types [28,29]. To decide the treatment option for breast cancer, understanding the hormone receptor status is vital [29-31]. The cancers which are hormone-positive are more expected to react to hormonal treatment than hormone-negative breast cancer [28]. Few examples of breast cancer cell lines are MCF-7 (ER+, PR-, HER2-), T47D (ER+, PR+/-, HER-), MDA-MB-435, MDA-MB-453 (ER-, PR-, HER2+), ZR-75 (ER+, PR+, HER2+), MDA-MB-231, MDA-MB-468 and HBL-100 (ER-, PR-, HER-). Though specific genes responsible for hormone related breast cancer are unknown, a few gene have been found to be involved in the pathogenesis [24]. Gene regulated in breast cancer 1 (GREB1), Trefoil factor 1 (pS2) and Stromal cell-derived factor 1 (SDF-1) are the genes found to be differentially regulated in ER+ breast cancer cells [25]. Whereas the gene BRACA1 is regulated by both steroid hormones estrogen and progesterone [32]. The Ca^{2+} binding protein-encoding gene, *mts1* (S100A4) gene is involved in the control of tumor metastasis [33]. Breast cancer risk is also found to be associated with estrogen-metabolizing genes like CYP17, CYP1A1, and COMT [23]. During the process of advancement of breast cancer, the pattern of hormone dependence changes with time, along with other characteristics like increased metastatic potential and resistance to different therapies [34]. The resistance of ER-positive breast cancers to endocrine therapies are mainly due to loss of ERα expression, and the expression of shortened isoforms of ERα and ERβ [35]. The other causes are post-translational modifications of ERα, increased Activator Protein 1 (AP1) activity, faulty regulation of ER co-activators, activation of the Erk and PI3K pathways, and disruption of the cell cycle as well as apoptotic components [35].

2.3. Mechanisms of cancer cell death

In earlier times it was believed that the only fate of cells, as well as life, is death [36,37]. The research from the previous decades has overturned this belief and made cell death not only essential for the developmental and protection of life but an event that is judiciously regulated by the body [36-42]. This cell death is manifested by a variety of mechanisms leading to morphological changes in the dead cell and based on these changes, and pathways followed by cells to death, they are classified into three types [36,43]:

1. Type I cell death known as apoptosis: Apoptosis is characterized by morphological changes like cytoplasmic shrinkage, condensation of chromatin i.e.

pyknosis, DNA fragmentation i.e. karyorrhexis, and membrane blebbing ending up with the formation of apoptotic bodies of small vesicles that are phagocytically taken up by neighboring cells and degraded within lysosomes.

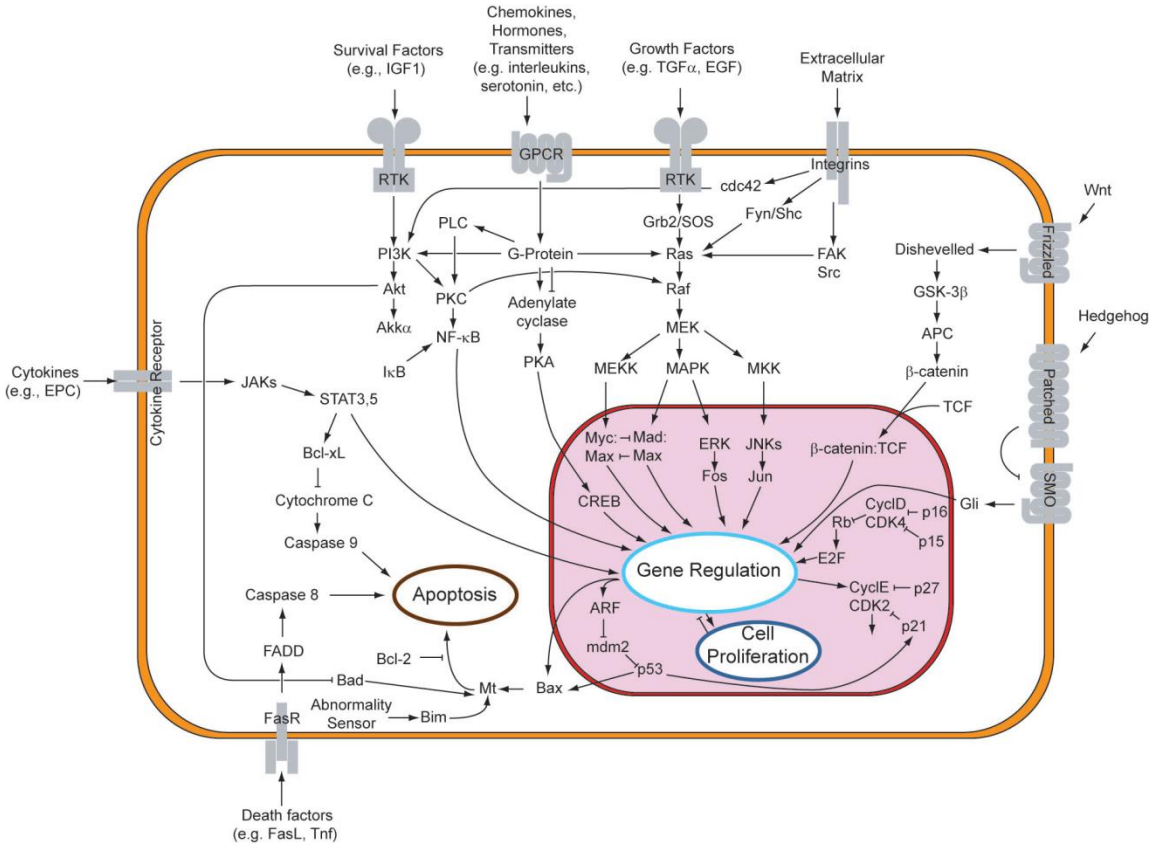
2. Type II cell death also known as autophagy: Autophagy is characterized by extensive vacuolization in the cytoplasm and terminating with phagocytic engulfment and degraded within lysosomes.

3. Type III cell death or necrosis: Cells undergoing necrosis do not display any typical features of type I and/or II cell death and ends with the disposal of cell bodies without the involvement of phagocytosis and lysosome [36,44,45].

Initially, apoptosis was considered as the most plausible mode of cell death, but contemporary studies discovered novel signaling pathways that point to conventional chemotherapeutic agents eliciting apoptosis and non-apoptotic cell death. These modes of non-apoptotic cell death may be categorized as pyroptosis, enucleation, necrosis, autophagy, mitotic catastrophe, senescence, etc [36,46-49]. Recently the Nomenclature Committee on Cell Death (NCCD) has given a list of different types of programmed cell death mechanisms but follow a common mode i.e. initiation, execution and transmission to cell death [36].

2.3.1. Intrinsic apoptosis

Intrinsic apoptosis is initiated by multiple microenvironmental factors like DNA damage, removal of growth factors, stress by reactive oxygen species or replication stress [50-53]. Mitochondrial outer membrane permeabilization in response to apoptotic stimuli is an irreversible process controlled by apoptosis regulator Bcl2 family proteins [50,54,55]. Bcl-2 associated X (Bax), Bcl-2 antagonist/killer 1 (Bak1) and Bcl2 family apoptosis regulator (Bok) are the pro-apoptotic members of Bcl2 family which activate in response to apoptotic signals and form pores across the outer mitochondrial membrane facilitating permeabilization [36,55-58]. The pro-survival or anti-apoptotic members of the Bcl2 family proteins i.e. Bcl2, Bcl2 like 1 (Bcl2L1; also known as Bcl-X), Bcl2 family apoptosis regulator (MCL1), Bcl2 like 2 (Bcl2L2; also known as Bcl-W), and Bcl2 related protein A1 (Bcl2A1; also known as BFL-1) are inserted into the outer mitochondrial membrane and exert anti-apoptotic effect by directly binding to the pro-apoptotic members of the Bcl2 family proteins [36,59-62].



Source: Wikipedia, Overview of signal transduction pathways,2008 [63]

Figure 2.1.: Schematic representation of proteins involved in cell proliferation and apoptosis

Mitochondrial outer membrane permeabilization facilitates the release of apoptogenic factors present in intermembrane space to cytoplasm like Cytochrome C, a second mitochondrial activator of caspases (SMAC) [64-68]. Cytochrome C in the cytoplasm binds to apoptotic peptidase activating factor 1 (APAF1) as well as pro-caspase 9 to form an apoptosome, which ultimately stimulates caspase 9 [68]. This stimulation of caspase 9 is mainly responsible for the catalytic activation of caspases 3 and 7, the main enzymes involved in intrinsic apoptosis [69,70]. Cytochrome C release for the pro-apoptotic signal is also possible in BAK and Bax independently for caspase activation **(Fig 2.1.)** [71,72]. The catalytic activation of executioner caspases leads to morphological changes like DNA fragmentation, externalization of phosphatidylserine in the membrane and the formation of apoptotic bodies [73-77]. Caspase 3 is involved in DNA fragmentation and exposure of phosphatidylserine by activating externalizing proteins and inactivating internalizing proteins [78-85]. Along with caspase 3, caspase 7 is also a putative executioner of apoptosis [86]. Hence intrinsic apoptosis is defined as a

form of regulated cell death, originated by the intracellular or extracellular microenvironment, followed by membrane permeabilization and advanced by executioner caspases [36].

2.3.2. Extrinsic apoptosis

Extrinsic apoptosis is originated by the extracellular microenvironment and mainly dependent on plasma membrane proteins like death receptors and dependence receptors [87-91]. Death receptors like FAS or CD95 or APO-1 and TNF receptor superfamily A1 are also known as TNFR1 and form the death-inducing signaling complex (DISC), that controls the activation of caspase 8 and 10 [90,92-95]. The mechanism involves maturation of caspase 8, through a cascade of events, where caspase 8 binds to FAS associated death domain (FADD) in the DISC, followed by autoproteolytic degradation for its activation [96-99]. The death receptor-dependent execution of extrinsic apoptosis is carried out in two different ways. The first type is the proteolytic activation of executioners caspase 3 and 7 by caspase 8, which cannot be inhibited by Bcl-2 overexpression or loss of BID function [100,101]. The second type is characterized by restriction of caspase 3 and caspase 7 activation, by X-chromosome linked inhibitor of apoptosis protein (XIAP) [102]. Death receptor ligation does not always end in regulated cell death, instead, the post-translational modification of the complex may decide the fate of such complexes [103,104]. In addition, TNF stimulation may promote inflammation and cell viability through mitogen-activated protein kinase (MAPK) or NF-kB activation pathway [105-107].

2.3.3. Necroptosis

Necroptosis or regulated necrosis or non-apoptotic cell death is also a form of regulated cell death controlled by death receptors like TNFR1 and FAS; or pathogen recognition receptors (PRRs) like TLR-3, TLR-4 and Z-DNA binding protein 1 (ZBP1) [108-112]. Necroptosis not only mediates the stress signals but also works as a protective driver and helps in maintaining T-cell homeostasis [38,113]. As long as caspase 8 is inactive, necroptosis initiation by TNFR1 mainly depends upon receptor-interacting serine/threonine-protein kinase 3 (RIPK3) which is activated by RIPK1, and forms complexes known as necrosome [114-118]. RIPK3 can also be activated by activation of TLR-3, TLR-4, and ZBP1 leading to NF-κB activation [111,119-121].

2.3.4. Transition (MPT)-driven necrosis

This is initiated by intracellular microenvironments like extreme oxidative stress and cytosolic Ca^{2+} burden, giving rise to necrotic morphology, where a discrepancy occurs in the permeability of mitochondrial inner-membrane (IMM) and mitochondrial outer-membrane (OMM); followed by an increase in membrane potential and osmotic breakdown of both the membranes [108,122]. It is believed that MPT-driven necrosis follows the opening of the permeability transition pore complex (PTPC) at the junction of IMM and OMM, but its role is controversial and still under intensive research [108,122-124]. Different PTPC interactors are reported to regulate transition (MPT)-driven necrosis like (i) both pro-apoptotic and anti-apoptotic family proteins viz. Bax, BID, BAK [125-128], Bcl-2, Bcl-XL [129-132]; (ii) Dynamin-1-like protein (DNM1L) which promote PTPC opening in response to receptor stimulation [133] and (iii) p53 which physically interacts with Cyclophilin D (CypD) [134].

2.3.5. Ferroptosis

Ferroptosis is another type of controlled cell death, initiated by a change in cellular microenvironment, characterized by lipid peroxidation, due to the generation of reactive oxygen species (ROS) and iron accessibility [135-138]. The occurrence of ferroptosis is neither dependent upon caspases or necrosome formation or autophagy but it does have a morphological resemblance with necrosis [139]. This mechanism is regulated by an antioxidant enzyme glutathione peroxidase 4 (GPX4); whereas p53 is reported to restrict ferroptosis by blocking dipeptidyl peptidase 4 (DPP4) activity [140,141].

2.3.6. Pyroptosis

Pyroptosis is also a programmed cell death manifested by a high level of inflammation as a result of infection with intracellular pathogens, which breaks the homeostasis between intracellular and extracellular membranes [142]. It can be compelled by activation of different caspases like caspase 1, caspase 3, caspase 4, caspase 5 and caspase 11 in case of a murine model; in response to inflammatory signals of intracellular lipopolysaccharides (LPS) [143-150].

2.3.7. Parthanatos

Parthanatos is a programmed cell death, differentiated from apoptosis and necrosis,

where an excessive accumulation of poly (ADP-ribose) polymerase 1 (PARP1) results due to genomic stress [151,152]. Parthanatos is facilitated by nuclear translocation of apoptosis-inducing factor (AIF) from mitochondria, followed by binding to PARP1, which results in DNA degradation and nuclear condensation [151-155]. This type of cell death is hypothesized to be a contributing factor in different pathological conditions like diabetes, cardiovascular disorders, renal diseases, neurodegenerative disorders [156,157].

2.3.8. Entosis

Entosis is a non-apoptotic, but regulated cell death process where other non-phagocytic cells cause either cell invasion or engulfment [158-161]. The cell invasion occurs by forming a junction between the two participating cells with the involvement of E-cadherin and catenin alpha 1 but without integrin involvement [158,160,162,163]. This is followed by the generation of actomyosin-contractility and finally, execution of the engulfed cell is carried out by lysosomes [164-166].

2.3.9. NETosis

NETosis is a unique form of cell death, associated with the release of chromatin and histones, in granular as well as cytoplasmic fiber like meshwork of neutrophil extracellular traps (NET), characterized initially in neutrophils, and restricted to cells of hematopoietic origin [167-169]. This NET framework binds and traps pathogens, after which the neutrophils are thought to kill them, either by engulfing or secretion of antimicrobials [167,170,171]. The precise mechanism of this type of cell death has not been elucidated to date; though the involvement of NADPH oxidases activation resulting in ROS generation is postulated [172-174].

2.3.10. Lysosome-dependent cell death

Lysosome-dependent cell death is a programmed cell death, where the permeabilization of the lysosomal membrane, leads to the release of lysosomal content. Thus proteolytic enzymes are released into the cytosol, which degrades most cellular macromolecules, contributing to various pathophysiological conditions like inflammation, aging, cardiovascular and neurodegenerative disorders [175-177]. In some particular cases, the lysosomal membrane permeabilization occurs only after mitochondrial outer

membrane permeabilization, as a result of apoptotic signaling and noncompulsory involvement of executioner caspases [178,179].

2.3.11. Autophagy-dependent cell death

Autophagy is a regulated and natural mode of cellular function, whereby cells remove the unwanted or non-functional components to protect other cells [180-183]. Autophagy is not always cytoprotective but can act as a pro-death pathway [184,185]. The autophagy-dependent cell death primarily depends on this machinery and its subsequent components [186-189]. It supports at least three other types of programmed cell death. Ferroptosis involves the autophagic degradation of ferritin; extrinsic apoptosis, with autophagic degradation of tyrosine phosphatase and necroptosis, where autophagic degradation of inhibitors of apoptosis proteins (IAP) occurs [190-192].

2.3.12. Immunogenic cell death

Immunogenic cell death is a specific type of programmed/regulated cell death, which gives rise to activation of adaptive immunity, in response to internal or external antigens expressed by the dying cells [193,194]. The stimuli of immunogenic cell death are restricted to viral infection, few chemotherapeutic agents, some radiation and photodynamic therapies [195-197]. These stimuli activate the release of damage-associated molecular patterns (DAMPs), which in turn establish the immunological memory [194,198].

2.4. Regulation of cell cycle and apoptosis

Tissue homeostasis is important for usual growth and development in multicellular organisms, for which a balance between cell proliferation, and regulated cell death is required. Apoptosis is the most plausible mode of cell death in normal as well as drug-treated cells. Manipulation in the cell cycle may either induce or inhibit apoptosis. The regulation of cell cycle and apoptosis is mainly dependent on factors like tumor suppressor genes p53 and retinoblastoma, the dominant oncogene c-Myc, and cyclin-dependent kinases (Cdks), and their regulators [199]. p53 is a regulator of apoptosis and cell cycle, as it regulates the inhibitory signals/proteins for cell cycle progression i.e. cell cycle arrest induces apoptosis in cells. p53 is a master regulator for both the G1/S phase as well as G2/M phase progression. Cyclins are required by cyclin-dependent

kinases (CDKs) for cell cycle progression as depicted in **Fig 2.2.** [199]. The c-Myc proto-oncogene is mainly responsible for cell cycle progression with the involvement of Max gene, but the overexpression of this gene leads to apoptosis in cells [199]. The pathways like Raf/MEK/ERK, PI3K/Akt, JAK1/2-STAT3, MAPK and NF-κB are well understood for their role in cell cycle progression, leading to the prevention of apoptosis in tumorigenic cells and are the most widely targeted pathways in cancer chemotherapy [200-203].

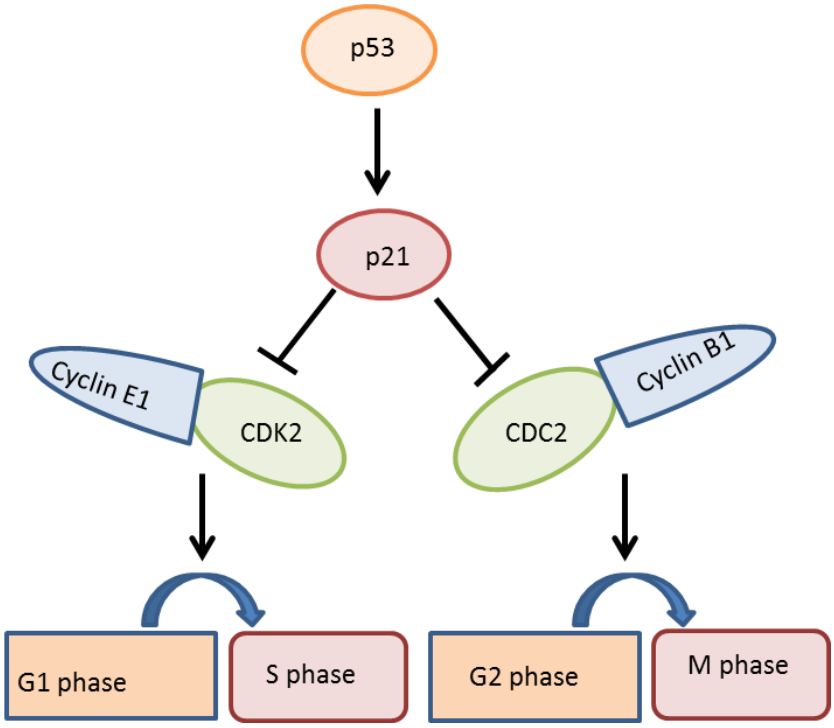


Figure 2.2.: Schematic representation of the role of cell cycle regulating proteins

2.5. Regulation of metastasis

Metastasis of cancer is a well-coordinated process of migration, adhesion and invasion of cancer cell lines from the source to the destination tissue [204,205]. Cancer cell migration is one of the earliest steps in this process and influenced by the tumor microenvironment, extracellular matrix (ECM) construction and other cell types of the tumor [206]. Tumor microenvironment fuels the progression of metastasis by recruiting macrophages and mesenchymal stem cells for various internal stimuli, suppressing immunity, developing a site for extravasation [207,208]. The alteration in ECM and collagen cross-linkage promotes tumor growth, motility, and invasion [209]. Collagen,

laminin and fibronectin are the primary components of ECM where the integrins bind and help the primary tumor cells to adhere to a distant site [210]. Other adhesion molecules vinculin, paxillin, tensin assist the program and with the help of proteases *e.g.* MMP-2, MMP-9, MT1-MMP, seprase, invadolysin, the cells invade the ECM [206]. Tumor hypoxia acts synergistically with ECM remodeling to include an extra drive in the metastasis process [209,211]. Matrix metalloproteinases (MMPs) play a vital role in metastasis progression, and many compounds are reported to have targeted MMPs, especially MMP-2 and MMP-9 **(Fig 2.3.)** [212]. MMPs are secreted by cancer cells, and their increased expression is a hallmark of disease metastasis. The secreted MMPs like MMP-2 and 9 degrade the extracellular matrix which allows the cancer cells to invade and migrate through blood vessels and grow secondary tumors in new tissue sites [213,214].

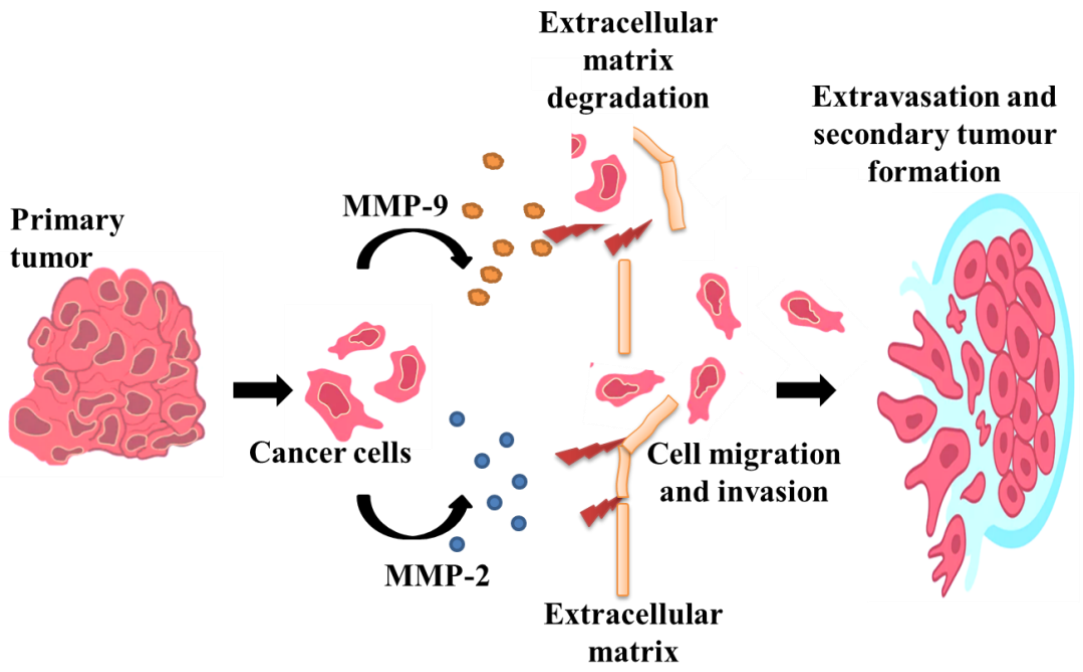


Figure 2.3.: A schematic representation of the role of MMPs in metastasis

TIMPs is a suppressor of metastasis that inhibits metalloproteinases to restrict migration, invasion and angiogenesis [215]. Till date, about 23 genes are identified that can act as a suppressor of metastasis. Cadherins (E-Cadherin, N-Cadherin and Cadherin-11) and CD44 inhibit cell to cell or cell to matrix adhesion thereby prevent epithelial-to-mesenchymal transition (EMT) and invasion. Other genes responsible for

inhibiting migration and invasion are DCC, DLC1, Gelsolin, MKK4, MKK7, p38, RKIP, RRM1 which function by regulating pathways like MAPK signaling, Raf-MEK signaling, ras signaling. Intercellular adhesion molecule-1 (ICAM-1), inflammatory chemokines CXCL4 and CXCL12, angiogenic factors VEGF, TGF-β and TNF-α are upregulated in metastatic cancers [216,217]. It is well known that more than 90% of cancer deaths are due to metastasis, and yet, the availability of a first-line commercial anti-metastatic drug has not been reported [218-220]. The development of anti-metastatic drugs from plant-based sources like baicalein and curcumin is ongoing. *In-vitro* studies have shown inhibition of metastatic properties like migration, adhesion, and invasion can be achieved by hindering phosphorylation of MAPK pathway [217,221]. TGF-β induces epithelial-mesenchymal transition for invasion and metastasis of cancer cells by Smad dependent and independent pathways. In addition, the JAK1/2-STAT3, PI3K/AKT, NF-κB, Hedgehog, MAPK/ERK, p38MAPK, Wnt/β-catenin signaling pathways are also involved in tumor invasion and metastasis [222,223]. Though the requirement of IAP ('Inhibitor of Apoptosis Protein) in apoptosis is not well understood, its role in metastasis stimulation through XIAP (X-linked inhibitor of apoptosis protein) and survivin complex formation leading to NF-κB activation is reported [224].

2.6. Targets for breast cancer treatment

The obvious way to target cancer by chemotherapeutic approaches is to kill cancer cells by targeting cell death pathways [48]. One of the therapeutic approaches may be by affecting the growth factors of receptor tyrosine kinases which inhibit tumor cell proliferation and angiogenesis [225]. Cisplatin and its analogs interact with the purine base of DNA and thereby affecting the DNA repair mechanism and inhibit proliferation [226]. Targeting metabolic regulators is another option that helps the cancer cells to modify the metabolic and apoptotic roles of Bcl-2 family proteins [227]. Doxorubicin is one such widely used anti-cancer drug which alters various molecular pathways by binding to DNA associated enzymes and influence the Bcl-2/Bax apoptotic pathway [228]. STAT3 pathway is another major target to contain cancer cells. Inhibition of STAT3 pathway *i.e.* diminishing STAT3 phosphorylation negatively affects survival and metastasis of cancer cells. Further, the AKT pathway, which down-regulates apoptosis and stimulates cell cycle progress to enhance cell proliferation and growth can

also be aimed. Everolimus and Temsirolimus are two drugs that inhibit PI3K/AKT/mTOR pathway in mammalian cancer cells [225]. The other important target is the ERK/MAPK pathway which transduces signals for explicit phosphorylation events, resulting in the manifestation of cell cycle progression proteins, apoptosis opposition, cellular motility, extracellular matrix renovation, angiogenesis and drug resistance. Activating proteasomal degradation of proteins involved in cell cycle progression, NF-kB activation, and angiogenesis can be an interesting therapeutic approach [229]. Inhibition of autophagy may be a promising approach where compounds like chloroquine and hydroxychloroquine are used in combination with other anticancer drugs [230]. Modulating tumor microenvironment is another strategy to overcome tumor progression and metastasis which can be achieved by altering the extracellular pH of the tumor [227]. Glycolytic enzymes like hexokinase, pyruvate kinase, lactate dehydrogenase A and transporters like GLUT1-4 involved in glucose catabolism can be aimed to make the cancer cells energy-deprived leading to death [227,231-233]. Targeting mitochondrial respiration and glutaminolysis in cancer metabolism are some other aspects of cancer targets [227]. The anti-hormonal treatment approach is a popular option to treat hormone-dependent breast cancer and tamoxifen is one such drug used for this purpose [234]. Tamoxifen is also used in hormone independent cancer therapy which induces apoptosis, prevent angiogenesis and metastasis and inhibit drug resistance [234]. Another key target is the drug transporters, mainly ATP binding cassette (ABC) transporters, as the cancer cells develop a high efflux pump that make them multidrug resistance [227,235,236]. Breast cancer resistance protein (BCRP) helps in forming ATP-binding transporter cassette which pumps out drugs like mitoxantrone, camptothecin, topotecan, and flavopiridol from the cells to make it multidrug resistance [237]. Therefore, any therapy with ability to target the metabolism of cancer cells, alter downstream signaling pathways of tumor cells, modulate tumor microenvironment can be considered as viable options for chemotherapeutic drug regimen [227].

2.7. Medicinal plants as an anti-cancer agent

Drug discovery from plant sources is a multi-dimensional approach that combines many areas like ethnomedicinal, phytochemical, pharmacological and molecular biology [238]. Medicinal plants are rich sources of bioactive molecules and can be exploited for

novel compounds for application in various treatments like cancer, diabetes, Alzheimer's, malaria, etc. [238]. The popularity of plant-derived compounds is garnering positive impact and approval from the scientific community as they are considered to be safe and less toxic in comparison to prevalent chemotherapeutic agents [239]. The North-Eastern part of India is a well-regarded reservoir of traditional medicinal plants, as it is one of the prominent biodiversity hotspots of the world [240]. Vinca alkaloids from *Catharanthus roseus* (Apocynaceae) i.e. vincristine and vinblastine are the very first anti-cancer compounds derived from plants revolutionized the concept of medicinal plant-based cancer treatment [241]. They were used individually or in combination to treat different types of cancers. After these two compounds, many other plant-derived anti-cancer molecules were discovered and commercialized. Some of the other important anti-cancer drugs from plant sources are already in the market like paclitaxel, vinorelbine, teniposide and various water-soluble analogs of camptothecin [241-246]. The anti-cancer efficacy of these compounds is attributed to their ability to target microtubules. Podophyllotoxin, a lignin derived from *Podophyllum peltatum* L. or *P. emodi* and their derivatives are also used commercially as anti-cancer drugs [247]. While podophyllotoxin acts by inhibiting microtubule assembly, its derivatives like etoposides and teniposide act by interacting with DNA and inhibition of DNA topoisomerase II [248]. Camptothecin, a quinoline alkaloid from *Camptotheca acuminata* also functions as an anti-cancer drug, which inhibits the DNA enzyme topoisomerase I [249].

Studies are ongoing to discover new prototypes of anti-cancer agents that can target cancer by novel pathways [239,245,250]. In search of novel medicinal plant-based therapeutic approaches, several plant extracts and polyphenols, are studied for their anti-cancer activity. *Moringa oleifera* leaf extract has shown anti-cancer activity in the KB tumor cell line by induction of apoptosis [251]. *Teucrium polium* plant extract inhibits proliferation and induces cell cycle arrest at S-phase. This extract also prevents cell invasion and motility of PC-3 and DU145 human prostate cancer cells by re-establishing the E-cadherin/catenin complex [252]. *Matricaria chamomilla* extract exhibits anti-cancer effects against a number of prostate cancer cell lines like LNCaP, DU145 and PC-3 [253]. Crude extract, as well as phenolic compounds present in *Terminalia chebula*, shows anti-proliferative activity in various cancer cell lines like human breast cancer, MCF-7; osteosarcoma cancer, HOS-1; prostate cancer, PC-3; and

mouse breast cancer, S115 [254]. Basil leaf extract induces apoptosis and inhibits metastasis of aggressive human pancreatic cancer cells *in vitro* and *in vivo* [255]. Purified plant polyphenols baicalin and fisetin, shows anti-cancer and apoptosis-inducing activity in breast cancer cell lines [221,256]. [257]. Fisetin, also known for its anti-inflammatory effect, is reported to induce apoptosis and cell cycle arrest [258] and autophagy through suppression of mTOR signaling in prostate cancer cells, LNCaP [259]. It is also reported to inhibit the COX2 and Wnt/EGFR/NF-κB-signaling pathways in HCT116 and HT29 in colon cancer cells and downregulate the expression of MMP2/9 in LNCaP cells [260-262]. Fisetin has shown anti-cancer activity against many other cancer cell lines by adopting different mechanisms; such as utilizing the NF-kB pathway in pancreatic cancer AsPC-1 cells [263], mediating the ERK1/2 pathway in human cervical cancer HeLa cells and lung cancer A549 cells [264], and through caspase-dependent pathways in human breast cancer MCF-7 and MDA-MB-231 cells [265,266]. Curcumin inhibited NF-kB pathway and subsequently, expressions of inflammatory cytokines CXCL-1 and -2 which are up-regulated during metastasis [267]. Extracts from different berries have shown anti-cancer activity in LNCaP, MCF-7, KB, HCT116, HT-29, and CAL-27 cell lines [268]. Mulberry anthocyanins, green tea and ellagic acid are reported to inhibit migration, invasion and metastasis of several cancer cell lines [269,270]. Andrographolide, a lactone derived from *Andrographis paniculata* inhibited migration and invasion in A549 cells, via down-regulation of PI3K/Akt signaling pathway [271].

2.8. *Ricinus communis* L

Ricinus communis L. *(Euphorbiaceae)* is commonly known as the castor plant, is abundant in North East India and well-known for its traditional and medicinal use globally [272]. In general, various parts of this plant have been used for the treatment of pain, paralysis, constipation, gastritis and warts [273,274]. Ethanolic extract of the leaves has shown hepatoprotective effect and anti cholestatic activity in hepatocytes isolated from rats [275]. Further fractionation of the extract followed by activity assessment has shown that butanolic fraction was most effective and Ricinine and N-dimethylricinine are reported to be the major compounds of the fraction[275]. 50% ethanolic extract of the roots of this plant have shown anti-diabetic and reversible anti-fertility activity in *in-vivo* rat models [276,277]. On the other hand, a methanolic extract

of the roots have shown anti-inflammatory activity in wister albino rats and demonstrate free radical scavenging activity *in-vitro* [278]. There are other reports which indicate the effectiveness of this plant as an anti-fungal agent and a pest control measure [276,279-281]. A volatile extract from the leaves of the plants has shown to induce apoptosis in human melanoma cells (SK-MEL-28) [272]. However, a detailed study on the anti-cancer efficacy of the fruits of *R. communis* L. is not reported.

2.9. *Amorphophallus paeoniifolius* (Dennst.) Nicolson

Amorphophallus paeoniifolius (Dennst.) Nicolson (Elephant Foot Yam) is a folk medicinal plant of India used in Ayurveda, Siddha, and Unani medicine. Reports on traditional use of this plant as medicine are available for the treatment of hemorrhoids, digestion, liver ailment, vomiting, anorexia, dyspepsia, colic, fatigue and anemia among others [282,283]. The tuber portion of the plant is used as a vegetable in India. Only a few reports of its anti-inflammatory, hepatoprotective, anthelmintic, analgesic are available [284-289]. The tuber is also reported to have antitumor, cytotoxic and anti-inflammatory properties [282,290,291]. Despite its wide traditional application as medicine, detailed mechanistic studies to demonstrate the basis of these activities are lacking [282].

Hence, prospecting for novel cancer therapeutic compounds from these two plants as representatives of the prolific bounty of biodiversity of North East India will be a worthwhile and viable option.

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