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Impact of COVID-19 on the Relapse and Reawakening of Dormant Tumor Cells in Breast Cancer

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Abstract

Worldwide, the study shows that breast cancer is one of the major cancer responsible for women death. All the effective therapies – immune-modulator therapy, chemo-radiation and cell targeted therapies can worsen the body immune system which majorly affects the lungs and these women with weak immune system and bronchi problems are more susceptible to major complications if they are exposed to COVID-19. In start of pandemic, it was difficult for healthcare system to manage the surgeries, scans and therapies of cancer patients without let them exposed to SARCoV-2, leads to delay in their treatment which can even more worsen condition for the patient. SARCoV-2 triggers the IL-6 release by the formation of neutrophil extracellular trap which can increase the complications in the breast cancer patient as well as it can also reactivate the relapsed dormant breast cancer cells. So, after seeing the condition of patients doctors decided that they can treat the patients by taking all measuring safety precautions during the admission to the hospital and found Anti-IL-6 receptor (tocilizumab) neutrophils inhibitor (alvestat) and JAK1/JAK2 inhibitors (baricitinib) effective and vaccines are also available in international market considering them safe and efficient for patient with breast cancer history or maybe undergoing in treatment.

Keywords- dormant cells, breast cancer, SARCoV-2, immunity, IL-6.

1. Introduction

Among all the gynecological cancers, breast cancer is predominant as 25% of the women (over 1.5 million) are diagnosed with breast cancer worldwide throughout the year. Approximately 570,000 deaths were recorded in 2015 [1, 2]. Phyllodes tumor categorized under sarcomas are rarely found whereas carcinoma breast cancer are very common. Breast cancer is the aggregation of different kind of malignancies that present in mammary gland here is a brief of various pathological and biological features of breast cancer which includes risk factors causing breast cancer, classification (figure-1), role of signaling pathways in breast cancer progression and role of mammary stems cells in breast cancer. Focusing on the effect of the SARs COV-2 virus on the breast cancer patient that starts from the lungs inflammation due to hyper activation of immune cells. Studies gives the account of reactivation of the dormant breast cancer cells like neutrophil extracellular trap (NETs) due to COVID -19 virus present in the body. There is an increasing risk of pulmonary metastasis due to reawakening of breast cancer promoted by NETs and pro-inflammatory microenvironment.

2. Classification based on pathophysiology of breast cancer

Different types of breast cancer cells can be found in different area of breast (between the tissues, duct, lobules) the cells that are affected specifically in the breast gives the indication and determine the type of breast cancer. Breast cancer can be classified into two broad categories – carcinoma and sarcomas.

Carcinoma – in this type of breast cancer , the malignancy is originates from the epithelial cells which covers the lobules and mammary ducts and it the common type of breast cancer that can be found in majority of female patients. Sarcomas- in this type of breast cancer, the malignancy starts from stromal part of the breast consist of blood vessels and fibroblast**.**

2.1 On the basis of pathological features breast cancer can be again classified into three categories

Non-invasive breast cancer also known as ductal carcinomas (DCIS) is the most common type of carcinomas having a great potential to convert into invasive carcinoma. **Invasive breast cancer** have the tendency to spread in the other part other than breast lobules and ducts such as lymph nodes and other major organs, it proliferates in stromal tissues of breast. After spreading in other body parts it categorizes under metastatic breast cancer. **It is further divided into two categories –** Invasive Ductal carcinoma (IDC) and Invasive lobular carcinoma (ILC). IDC is the common type of breast carcinoma which sub divided into tubular carcinoma, papillary carcinoma and cribriform carcinoma. And invasive lobular carcinoma is 2nd most common breast carcinomas and it is majorly found in older women. **Metastatic breast cancer** is a fourth and last stage of the breast cancer because it can be easily spread to the other major organ of the famine body includes lymph nodes present in the armpits and distal sites of brain, liver and bones it has the tendency to relapse, which make it more dangerous and deadliest stage of the breast cancer (figure -1) [3, 4, 5, 6, 7].

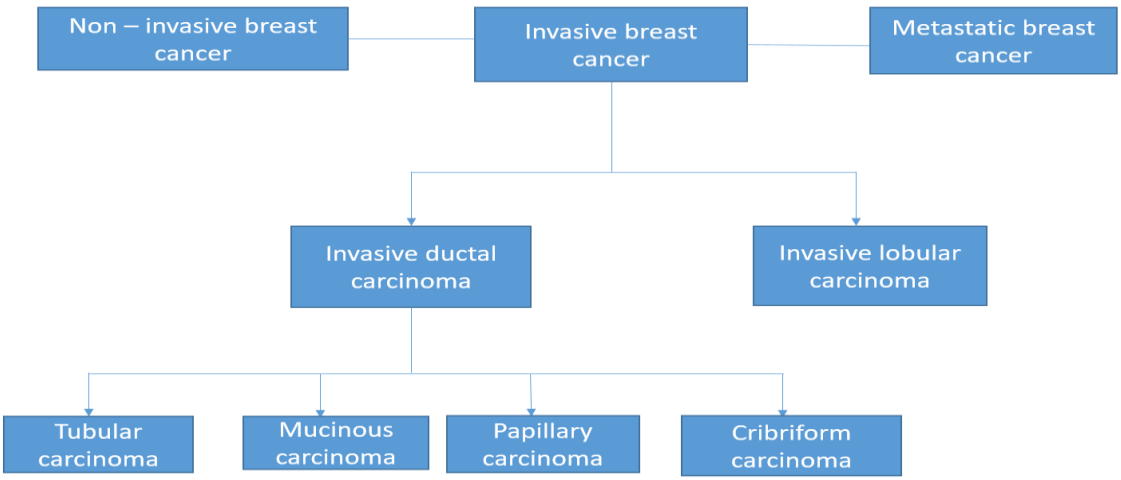

Figure-1 classification of breast cancer on the basis of pathophysiology of carcinoma.

2.2 Rare type of breast cancer

Inflammatory breast cancers (IBC): it is one of the rare type of invasive breast cancer very aggressive in the nature and spreads faster than any other type of breast cancer. It shows different kind of symptoms in comparison to commonly occurring breast cancers, it shows inflammatory symptoms like – change in the skin color of the breast (pink, purple and red) edema and heaviness due to thickening of the breast skin layers results in the lymph vessels blockage.

Luminal breast cancer (A): It is a kind of very low grade and slow progressing type of breast cancer. It has decreased level of Ki-67, subtype luminal A cancer is HER2 negative, progesterone- receptor positive or estrogen receptor.
Luminal breast cancer (B): It is a kind of fast growing type of cancer, having elevated levels of Ki-67and is ER or PR positive either HER2 positive or HER2 negative [3, 4, 5, 6, 7].
HER2-enriched breast cancer: This breast cancer is recognized by the absence of ER and PR expressions. There will be a less expression of luminal and basal cluster and more expression of proliferated gene cluster and HER2 expression.

3. Risk factors causing breast cancer

Genes related to breast cancer - On chromosome 17q21 and 13q12 the two genes are found BRCA1 and BRCA2 respectively falls under anti-oncogene category responsible for breast cancer. The tumor suppressor proteins are encoded by both of them. Deregulation of check points in cell cycle, duplication of chromosome, instability in genetics and apoptosis is only due to the deficiency of BRCA1 [8, 9] (Deng (2006) Dine and Deng (2013) Inherited mutated gene either BRCA1 or BRCA2 genes increases the risk of breast cancer in an individual [10, 11]. BRCA2 is responsible for invasive ductal carcinoma fourth stage of breast cancer [12].
HER2 -Present on the long arm of chromosome 17(17q12) it is an important oncogene responsible for breast cancer [13]. Amplification and re-arrangement in genes activates the HER2 expression. It belongs to tyrosine kinase family which activates the downstream signaling pathways by forming heterodimers with other ligand bound epidermal growth factor receptor (EGFR) [14].
Early puberty and delayed menopause. Women who have started there menstruation in very early age 11or 12 and the women who have their menopause at the age of 55 or later are at the high risk of breast cancer due to the long time exposure of estrogen and progesterone to the breast cells.
Timing of pregnancy. Pregnancy is the important period of women's life as it helps in completing the cycle of breast cells and allow them to mature completely. So the women who conceive first time after the age of 35 or who have went through multiple miscarriages are at the high risk of breast cancer.
Hormone replacement therapy after menopause. It is also called post menstrual hormone therapy, in this estrogen and progestin hormones are given to the women after menopause which leads to longer exposure of the breast cells to the hormones which increases the risk of breast cancer in the women taking hormone replacement therapy.
Oral contraceptives or birth control pills. Some studies shows that oral contraceptive pills prevent the pregnancy but on the other hand it may increase the risk of breast cancer.
Lifestyle factors.
Weight -Few recent studies shows that women who gain weight after menopause will be at high risk of breast cancer as well as come back of the cancer after the treatment also.
Physical activity-Lack of physical activities leads to weight gain in the body which can develop the high risk of breast cancer, so it is very necessary to maintain a healthy body weight by performing some moderate exercise which can lower risk of breast cancer by lowering the hormone count. It may also prevent the coming back of the treated cancer.
Radiation exposure at a young age- Women suffering from Hodgkin lymphoma goes under therapeutic ionizing radiation may increase the risk of breast cancer in both the breast [15].

4. Initiation of breast cancer cells, of mammary gland and stem cells

Regulation of epithelium mesenchymal interactions leads to development of mammary epithelium during the fetal development from the placode of an epidermal [16]. The mammary glands are present in the complex stroma in the form of branch network go down to the primary mesenchyme and produce basic ductal structure of gland during birth [16, 17] .it is formed by 10-12 basic stage of mammary duct components are placed under the nipple areola area. At the time of puberty, pregnancy and lactation the breast goes under modification in shape, size and its functions because of growth factor receptor signaling and steroid hormones like- estrogen and progestin. Mammary epithelium of breast possess a unique function, they are highly reactive to systemic and local signals and shows morphological changes during the puberty and lactation in the ductal tree [18]. The study suggests that the stem and progenitor cells are also present within the mammary epithelium [18, 19], there is also a evidence of presence of bipotent mammary stem cells (MaSCs) which causes morphogenic and homeostasis in the ductal structure [18, 20]. Mammary stems cells are present in the mammary gland in a very small count but have the tendency of self -renewal and produce new MaSCs through even and uneven divisions [21]. They are deliberately to operate by interacting closely with their unique cellular milieu, which is also known as the mammary stem cell niche [21, 22, 23].

5. Roles of mammary stem cells in breast cancer development

As MaSCs plays an ordinary part in the body called as cancer stem cell theory which explains the relation between the MaSCs and breast cancer [24, 25]. Whereas cancer stem cell theory has a past record which explains the advancement of the theory related to breast carcinoma [26, 27]. The essential part of this hypothesis is whether cancer stem cells are the cell of beginning from which disease cells create, a speculation dependent on perceptions of the similitudes between tissue renewal and carcinogenesis, or then again if cancerous cells achieve immature SC potential. [28, 29].Viably, the discussion unifies throughout the significance of bipotent and unipotent luminal and myoepithelial undifferentiated stem cell during both ordinary development of cell and cancer [26, 27]. The CSC hypothesis is based on a generally acknowledged cellular hierarchy structure in both normal and cancerous cells, with stem cells at the top and cells developing from there. CSC hypothesis lays on a generally acknowledged design of cell chain of command in both ordinary and cancer-causing cells with stem cell living at the peak point and cells start separating out there [29]. The outcome of this frame is that MaSCs, as particular from mammary reproducing cells, are bi-or multipotent. These mammary reproducing cells can be distinguished as taking on multipotent attributes under reconstructive conditions can be seen through transplantation [30, 31]. MaSCs are put forward to live in different microenvironment – stem cell niche, which shows the valuable relationship within epithelial cells that arises from MaSCs, surrounds the extracellular matrix and stromal cell (figure-2) [27].MaSCs carcinogenic role and its signaling pathway is still not well understood [26, 27].Two significant cell lineages lie at the foundation of this contention as far as breast CSC beginning: basal cells and luminal cells. Basal cells are found on the epidermal layer of the mammary gland, and the other being luminal cells. Basal cells are responsible for the formation of luminal cells layer, it surrounds the lumen of the mammary ducts and alveoli. Cytokeratin-8 are exhibited by luminal cells whereas cytokeratin-5,-14 by basal cells [26, 27].

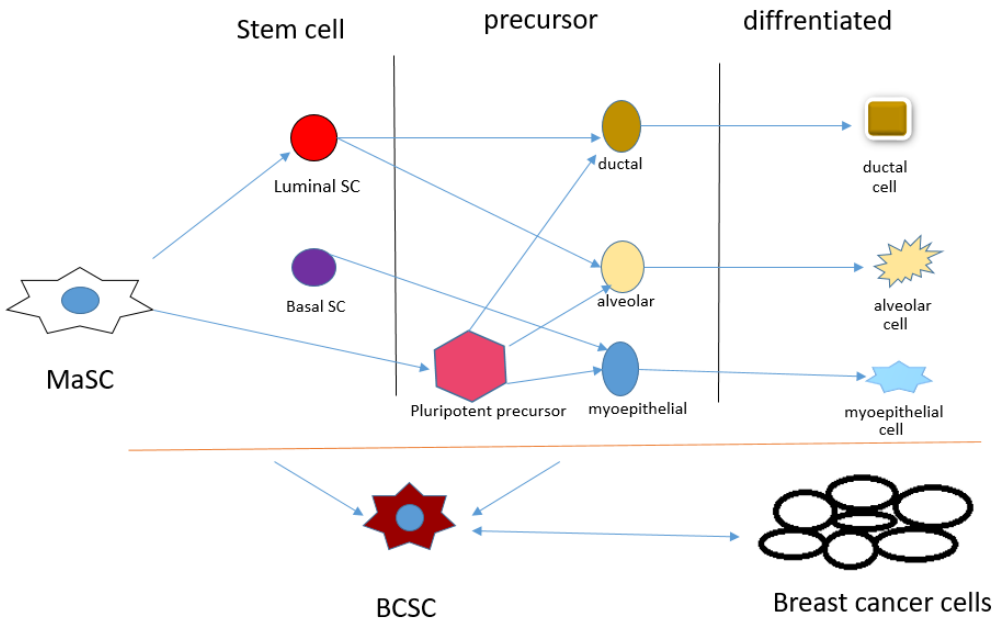

Figure 2 - stem cells from breast cancer Mammary stem cells (MaSCs) are multipotent self-regenerating cells that play a role in the development and healing of the mammary gland, as well as in the development of breast cancer stem cells (BCSCs)

6. SPECIFIC CELL SIGNALING IN BREAST CANCER

6.1 CDKs

To block the kinase activity the endogenous protein CDKI interact with Cyclin- CDK complex as a response from damaged DNA. The two major CDKs families are – INK4 and cip/kip family. INK4 family inhibit and binds to CDK monomer without failing. Complex of CDK6-INK4 indicates the twist in CDK to interrupt Cyclin binding and kinase activity. The cip/kip protein family makes the complex with cyclins as well as CDKs which shows inhibitory as well as activatory action [32]. The activation of subunits, cyclins D_1, D_2, and D_3 are necessary for forwarding the cell cycle from G_1 to S phase for phosphorylation by retinoblastoma (Rb) protein complexing of CDK_4 or CDK_6 responsible for activation of subunits. Activation of E2F by the segregation of hyper activated phosphorylated Rb protein from E2F/ DP1/Rb complexes, causes transcription in the genes – cyclin E, cyclin A, DNA polymerase and thymidine kinase. Formation of complex cyclin E-CDK_2 helps to process cell cycle from G_1-S phase. Completion of S phase takes place by the CDK_2 - cyclin A and CDK_1 – cyclin A. This process helps in the transition of G_2 to M phase [33]. Results in the completion of cell cycle and cell will start proliferation. According to the information, the prevention and proliferation of the cancer cell and inhibition of hyperactive phosphorylation can be done by targeting CDK function (figure-3).

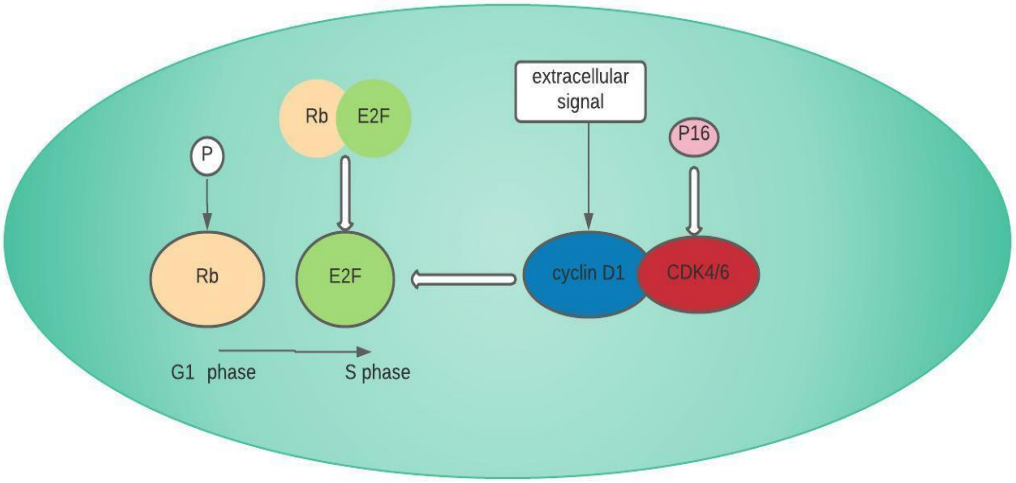

Figure 3 - CDKI protein is an endogenous protein that interacts with a cyclin CDK complex to block kinase activity.

6.2 Notch signaling pathway

Notch signaling regulates the differentiation in cell and their destination. Activation of inflammatory cytokines (IL-6, IL-1) and hypoxia by ligand binding regulates the Notch expression. The Notch signal have four Notch receptors which are present on arterial and not venal vessels, these proteins conducts paracrine signal and are membrane bound. The four Notch receptors are Notch-1, Notch-2, Notch-3, Notch-4 and five ligands related to it, Jagged-1, Jagged-2, DIL-1, DIL-3, DIL-4 (delta like). It is a fundamental pathway which works in cell specification and organ development [34, 35]. The signaling depends on the receptor binding, endocytosis process and cell-cell communication for DELTA/SERRATE ligands. DIL-4 is a positive regulator for tumor progression and a negative regulator for tumor genesis. DIL-4 triggers the large diameter blood vessel formation with accurate perfusion and oxygenation capability whereas its presence and expression in cancer cells inhibit the process of new blood vessels formation. Because the vessel system is not in proper functionality there is increase in angiogenesis, tumor growth and expansion in solid mass [34, 36]. In the arterial endothelial luminal region there is start point of up-regulation for DIL-4 and there is a sprouting new vessels in response to angiogenic stimulus due to up- regulation of DIL-4 ligand in cardiovascular system. There is a negative impact on vessel formation due to down regulation of the DIL-4, and if there is new vessel formation then there functionality is inhibited which leads to impaired tumor growth. There is also a nonfunctional vasculature in neoplasm because of the down regulation of DIL-4 ligands, and this nonfunctional vasculature is not capable to transport blood to the neoplasms leads to tumor growth. There will be a different type of cell to cell communication due to lateral inhibition and boundary formation [37, 38]

6.3 Wnt signaling pathway

The Wnt signaling is the primary pathway whose elements can be changed by epigenetic processes. It has played an important role in the formation of several organ systems throughout evolution. A multipotent scaffold is made up of APC, GSK-3, axin and –catenin are located at the center of the pathway which is encoded by CTNNB1 gene. –Catenin level remain low in the absence of Wnt ligand due

to continuous phosphorylation by GSK-3, which results in uniquitynylation and destruction of –catenin [39]. When ligands bind to frizzled (Fz) receptor, the activation of disheveled (DvI) will happen and activity of GSK-3 is inhibited which results in the decrease in phosphorylation and continuous destruction of –catenin, it is established and translocated in nucleus, it is attached to Tcf (T- cell factor) member which stimulates target genes regulation such as CCND1 and CMCY [40]. Nuclear –catenin a hallmark of active WNT/-catenin signaling is enhanced in a variety of human malignancies, but mutation in the APC, AXIN, or CTNNB1 genes are not common. The elements of pathway are up-regulated such as transforming gene WNT ligands, members of Fzd receptors can also cause aberrant WNT/-catenin signaling [41, 42]. Study proves that deactivation of WNT/-catenin pathway inhibitors are linked to a tumor-favorable phenotype result in a range of human cancers. WNT signaling abnormalities are the solid reason for cancers, including cancer of colon and lung carcinoma [43]. The activation of aberrant WNT/-catenin signaling in cancer has been linked to loss of functionality of negative Wnt regulator via epigenetic silencing of gene, which involves both modification in histone of gene-associated promoters of tumor suppressors and methylation of DNA [44]. Several human malignancies have been found to exhibit poor balancing of antagonists of Wnt due to high methylation rate [45, 46]. In breast cancer, colon cancer, hepatic carcinoma and cancer of prostate glands it is found that there is up-regulation of Wnt proteins [47, 48]. WNT5A is a tumor suppressor that limits tumor cell proliferation by antagonizing WNT/-catenin signaling and is constantly suppressed by methylation process in particular tumor and blood cancers [49, 50]. As WNT/-catenin signaling deregulation constantly play their role in pathogenesis of tumor, identifying abnormal epigenetic incidence that stimulate WNT/-catenin signaling could be very effective as a biomarker in the detection of cancer. Methylation in secreted frizzled related protein 2 is found to be biomarker for particular tumor in initial stage of breast cancer [51, 52].

6.4 ER signaling pathway

Estrogen receptors includes mostly GPCR (membrane estrogen receptors) and ERα and ERβ (nuclear estrogen receptors) [53, 54, 55, 56]. ESR1 codes ERα and ESR2 codes ERβ having common functions and structural ability [55, 56, 57]. The highest binding 96% is of DNA binding domain (DBD) among the all six functional domains having the ability to form heterodimers [53, 55]. In target gene, estrogen response elements (EREs) interacts with ER dimers mediated by DNA binding domain [55, 56, 57, 58]. ERs are also responsible for transcription regulation by involving co-activators and co-suppressors [59, 60], including BRCA1. Partial inhibition of ERα signal due to tumor suppressor activity of BRCA1 [61]. ERα is majorly responsible in the amelioration of breast cancer [62]. The amelioration of cancerous cells are due to the interaction of cyclin D1 [63, 64, 65]. As cyclinD1 is an activator in coordination for transition of cell cycle G_1 to S phase. ERβ are expressed by healthy breast tissues are gaining attention over ERβ decreasing level with the increase in tumor cells 98 [66]. Many in-vitro and in-vivo supports its function as breast cancer suppressor [67, 68].

6.5 HER2 signaling pathway

HER2 is an individual from the EGFRs [69]. It is a receptor tyrosine kinase that comprises of an extracellular ligand-binding transmembrane area, and an intracellular domain. [70, 71] The Breast cancer cells have generally high level of ERa expression and low level of ERb articulation. These two types of nuclear hormone receptors form homo- or heterodimers upon ligand binding and translocate

into the cell nucleus for transcriptional regulation, which is the main function of ERs. The main function of ERs is transcriptional regulation by translocate into the nucleus of the cell and forming two dimers, homo- and hetero- on the ligand binding. ER dimers recruits all co-regulators and get themselves attached to targeted genes at ERE region and regulates the transcriptional. Expression of target genes can also be controlled by acting as a co-regulator for other transcription factor to form the dimers with other molecules HER2 is the preferred component [72, 73]. Phosphorylation of tyrosine residues present in the intracellular domain of HER2 is activates by subsequent and ligand binding, which results in the stimulation of various downstream signaling pathways like- PI3K and MAPK pathways [74,75].These both signaling pathways are extremely related with the tumor genesis of breast [70, 71,76]. Multiple human breast cancer cell lines are amplified with HER2 [77] and there will be over activity of HER2 proteins which results in cancer progression and cell proliferation [78]. It has been recently discovered about the mechanism of relationship between HER2 and breast cancer [70, 79]. Whereas the role of ERs and HER3 has been discover long ago [80]. The recent study suggests about the remarkable impression on HER2- driven tumor genesis by a new intermediate factor MED1 [79]. The inflammation and expansion of cancerous stem cells in breast cancer has found to be connected with precancerous effect of HER2 [81].It is newly come under knowledge about target locus of HER2 regulator, TFAP2C who is situated at the 30 gene body of HER2 [82].Progression of metastasis is more likely because of HER2 which is expresses by breast cancer cells. Induction of migration in primary tumor cells is mainly due to progesterone and progesterone induced paracrine signals and this is how they activate mammary stem cells.

6.8 m-TOR/ AKT/PIK3 signaling pathways

These are the major signaling pathways which plays important role in the regulation of cell cycle, cell multiplication and cancer cell survival. Activation of tyrosine kinase receptor stimulates PI3K pathway which triggers the m-TOR and AKT phosphorylation. The breast carcinoma these signaling pathways are responsible for genetic abnormal behavior, which includes- genetic mutation in PI3CA, loss of function due to mutation in phosphatase tensin homologue [83, 84]. In triple negative breast cancer these pathways are overexpresses the regulation because of oncogene activation example – EGRF.

Table -1 Systemic and localized targeted therapy for breast cancer.

Localized therapy	**Methods**	**Systemic therapy**	**Drugs**
Surgery for breast cancer	Breast conserving surgery (BCS) Mastectomy	**Chemotherapy** 1. Adjuvant chemotherapy 2.Neoadjuvant chemotherapy	Anthracyclins Taxanes 5-flurouracil Cyclophosphamides Carboplatin
Radiation therapy	External beam radiation therapy Whole breast radiation	**Hormone therapy** 1.Selective ER modulator	Tamoxifen Toremifene

	Accelerated partial breast irradiation Brachytherapy Chest wall radiation Lymph node radiation	2. Selective ER suppressor 3. Lower ER level	Fulvestrant Letrozole Anastrozole
		Targeted drug therapy HER2 targeted Kinase inhibitor CDK 4/6 inhibitor	 Trastuzumab Pertuzumab Lapatinib Neratinib Palbocilib Ribocilib Abemacilib
		M-TOR inhibitor	Everolimus
		PI3K- inhibitor	Alpetisib
		Immunotherapy	Pembrolizumab

7. COVID-19 effects on breast cancer patients

Serious intense respiratory disorder COVID 2 (SARSCoV-2) pandemic is spreading in reality as we know it where malignant growth pervasiveness is quickly developing, raising worries about expected interlink between the two diseases. SARSCoV-2 volunteers proteins engaged with cell replication, DNA damage, metabolism that are additionally involved in cancer pathogenesis [85].Inflammation induced by COVID-19 at the same time affect tumor cells and their microenvironment. The facts are still missing about the effect of corona virus on breast cancer. The study suggest that particular tumor cell stage presented by dormant cancer cells may get affected due to COVID-19. At times because of microenvironment the DCCs get reawake which results in stimulation of signaling pathway mediated by immune system and inflammatory pathways also. Because of high chances of tumor recurrence in breast cancer, which can last up to 20 years following prognosis, understanding the processes causing cancer cell dormancy and reactivating is critical. Continuous release of damaged associated molecular pattern (DAMPs) with blocked airway epithelial cells is induced by SARS-CoV-2 infection. Recruitment of neutrophils, monocytes and T-lymphocytes to the lungs along with inflammatory cytokines and chemokine's production is stimulated by DAMPs. Lung inflammation will results in ARDS in high level infection of COVID-19. Multiorgan dysfunctioning, systemic inflammation will occur after the activation of immune cells and alteration will be there in immune system upon COVID-19 infection. In peripheral blood stream the level of natural killer cells and T-cells level will decrease, and all the tissue macrophages, monocytes and neutrophils are poorly regulated [86].The proteins and DNA called as neutrophil extracellular trap (NETs) are tissue damaging components released by the activated neutrophils. The NETs will make

physical barrier to stop the local access of immune cells, it also increases the local concentration of antimicrobials by entrapping the pathogens. As NETs and neutrophils are the most involving

components in the pathogenesis of COVID-19 and the corona virus will leads to reawakening tumor cells. The NETs involvement was recorded while there is neutrophil infiltration in lungs when the patient is seriously affected by COVID-19 [87]. The immune-thrombosis will occur because of the NETs presence during COVID – 19 infection in the patient [88]. The metastasis formation will occur in the breast after the exit from dormancy of breast DCCs due to lung inflammation and NETs [89, 90]. Bacterial lipopolysaccharide cause lung inflammation induce metastasis reactivation of breast DCCs and epithelial to mesenchymal transition (EMT) [90]. Activation of lung- relapse DCCs due to laminin (high molecular protein of extracellular matrix) destruction by NET associated proteases and thus cause proliferation and lung metastasis [89]. DCCs reawakening was stimulated due to NET generation and lung inflammation in COVID-19 infection and act with other pro-inflammatory factors. During the serious COVID-19 infection the level of intraleukin-6 (IL-6) and other pro-inflammatory factors will increased and activates the NF-κβ in immune as well as non-immune cells. This activation of NF-κβ can act in directly and indirectly also and reawakes the DCCs by triggering multiplication of cancerous cells directly or by promoting the formation of a pro-metastatic microenvironment indirectly in COVID-19 Patients hypoxia is the very prominent condition because of respiratory stress and thrombosis. In Patients diagnosed with breast cancer the hypoxia condition during COVID-19 results in reawakening of DCCs by stimulating the gene expressions induced in dormancy, drug resistance and EMT [90] (figure-4). The hypoxia condition in COVID-19 suffering Patients act by double action by causing drug resistance that leads to tumor relapse and inducing dormancy. The anti-inflammatory agents can be very helpful by interfering in NET formation and inflammatory pathways mediated by immune system which can decrease the risk of tumor relapse.

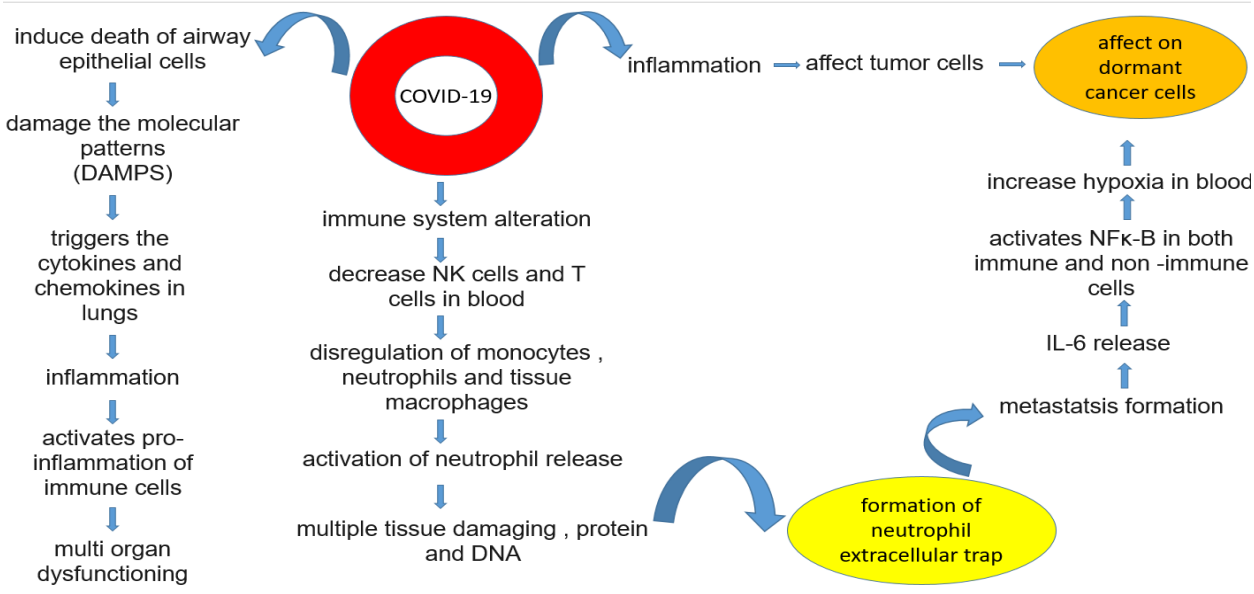

Figure 4- reactivation of dormant cancerous cells in already treated breast cancer patients due to release cytokines and chemokines, causing immune system imbalance results in the formation of NET and triggers the release of IL-6 and follows the inflammatory pathway.

8. Effect of angiotensin converting enzyme-2 on inflammatory pathways in COVID-19 infection

After COVID-19 pandemic, Angiotensin converting enzyme was recognized as the passage receptor for spread of corona virus and the serine protease TMPRSS2 as the efficient for spike (S) protein priming [91]. Viral genome is released after the cleavage of S protein in the presence of enzyme endosomal acid proteases, which is the major path of viral replication [92]. The cascade of catastrophic event will cause when the viral infection stimulate this process after the ACE2 down regulation of severe COVID-19 [93]. In reports the ACE2 was proved to be showing multiple effects- angiogenesis, metastasis and inhibition of cancer resulting in anti-tumor activity. But in COVID-19 condition the ACE2 will be down regulated and show its effects on tumor progression [94, 95]. By renin angiotensin system (RAS) the cardio homeostasis and inflammation is controlled [96], when ACE2 converting enzyme converts the angiotensin II into angiotensin 1-7.When the levels of AngII/ Ang (1-7) got altered the cardiovascular problems will occur in COVID-19 patients and results in prothrombic effects, vasoconstriction and pro-inflammatory effects 23 [96]. Lungs fibrosis occur due to the elevated expression of pro-inflammatory cytokines and TGF-b because of alteration in RAS follows SARS-CoV-2 infection [97]. Critically, the AngII/AT1R pivot follows up on an assortment of non-invulnerable cells to initiate nuclear factor κβ (NF-κβ), for inflammatory process it is an essential transcriptional factor [98]. However, the soluble IL-6 release is activated by AgII , it is also responsible for STAT3 activation 27, NF- κβ hyper activation resulting to Angiotensin converting enzyme decreased level of regulation cumulates with NF-κβ enactment initiated by MyD88 and pattern recognization receptors stimulated by viral particles [99],In cancer cells when NF-is κβ activated it regulates proliferation, invasion and resistance to chemo therapy , but in tumor micro environment (TME) it promotes immune suppression and angiogenesis and together they stimulate the process of metastasis [100].

9. Consequences of IL-6 AND IL-1 signaling activation in COVID-19 during cancer

It is found that the COVID-19 patients faces the respiratory problems and cytokine release syndrome (CRS) which is the very serious condition and patients need to be admitted in intensive care units(ICU), the CRS will results to be very toxic for the patient which sustain the fever , failure of organs , neurological problems edema which are life threatening 26 [101], cytokines which are found in the plasma of corona virus infected patients are intraleukin-1b, IL-6, IL-7, IL-8, IL-9, IL-10, MIP, G-CSF, monocyte chemo attractant protein-1, GM-CSF, PDGF, VEGF ,TNF-α 30-32.In the pathophysiology of CRS, IL-6 plays a critical role [102, 103]. Inflammation and tissue damage may ensue from uncontrolled IL-6 signaling [104]. IL-6 signaling is stimulated in white blood cells and macrophages and dendritic cells while in corona virus infection, generated interleukin (IL-6) which amplify the inflammatory process, a positive feedback loop that results in the creation of more IL-6 (figure-5), Vascular endothelial growth factor, and other chemo attractant proteins [105, 106]. In addition to its important part in the inflammation mediated by immune system, IL-6 promotes carcinogenesis by stimulating cancer cells directly and indirectly through the TME. In several tumor types, IL-6 promotes tumor development, metastasis, and immune evasion [107, 108].In addition, IL-6 has direct effects on cancer cells, such as the potential to increase stem cell properties [108, 109], development of mesenchymal properties [110], and therapy resistance [111]. It has also been demonstrated to drive immune entry by promoting the stability of programmed death-ligand 1 [112]. Although a molecular connection between IL-6 and DCC reawakening has yet to be discovered, increasing IL-6 levels have been linked to higher rates of tumor

recurrence in breast carcinogenesis [113, 114].In animal models for breast carcinoma, head & neck, and hepatic carcinoma, inhibiting IL6/STAT3 signaling reduced cancer recurrence [115, 116]. IL-6 has been demonstrated to have anti-cancer effects via boosting T-lymphocyte progression and adhesion to the endothelium of cancer, in addition to its pro-carcinogenic effects [117]. Overall, IL6 may have numerous and possibly play opposing part in cancer patients and corona virus infected patients, which can be investigated further. In addition to IL-6, COVID-19 patients have been found to have higher levels of IL-1b than controls [102]. In COVID-19 patients, high dosages of the recombinant IL-1R antagonist anakinra resulted in clinical improvement [118]. IL-1b, like IL-6, is thought to have a complicated function in inflammation and cancer. IL1b appears to have a pro-tumorigenic role, since it causes constantly recurring inflammation, attracts myeloid-derived suppressor cells (MDSCs), promotes the process in cancer that allows for the formation of new blood vessels to nourish and maintain the development of malignant tumor and promotes invasion and metastasis [119]. However, IL-1b has been shown to have anti-tumor properties.

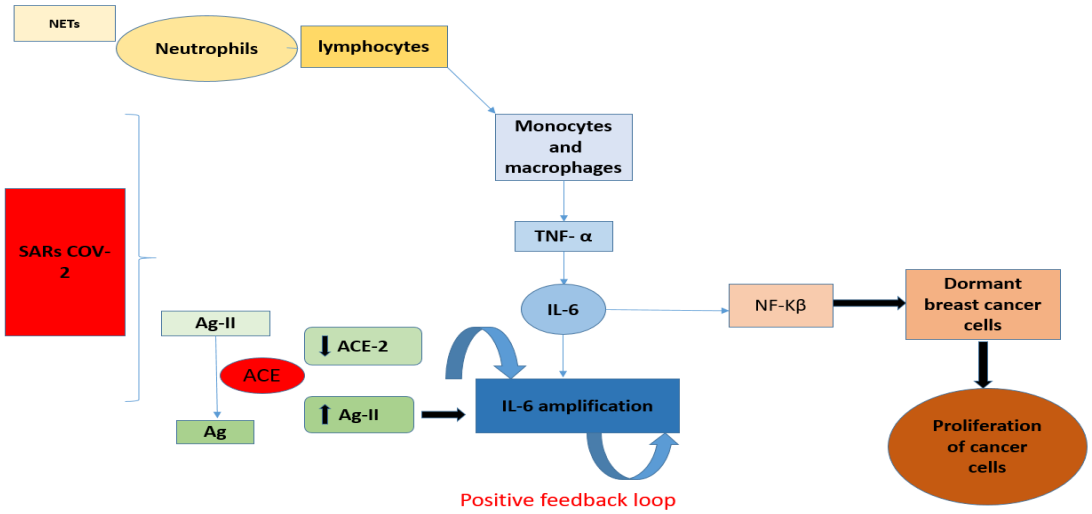

Figure - 5 Inhibition of ACE, leads to increase in Ag which amplifies the IL-6 by positive feedback mechanism results in the proliferation of cancerous cells by reawakening of DCCs.

Table-2 Potential drivers for inflammation in COVID-19 and their inhibitors.

Molecular focused pathway	Possible part in COVID-19	Drug category	Name of drug
IL-6 signaling	More likely to cause inflammation	Anti-IL-6 receptor	tocilizumab
NETs formation	Possibly suppression of immune system	Neutrophils inhibitor	alvelestat
JAK-STAT signaling	Cytokine signaling	JAK1/JAK2 inhibitors	baricitinib

11. Conclusion

Previously at the beginning of pandemic, the patients of breast cancer faced many problems due to delayed surgeries and lack of treatment availability. The doctors and healthcare system was miserably failed in providing medical facilities to the women suffering from breast cancer as the system was afraid to admit them it the hospitals and let them exposed to the COVID-19. As the study shows, SARCoV-2 marks it effects on lungs and weaken the immunity. So, it was thought that breast cancer patients who are already gone under treatment of several cancer therapies already have weak immune system, which make them more susceptible to COVID infection and can worsen their condition and can also be responsible for their death. But later when doctors and medical staff went through all data and medical study for breast cancer patients and all COVID history, and concluded that there is no need to delay the surgeries and treatment as it can also worsen the condition of patient especially for the patients who are at late second stage and third stage of breast cancer. It was also in the records that there are high chances of reactivation of relapsed breast cancer by activating DCCs if they get exposed to the virus. In that case studies suggested that if the IL-6 signaling and STAT pathway will get inhibited the chance of breast cancer recurrence will get very low. And as vaccines are available in worldwide market and are found to be very safe and effective for breast cancer patients and they can get themselves vaccinated and can save them to get infected from SARCoV-2. As breast cancer is a life threatening disease so, it should not get avoided and delayed in treatment.

12. Abbreviations

1. APC- adenomatous polyposis coli
2. GSK–3- glycogen synthase kinase,
3. NETs - neutrophil extracellular trap
4. MaSCs- mammary stem cells
5. CSCs- cancer stem cell
6. SC- stem cells
7. Tcf- T-cell factor
8. Lef- lymphoid-enhancing factor
9. HEGFR- Human epidermal growth factor receptors
10. PI3K- phosphatidylinositol 4, 5- biphosphate 3- kinase
11. MAPK- mitogen activated protein kinase
12. EMT- epithelial to mesenchymal transition
13. ACE2- angiotensin converting enzyme 2
14. CRS- cytokine release syndrome
15. ICU- intensive care units
16. MIP- macrophage inflammatory proteins
17. G-CSF- granulocyte colony stimulating factor
18. M-CAP1-monocyte chemo attractant protein-1,
19. GM-CSF- granulocyte-macrophage colony-stimulating factor
20. PDGF- platelet derived growth factor
21. VEGF- vascular endothelial growth factor
22. TNF-α- tumor necrosis factor α

23. ARDS- alveolar damage and respiratory distress syndrome

Conflict of interest

The author has no conflict of interest.

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