# Innate Immunity in Breast Cancer

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The innate immune system is the first line of defense against invading pathogens and has a major role in clearing transformed cells, besides its essential role in activating the adaptive immune system. Macrophages, dendritic cells, NK cells, and granulocytes are part of the innate immune system that accumulate in the tumor microenvironment such as breast cancer (BC). These cells induce inflammation in situ by secreting cytokines and chemokines that promote tumor growth and progression, in addition to orchestrating the activities of other immune cells. In breast cancer microenvironment, innate immune cells are skewed towards immunosuppression that may lead to tumor evasion. However, the mechanisms by which immune cells could interact with breast cancer cells are complex and not fully understood. Therefore, the importance of the mammary tumor microenvironment in the development, growth, and progression of cancer is widely recognized. With the advances of using bioinformatics and analyzing data from gene banks, several genes involved in NK cells of breast cancer individuals have been identified.

Keywords: Breast cancer ; BC ; NK ; DC ; Macrophages ; Neutrophils ; Microenvironemnt ; TME ; Natural killer ; Monocytes ; Dendritic cells

## 1. Breast Cancer Heterogeneity and the Role of Immune Cells

Among all types of cancer, breast cancer is the most frequent type in women worldwide. Each year, this malignancy affects more than two million women globally, which is the primary cause of death [1]. In 2018, it is estimated that 627,000 women died from breast cancer, approximately 12% of all cancer deaths among women [2]. Despite the advances in management strategies in diagnosis and treatment, the high heterogeneity of this cancer makes it difficult to treat. Breast cancer (BC) can be histologically classified to luminal A, luminal B, Her2 positive, basal-like, and normal-like, with respect to the biomarkers status of estrogen receptor (ER), progesterone receptor (PR), and HER2 [3][4]. It has been found that triple negative breast cancer is the most aggressive and has the lowest overall survival rate between other types of breast cancer [5]. Besides, the tumor microenvironment (TME) plays a dual role in tumor progression and immune repression. The tumor microenvironment influences immune cells to be activated and differentiated towards enhancing tumor progression and favors inhibition of anti-tumor activities. However, the complete interaction between breast cancer cells and the immune cells in the tumor microenvironment is not very well understood [6][7].

The cells of the immune system that are implied in the immune defense are components of either the innate or the adaptive immune system. The first early response to a pathogen or transformed cells is a function of the innate immune cells that act rapidly and non-specifically to an attack to prevent spreading of the foreign pathogen [8]. The cells of the innate immune system control and clear invasion via various mechanisms, such as release of cytotoxic molecules, engagement of more immune cells, complement pathway activation, or activation of the phagocytosis process [9]. In cancer, tumor cells may release some cellular components that may activate the innate immune cells, which in turn establish antitumor immunity in the microenvironment and hence induce tumor eradication [10][11].

The activation of innate immune cells results in the interplay of events that work together to control and destroy tumor cells. For instance, upon encounter with transformed tumor cells, some immune cells such as macrophages and dendritic cells become activated and release large amounts of pro-inflammatory cytokines such as IL-12, IL-15, and type 1 interferon (IFN) that activate natural killer (NK) cells and T helper cell differentiation [12][13]. The activation of innate cells in turn stimulates adaptive immune system by releasing large amounts of IFN-γ and chemokines including CCL3 and CCL4 [14][15][16]. In addition, the release of IFN-γ and IL-12 is necessary to destroy tumor cells by switching anti-inflammatory M2 to M1 phenotype, along with an increase of MHC I molecules on tumor cells [17][18]. Therefore, understanding the cross talk among these cell types and tumor cells can advance the knowledge of how immune cells infiltrate into the tumor microenvironment, which may help in choosing the best personalized immunotherapy therapeutic approaches.

## 2. Components of the Tumor Microenvironment

Apart from tumor cells present in breast cancer, the tumor microenvironment (TME) contains other cells such as fibroblasts and immune cells, extracellular matrix (ECM), blood vessels, and some signaling molecules [19]. TME is important for tumor angiogenesis, immune cells' inhibition, escape from immune surveillance, as well as tumor proliferation and survival. ECM plays a major role in breast cancer microenvironment, as it provides the physical support to solid tumors by its protein components such as collagen and proteoglycan. Additionally, ECM is rich in several growth factors that can regulate angiogenesis and inflammation [20]. In advanced stages, ECM becomes disrupted and dysregulated allowing tumor growth by metalloproteinases (MMPs), aiding in cells migration from or into the TME, and thus assisting tumor metastasis [21][22].

In addition to ECM disruption, rapid growing tumors lack sufficient blood supply, creating a hypoxic and acidic environment. This environment will induce tumor cells to release vascular endothelial growth factor (VEGF) and other angiogenic molecules, causing the formation of new blood vessels from the existing vessels for the tumor[23][24], as shown in Figure 1. Furthermore, the newly formed vessels have irregular wall layers, making them leaky with disrupted blood flow, thus providing inadequate blood and nutrient supply that further enhances angiogenesis and tumor growth [25][26].

TME makes a niche for the proliferation of tumor cells and the neighboring different types of cells such as endothelial and immune cells. The interaction between cancer cells and immune cells promotes modifications in the tumor microenvironment, which induce tumor angiogenesis, growth, progression, and metastasis [27][28]. Moreover, immune cells secrete chemokines and cytokines that attract other cells into the microenvironment, consequently contributing to tumor progression [29]. The immune cells could inhibit or promote tumor growth and their possible dual roles have been previously investigated intensively. For instance, immune suppressive TME has been reported to be essential for tumor survival and growth. Indeed, the importance of immune cells is illustrated by the fact that chronic inflammation correlates with a higher chance of tumor incidence [30]. For this reason, innate immune cells present in the tumor microenvironment such as macrophages, myeloid-derived suppressive cells (MDSC), and neutrophils are associated with immunosuppression, poor prognosis, and tumor progression [31]. On the other hand, the presence of other innate immune cells such as NK cells in TME indicates good prognosis and tumor clearance. Therefore, understanding the TME development and its components, as well as the interaction between various cell types in TME is quite crucial for development and progress of breast cancer (Figure 1).

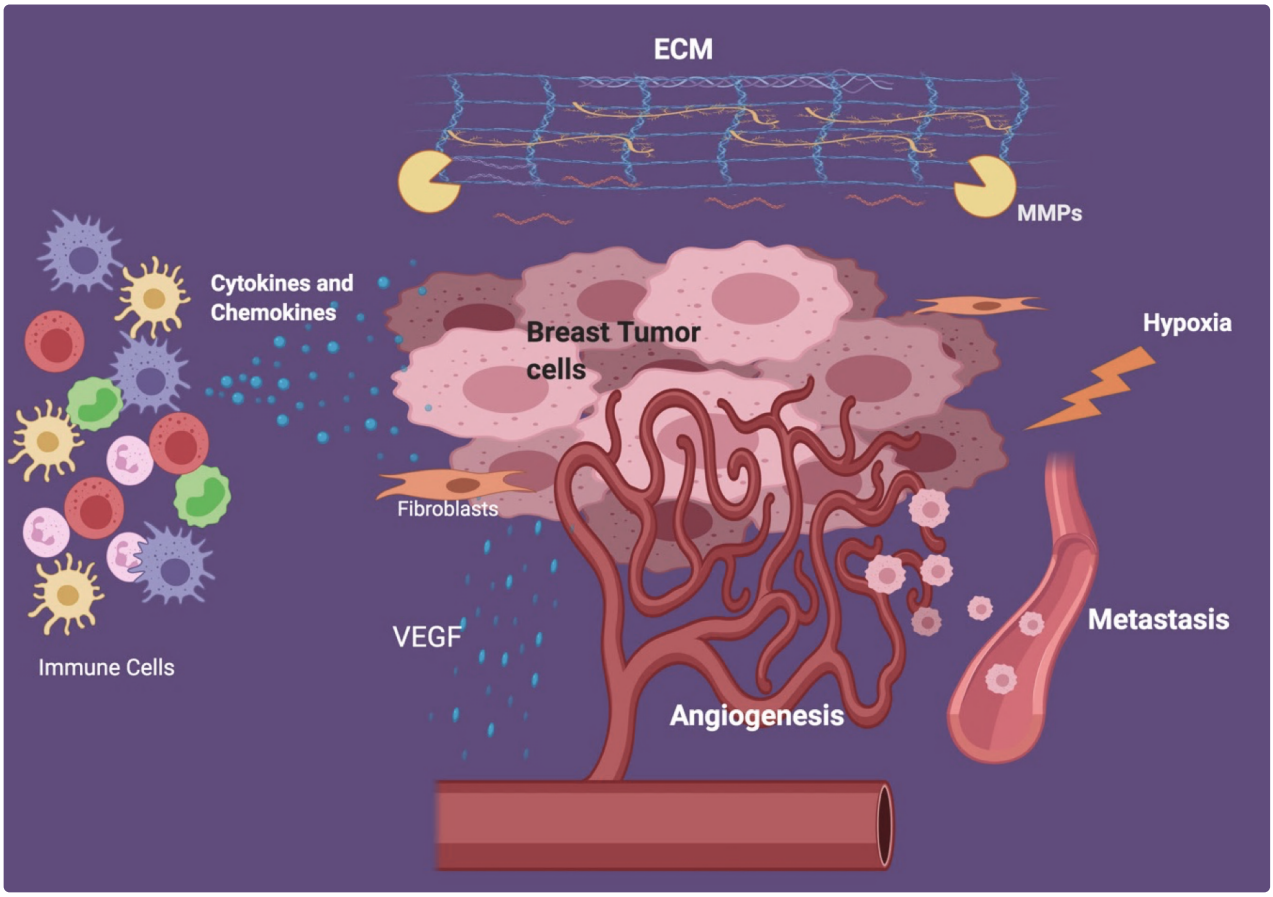


**Figure 1.** Breast tumor microenvironment (TME). Interaction among breast cancer cells and different processes involved in tumor microenvironment development. These include angiogenesis, tumor metastasis, ECM degradation and remodeling, cytokines and chemokines release, hypoxia, and VEGF release.

## 3. Effects of Innate Immune Cells on Breast Cancer Microenvironment

The effect of the immune cells on breast cancer growth and survival depends on both the subtype of cancer and the presence of inflammatory cells in the breast cancer microenvironment [32]. Breast cancer cells interact with various types of immune cells, among which are innate immune cells including monocytes, macrophages, NK cells, and neutrophils. These immune cells can regulate tumor cells proliferation, development, and progression. In the initial stages, continuous cell death occurs at a great pace causing an inhibition of the immune system present in the tumor microenvironment. Additionally, the clearance of the dead cells by the phagocytosis pathway may create an anti-inflammatory environment which further inhibits the local immune system [33]. On the contrary, inflammation could be induced by innate immune cells upon encounter with transformed cells. For example, upon contact with tumor cells, macrophages become activated, thus releasing inflammatory cytokines and chemokines such as TNF, IL-1, IL-6, IL-8, and IL-12 [34][35]. In addition, macrophages produce reactive oxygen species, nitrogen oxide species, and different growth factors promoting the generation of an inflammatory environment. Other studies have reported that macrophages could suppress the activity of anti-tumor immune cells and promote tumor progression, survival, and growth [36], as well as stimulate MDSCs to secrete the anti-inflammatory cytokine IL-10 [37]. Many clinical studies have shown that macrophages may increase the metastasis of breast cancer into the lungs, which correlates with poor prognosis of this tumor [38]. Moreover, recruitment of tumor associated macrophages (TAMs) in the cancer environment may promote immunosuppression, angiogenesis, and cancer protection from the cytokine-induced cell death due to activation of Akt pathway [39]. It is worth mentioning that lymphocytes play a crucial function in early tumor immune surveillance, via recognizing and killing early tumor cells, hence preventing breast cancer tumorigenesis [40].

NK cells act as anti-tumor effectors by producing cytotoxic molecules which lyse tumor cells or by secreting large amounts of cytokines and chemokines that can activate and recruit cells of the adaptive immune system [41][42][43][44]. NK cells become activated upon cross-linking and binding of their activating receptors and the target tumor cells, thus increasing the threshold of activation signals above the inhibitory signals [45]. NKG2D is an essential NK activating receptor that can recognize tumor cells via binding to stress ligands (MICA, MICB, and ULBPs) expressed by transformed cells. However, tumor cells try to evade NK cell activity by shedding these NKG2D ligands in order to obstruct NK cells from recognizing tumor cells and performing their cytolytic activity, thus resulting in the escape of breast cancer cells [46][47].

### References


1. Coughlin, S.S. Epidemiology of breast cancer in women. Adv Exp Med Biol. 2019, 1152,9-29.
2. Bray, F.; Ferlay, J; Soerjomataram I.; Siegel, R.L.; Torre, L.A.; Jemal, A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin.2018,68,394–424.
3. Fitzpatrick, A.; Tutt, A. Controversial issues in the neoadjuvant treatment of triple-negative breast cancer. Ther Adv Med Oncol. 2019,11:175883591988258.
4. Perou, C.M.; Sorlie, T.; Eisen, M.B.; Rijn, M.V.D.; Jeffrey, S.S.; Rees, C.A.; Pollack, J.R.; Ross, D.T.; Johnsen, H; Akslen, L.A.; et al. Molecular portraits of human breast tumours. Nature. 2000,406,747–752.
5. Molinero, L.; Li, Y; Chang, C.W.; Maund, S.; Berg, M.; Harrison, J.; Fasso, M.; O'Hear, C.; Hegde, P.; Emens, L.A. Tumor immune microenvironment and genomic evolution in a patient with metastatic triple negative breast cancer and a complete response to atezolizumab. J Immunother Cancer. 2019,7,
6. Denkert, C.; Minckwitz, G.V.; Darb-Esfahani, S.; Lederer, B.; Heppner, B.I.; Weber, K.E.; Budczies, J.; Huober, J.; Klauschen, F.; Furlanetto, J.; et al. Tumour-infiltrating lymphocytes and prognosis in different subtypes of breast cancer: a pooled analysis of 3771 patients treated with neoadjuvant therapy. Lancet Oncol. 2018,19,40–50.
7. Hanahan, D.; Weinberg, R.A. Hallmarks of cancer: The next generation. Cell. 2011,144,646–674.
8. Cerny,; Striz, I. Adaptive innate immunity or innate adaptive immunity? Clin Sci. 2019,133,1549–1565.
9. Iwasaki, A.; Medzhitov, R. Control of adaptive immunity by the innate immune system. Nat Immunol. 2015, 16,343–353.
10. Hagerling, C.; Casbon, A.J.; Werb, Z. Balancing the innate immune system in tumor development. Trends Cell Biol. 2015,25,214–220.
11. Rolin, J; Maghazachi, A.A. Effects of lysophospholipids on tumor microenvironment. Cancer Microenviron. 2011,4,393-403.
12. Bellora, F.; Castriconi, R.; Dondero, A.; Reggiardo, G.; Moretta, L.; Mantovani, A.; Moretta, A.; Bottino, C. The interaction of human natural killer cells with either unpolarized or polarized macrophages results in different functional outcomes. Proc Natl Acad Sci. 2010,107,21659–21664.

13. Helms, M.W.; Prescher, J.A.; Cao Y.A.; Schaffert, S.; Contag, C.H. IL-12 enhances efficacy and shortens enrichment time in cytokine-induced killer cell immunotherapy.Cancer Immunol Immunother. 2010,59,1325–1334.

14. Eisenring, M.; Berg, J.V.; Kristiansen, G.; Saller, E.; Becher, B. IL-12 initiates tumor rejection via lymphoid tissue–inducer cells bearing the natural cytotoxicity receptor NKp46. Nat Immunol. 2010,11,1030–1038.

15. Marcus, A.; Gowen, B.G.;Thompson, T.W.; Iannello, A.; Ardolino, M.; Deng, W.; Wang, L.; Shifrin, N.; Raulet, D.H. Recognition of tumors by the innate immune system and natural killer cells. Adv Immunol. 2014,122,91–128.

16. Corrales, L.; Matson, V.; Flood, B.; Spranger, S.; Gajewski, T.F. Innate immune signaling and regulation in cancer immunotherapy. Cell Res. 2017,27,96-108.

17. Berraondo, P.; Etxeberria, I.; Ponz-Sarvise, M.; Melero, I. Revisiting interleukin-12 as a cancer immunotherapy agent. Clin Cancer Res. 2018,24,2716–2718.

18. Albini, A.; Brigati, C.; Ventura, A.; Lorusso, G.; Pinter, M.; Morini, M.; Mancino, A.; Sica, A.; Noonan, D.M. Angiostatin anti-angiogenesis requires IL-12: The innate immune system as a key target. J Transl Med. 2009,7,5.

19. Foster, D.S.; Jones, R.E.; Ransom, R.C.; Longaker, M.T.; Norton, J.A. The evolving relationship of wound healing and tumor stroma. JCI Insight.2018,3,

20. Walker, C.; Mojares, E.; Hernandez, A.D.R. Role of extracellular matrix in development and cancer progression. Int J Mol Sci. 2018,19,

21. Insua-Rodriguez, J.; Oskarsson, T. The extracellular matrix in breast cancer. Adv Drug Deliv Rev. 2016,97,41-55.

22. Jabłonska-Trypuc, A.; Matejczyk, M.; Rosochacki, S. Matrix metalloproteinases (MMPs), the main extracellular matrix (ECM) enzymes in collagen degradation, as a target for anticancer drugs. J Enzyme Inhib Med Chem. 2016,31,177–183.

23. Ronca, R.; Benkheil, M.; Mitola, S.; Struyf, S.; Liekens, S. Tumor angiogenesis revisited: Regulators and clinical implications. Med Res Rev. 2017,37,1231–1274.

24. Falcon, B.L.; O'Clair, B.; Mcclure, D.; Evans, G.F.; Stewart, J.; Swearingen, M.L.; Chen, Y.; Allard, K.; Lee, L.N.; Neote, K; et al. Development and characterization of a high-throughput in vitro cord formation model insensitive to VEGF inhibition. J Hematol Oncol. 2013,6,31.

25. Dvorak, H.F. Vascular permeability factor/vascular endothelial growth factor: A critical cytokine in tumor angiogenesis and a potential target for diagnosis and therapy. J Clin Oncol. 2002,20,4368–4380.

26. Yi, M.; Jiao, D.; Qin, S.; Chu, Q.; Wu, K.; Li, A. Synergistic effect of immune checkpoint blockade and anti-angiogenesis in cancer treatment. Mol Cancer. 2019,18,60.

27. Shurin, M.R. Cancer as an immune-mediated disease. Immunotargets Ther. 2012,1,1-

28. Deepak, K.; Vempati, R.; Nagaraju, G.P.; Dasari, V.R.; S, N.; Rao, D.; Malla, R.R. Tumor microenvironment: Challenges and opportunities in targeting metastasis of triple negative breast cancer. Pharmacol Res. 2020,153,104683.

29. Nagarsheth, N.; Wicha, M.S.; Zou, W. Chemokines in the cancer microenvironment and their relevance in cancer immunotherapy. Nat Rev Immunol. 2017,17,559–572.

30. Taniguchi, K.; Karin, M. NF-κB, inflammation, immunity and cancer: coming of age. Nat Rev Immunol. 2018,18,309–324.

31. Wang, J.; Li, D.; Cang, H.; Guo, B. Crosstalk between cancer and immune cells: Role of tumor-associated macrophages in the tumor microenvironment. Cancer Med.2019,8,4709–4721.

32. Cimino-Mathews, A.; Foote, J.B.; Emens, L.A. Immune targeting in breast cancer. Oncology (Williston Park). 2015,29,375-85.

33. Birge, R.B.; Ucker, D.S. Innate apoptotic immunity: the calming touch of death. Cell Death Differ.2008,15,1096–1102.

34. Qian, B.Z.; Pollard, J.W. Macrophage diversity enhances tumor progression and metastasis. 2010,141,39–51.

35. Condeelis, J.; Pollard, J.W. Macrophages: Obligate partners for tumor cell migration, invasion, and metastasis. 2006,124,263–266.

36. Xie, H.Y.; Shao, Z.M.; Li, D.Q. Tumor microenvironment: driving forces and potential therapeutic targets for breast cancer metastasis. Chin J Cancer.2017,36,

37. Gabrilovich, D.I.; Nagaraj, S. Myeloid-derived suppressor cells as regulators of the immune system. Nat Rev Immunol. 2009,9,162–174.

38. Chen, Q.; Zhang, X.H.; Massague, J. Macrophage binding to receptor VCAM-1 transmits survival signals in breast cancer cells that invade the lungs. Cancer Cell.2011,20,538–549.

39. Pathria, P.; Louis, T.L.; Varner, J.A. Targeting tumor-associated macrophages in cancer. Trends Immunol. 2019,40,310-327.
40. Imai, K.; Matsuyama, S.; Miyake, S.; Suga, K.; Nakachi, K. Natural cytotoxic activity of peripheral-blood lymphocytes and cancer incidence: an 11-year follow-up study of a general population. Lancet2000,356,1795–1799.
41. Inngjerdingen, M.; Damaj, B.; Maghazachi, A.A. Expression and regulation of chemokine receptors in human natural killer cells. 2001,97,367-75.
42. Caligiuri, M.A. Human natural killer cells. Blood. 2008,112,461–469.
43. Cheng, M.; Chen, Y.; Xiao, W.; Sun, R.; Tian, Z. NK cell-based immunotherapy for malignant diseases. Cell Mol Immunol. 2013,10,230–252.
44. Ames, E.; Murphy, W.J. Advantages and clinical applications of natural killer cells in cancer immunotherapy. Cancer Immunol Immunother. 2014,63,21–28.
45. Maghazachi, A.A. Insights into seven and single transmembrane-spanning domain receptors and their signaling pathways in human natural killer cells. Pharmacol Rev. 2005,57,339-57
46. Costello, R.T.; Sivori, S.; Marcenaro E, Lafage-Pochitaloff, M.; Mozziconacci, M.J.; Reviron, D.; Gastaut, J.A.; Pende, D.; Olive, D.; Moretta, A. Defective expression and function of natural killer cell–triggering receptors in patients with acute myeloid leukemia. Blood. 2002,99,3661–3667.
47. Mamessier, E.; Sylvain, A.; Bertucci, F.; Castellano, R.; Finetti, P.; Houvenaeghel, G.; Charaffe-Jaufret, E.; Birnbaum, D.; Moretta, A.; Olive, D. Human breast tumor cells induce self-tolerance mechanisms to avoid NKG2D-mediated and DNAM-mediated NK cell recognition. Cancer Res.2011,71,6621–6632.