

REVIEW

Editorial Process: Submission:04/01/2025 Acceptance:09/27/2025 Published:10/17/2025

Bringing DARC to Light: Role of Duffy Antigen/Receptor in Breast Cancer Progression and Cancer Prevention

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Abstract

Background: Duffy Antigen/Receptor for Chemokine (DARC), also called Atypical Chemokine Receptor 1 (ACKR1), is a seven-transmembrane receptor expressed on erythrocytes, lymphatic and vascular endothelial cells, keratinocytes, neurons, etc. ACKR1 is incapable of traditional G protein-coupling signaling and instead functions as a “decoy receptor,” binding multiple chemokines and facilitating their internalization and degradation. This regulates immune responses and inflammation, making it significant in the context of breast cancer. **Methods:** A comprehensive literature search was performed using keywords including “Duffy Antigen/Receptor for Chemokine (DARC)”, “Atypical Chemokine Receptor 1 (ACKR1)”, and “breast cancer”. Studies assessing ACKR1 expression in various breast cancer subtypes and its correlation with patient outcomes were analyzed. **Results:** Reduction in the levels of pro-angiogenic chemokines such as CCL2 can inhibit tumor growth, angiogenesis, and metastasis. High expression of ACKR1 is related to improved patient outcomes, such as enhanced disease-free survival. Conversely, low ACKR1 expression is associated with increased metastatic risk, especially in aggressive subtypes like triple-negative breast cancer. **Conclusions:** Given its potential as a biomarker and therapeutic target, further investigation into DARC’s mechanisms may reveal new strategies for cancer prevention and treatment. Overall, ACKR1 is a promising area of research, providing information about the interplay between inflammation, tumor progression, and immune surveillance.

Keywords: Duffy Antigen/Receptor for Chemokine- DARC- Atypical Chemokine Receptor 1- ACKR1

Asian Pac J Cancer Prev, 26 (10), 3581-3588

Introduction

Duffy Antigen/Receptor for Chemokine (DARC), also known as Atypical Chemokine Receptor 1 (ACKR1) is a seven-segment transmembrane receptor found on erythrocytes, vascular endothelial cells, alveolar epithelial cells, Purkinje cells in the brain, and collecting tubules of the kidney [1-3]. It was discovered as a blood group antigen in 1950 (Duffy antigen and hence Duffy blood group) from the antibody against it found in the serum of a multiply-transfused hemophiliac man named Duffy and was the first gene locus assigned to a specific human autosome [3, 4]. ACKR1 is a promiscuous or multispecific receptor as it binds to CC and CXC subfamilies of chemokines, unlike other chemokine receptors, which bind to ligands restricted to the same subclass (Figure 1).

Chemokines are a family of small proteins that act via G protein-coupled receptors and play a role in immune cell trafficking in immunoregulatory processes like inflammation. Of the four structural subclasses of chemokines, CC and CXC bind to ACKR1 with

high affinity [5, 6]. The function of chemokines also extends to leukocyte migration, activation of integrins, epithelial homeostasis, angiogenesis, cancer progression, etc. Chemokines can be inflammatory or homeostatic [7]. The major function of ACKR1 is to act as a ‘sink’ for chemokines- inflammatory and homeostatic chemokines, once bound, are internalized and targeted into lysosomes for degradation. This reduces the concentration of chemokines in the systemic circulation, reaching distant organs, including bone marrow, where they could stimulate leukocyte release [8]. Decreased plasma chemokines also prevent leukocyte activation and desensitization. Studies show that higher ACKR1 expression in breast cancer is associated with better outcomes, including enhanced disease-free survival (DFS) and lower rates of metastasis. Conversely, loss of ACKR1 expression is linked to increased cancer development and metastasis. Furthermore, ACKR1 expression varies among populations, with African-American patients showing a higher proportion of tumors with low ACKR1 expression, highlighting its potential as a prognostic biomarker for

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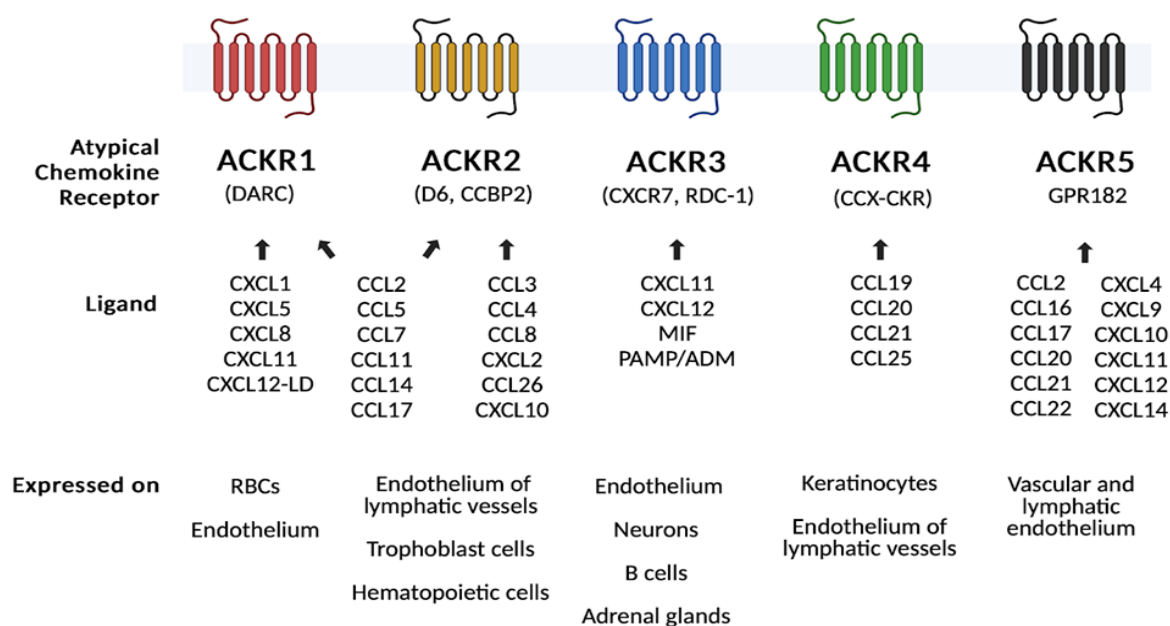


Figure 1. Atypical Chemokine Receptors and Their Ligands. Created with BioRender.com

breast cancer.

It is uncertain whether ACKR1 is a prerequisite for developing inflammatory lesions or a result of it. *In vivo* and *in vitro* studies have shown that ACKR1 is preferentially expressed on endothelial cell junctions and basolateral or abluminal surfaces but not on apical surfaces [9]. In this location, extravascular chemokines accumulate and internalize at the abluminal surface, followed by transcytosis and transfer onto the luminal surface [10]. A significant portion of this is not secreted, and a greater concentration of chemokines on the luminal surface of endothelial cells stimulates firm adhesion of rolling leukocytes. Inflammation can increase the expression of ACKR1 in post-capillary venules and even lead to its expression in vascular segments devoid of it [11, 12]. Lee et al. showed that CXCL-1-induced neutrophil transmigration was higher in human endothelial cells transfected with ACKR1 than in controls [13]. Similarly, CCL2 and CCL5-induced transmigration of monocytes was higher in MDCK cells transfected with ACKR1 than in controls [9]. Although this mechanism of chemokine transport does not lead to its degradation, it reduces pro-inflammatory extravascular chemokines circulating in the extracellular environment, thus impeding tumor growth [14].

The aim of this review was to integrate existing research into a broader context, focusing on novel therapeutic and diagnostic opportunities in breast cancer, and emphasizing how population-specific genetic variations in ACKR1 could impact cancer risk and treatment strategies. This was done based on a literature survey of articles on PubMed using the keywords “ACKR1” and its synonyms, yielding 2151 articles. It was further filtered by adding the term “breast cancer” which in turn yielded 78 articles. We then evaluated these articles to look into the specific role of ACKR1 in breast cancer prevention and progression, resulting in 26 articles, which were finally taken into

consideration in this manuscript (Figure 2). By identifying ACKR1 as both a potential biomarker and therapeutic target, we could improve early diagnosis, personalize treatment plans, and develop strategies to prevent metastasis, ultimately increasing patient survival rates and quality of life.

Structure of ACKR1

ACKR1 is a glycosylated membrane protein encoded by the gene ACKR1, also known as FY gene. Polymorphisms in this gene are responsible for the two alleles FYA and FYB, which code for Fya and Fyb antigens, respectively, leading to the Duffy blood group system. Although initially described as having nine transmembrane domains, ACKR1 contains 336 amino acids (molecular weight 35733) and seven transmembrane domains [15-17]. It has four extracellular domains (ECDs), all of which bind to chemokines, whereas the highly flexible ECD1 binds to malarial parasites via their Duffy-Binding Protein (DBL) domain [18]. *Plasmodium vivax* and *Plasmodium knowlesi*, the causative agents of malaria, invade RBCs by binding of their DBL domain to the Duffy antigen (specifically epitope of Fy6 antigen) present on erythrocytes. Mutation in GATA promoter region of the ACKR1 gene leading to its downregulation (Duffy-negative individuals with Fy(a-b-) genotype) confers protection against malaria by preventing this invasion [19]. *Staphylococcus aureus* exploits ACKR1 as a receptor to lyse RBCs, releasing iron from the cells which is needed for its growth and survival [20].

A characteristic feature of ACKR1 is its inability to generate second messengers. Since it lacks an Asp-Arg-Tyr (DRY) motif- a conserved sequence of amino acids needed for coupling of G protein- ACKR1 can not lead to cell signaling in the form of calcium flux, gene transcription or GTPase activity [21, 22]. This has earned it the title of a “decoy” or “atypical” receptor.

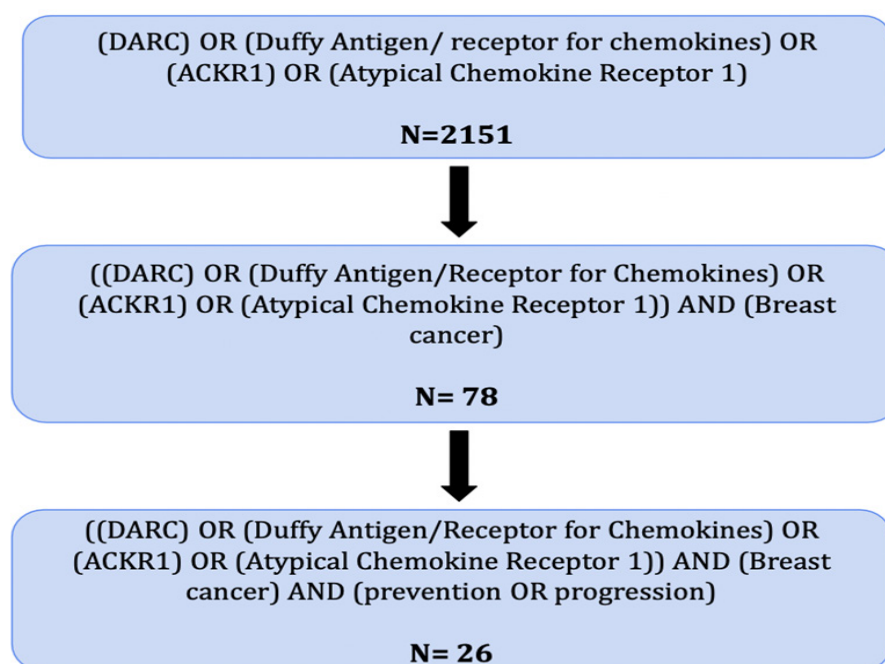


Figure 2. Workflow of Literature Review Performed on PubMed.

ACKR1 and Breast Cancer

Breast cancer has a distinct metastatic pattern involving regional lymph nodes, bone marrow, lung, and liver. Chemokine signaling is necessary for tumorigenesis, angiogenesis, and metastasis. The same chemokines also recruit immune cells against tumor cells. For example, CCL5 signaling through CCR5 recruits anti-tumor natural killer cells and cytotoxic T cells, but also stimulates pro-tumor, tissue-resident myeloid cells and lymphocytes [23]. CCL2, known as monocyte chemoattractant protein-1 (MCP-1), is mainly produced by monocytes, macrophages, and dendritic cells. Elevated levels of CCL2 in the bloodstream have been linked to the invasion and spread of breast cancer. ACKR1 overexpression was shown to interfere with the signaling pathway of CCL2, thus decreasing its level and protecting against tumor angiogenesis and metastasis [24]. Chemokines and their receptors are implicated in cancer due to their role as regulators of inflammation, as chronic inflammation can increase the risk of the development of cancer (Figure 3). The spatial and temporal expression of chemokines influence the composition of TME. Tumor cells produce chemokine receptors, which enable them to respond to specific chemokines. As mentioned above, ACKR1 maintains homeostatic chemokines and prevents excess leukocyte activation, thus avoiding tumorigenesis. It internalizes pro-angiogenic chemokines such as CCL2, CXCL2, CXCL8, etc., preventing tumor vascularisation and tumor growth [25]. Shen et al., using a transgenic model of prostate cancer with ACKR1-deficient mice, observed that the tumor had higher vessel density, higher levels of intratumoral angiogenic chemokines, and augmented growth [26]. ACKR1 also binds to CXCL12, which is responsible for tumor migration and metastasis [27]. Negative ACKR1 expression was strongly associated with neoangiogenesis as well as lymph node, bone, and

hepatic metastasis in breast cancer patient tissue. We analysed the expression of ACKR1 in the TCGA cancer database (Figure 4), which showed a lower expression of this gene in both breast cancer samples and breast cancer cell lines as compared to the controls, thereby implying that a loss of ACKR1 expression is vital for cancer development, whereas high ACKR1 is protective. Further, there is an elevated trend of ACKR1 in well-differentiated cancers (Figure 5), implying a good prognosis in high in high ACKR1 tumors.

Liu et al. showed that patients with the Duffy-positive phenotype had a lower incidence of breast cancer occurrence and metastasis, while Duffy-negative patients had a higher one [28]. Breast cancer tissue with higher expression of ACKR1 led to lower levels of chemokines, creating an inhospitable milieu that is less conducive to supporting tumor growth and progression. ACKR1-enriched tumors have better outcomes with enhanced disease-free survival (DFS) as compared to ACKR1-negative/low expressive tumors. Jenkins et al., investigated the role of ACKR1 in triple-negative breast cancer (TNBC). They found that African-American patients had a higher proportion of tumors with low ACKR1- expression when compared to White Americans [29]. Thus, ACKR1 can serve as a potential biomarker of good prognosis.

Role of ACKR1 in Other Diseases

Apart from breast cancer, ACKR1 is associated with other subtypes of cancer such as prostate, thyroid, melanoma, non-small cell lung carcinoma (NSCLC), etc. [26, 30]. Addison et al. found that NSCLC expressing ACKR1 had more necrosis and less tumor cellularity than controls [31]. Downregulation of ACKR1 has also been suggested to potentiate colorectal and melanoma tumor development and progression via increased angiogenesis

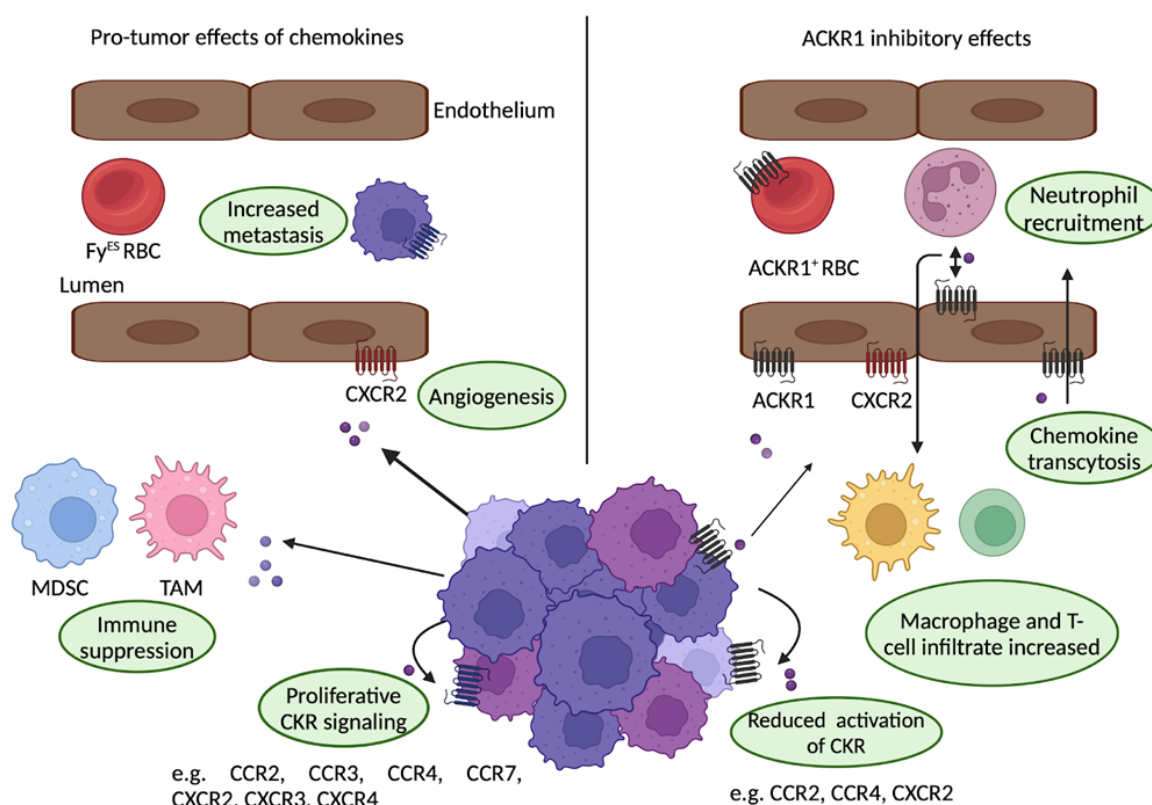


Figure 3. Interaction of Tumor Cells and Chemokines. MDSC: Myeloid-derived suppressor cell; TAM: Tissue associated macrophage. Created with BioRender.com

[32, 33]. ACKR1 is associated with several inflammatory diseases, including rheumatoid arthritis, atherosclerosis, giant cell arteritis, etc. [34, 35]. A recent study showed that the deletion of ACKR1 results in insulin resistance and glucose intolerance [36]. A mutation in ACKR1 makes the individual susceptible to HIV-1 infection because

ACKR1 acts as a sink for HIV inoculum, preventing its entry. However, HIV-1 can viably remain bound to Duffy antigen on the surface of RBCs and later be transferred to susceptible T helper cells, enabling survival of the virus [37, 38]. ACKR1 also regulates the recruitment of osteoclast precursor cells by modulating chemokine

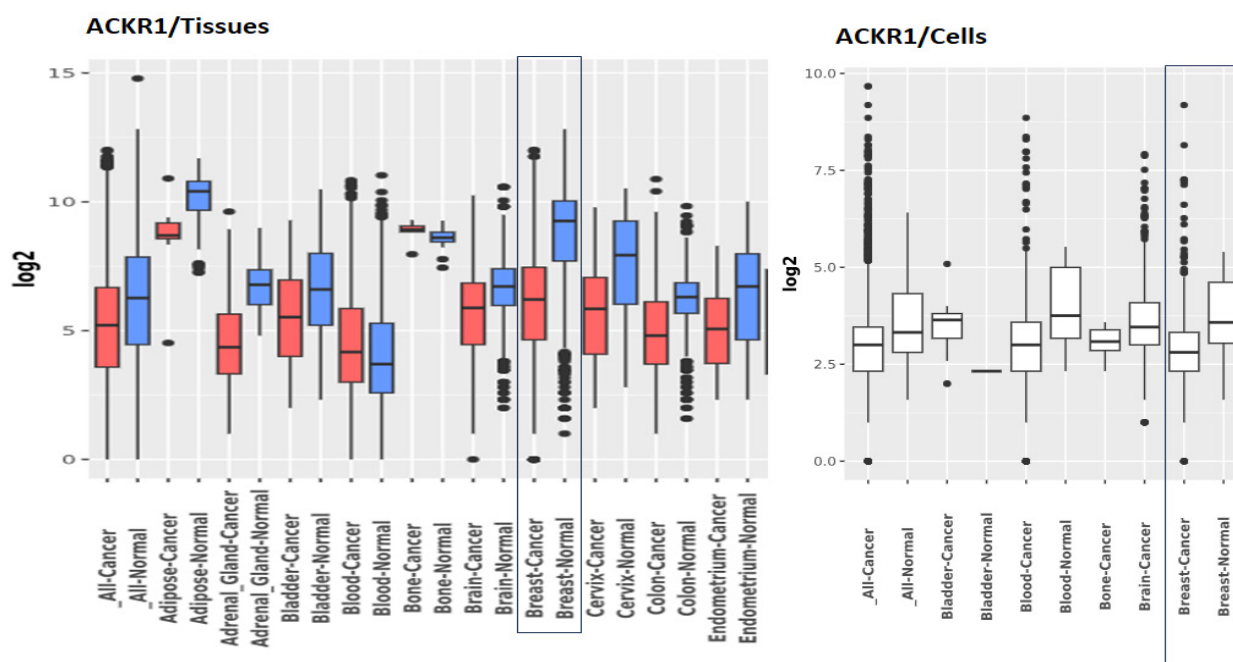


Figure 4. ACKR1 Expression Across Some TCGA Cancers. The box shows reduced ACKR1 in breast cancer compared to controls (normal) in A: tissues, B: Breast cancer cell lines

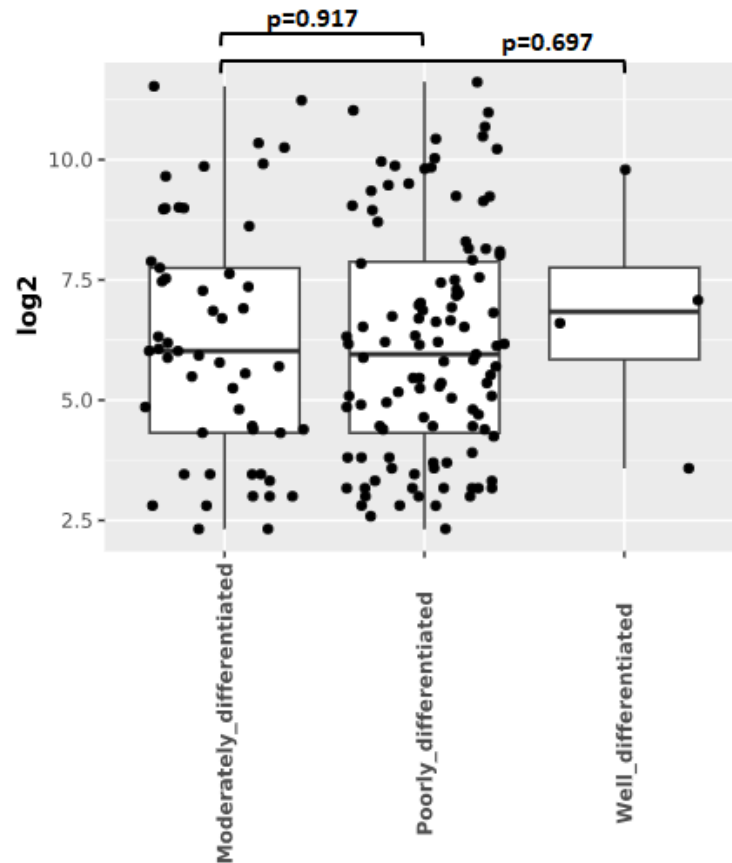


Figure 5. ACKR1 Expression Across Different Histological Tumor Grades. Although it lacks statistical significance, there seems to be a generalized trend of higher ACKR1 in well-differentiated and treated cancers as compared to poor or moderately differentiated ones.

transcytosis across endothelial cell barriers [39].

Status of ACKR1 in Breast Cancer: Cancer Surveillance And Prevention

ACKR1 is increasingly recognized for its involvement in cancer, particularly in breast cancer. Although its specific function in breast cancer prevention is still under investigation, ACKR1 is recognized for its ability to attach to and remove chemokines, decreasing inflammation and adjusting immune reactions. In the realm of cancer, inflammation plays a significant role in stimulating tumor expansion and spread.

Consequently, by regulating chemokine levels, ACKR1 could potentially diminish the inflammatory conditions that foster cancer advancement. Its expression on endothelial cells, particularly in the breast tissue microenvironment, can potentially assist in recruiting immune cells. This support in immune surveillance could aid in enabling the immune system to identify and eradicate cancer cells before tumor formation. A few studies indicate that the presence of ACKR1 may have a tumor-suppressing effect. More aggressive subtypes of breast cancer often show low or no ACKR1 expression. Increasing the function of ACKR1 could lower the chances of developing or spreading breast cancer. ACKR1 is thought to regulate the spread of cancer to other parts of the body. By restricting the availability of specific chemokines (such as CXCL8/IL-8) that encourage the

movement and invasion of cancer cells, ACKR1 could potentially decrease the ability of breast cancer cells to spread. Further, individuals of African descent have a higher prevalence of the Duffy-null phenotype, which is caused by a particular mutation in the ACKR1 gene. This phenotype protects against malaria but is also connected to an elevated risk of inflammation and specific cancers, such as breast cancer. Exploring the impact of ACKR1 variations on breast cancer susceptibility could result in the development of more tailored prevention approaches for various population groups.

Role of ACKR1 in Breast Cancer Metastasis

Breast cancer metastasis accounts for a majority of deaths due to breast cancer. Early detection of metastasis is crucial to predict and manage the disease progression. Breast cancer has been observed to preferentially metastasize to the bone, lungs, liver, and brain [40]. Breast cancer tissue has high expression of the chemokine receptor CXCR4, while tissues like lung, liver, bone marrow, and lymph nodes express its ligand CXCL12. Thus metastasis shows tissue tropism, as demonstrated by Muller et al., that the interaction between CXCR4 and CXCL12 promoted the migration of breast cancer cells to typical metastatic sites [27, 41]. Metastasis is also dependent on tumor vasculature, hence on angiogenesis. Chemokines like CCL2, CCL5, CXCL8, and CXCL12 induce epithelial-to-mesenchymal transition (EMT) and

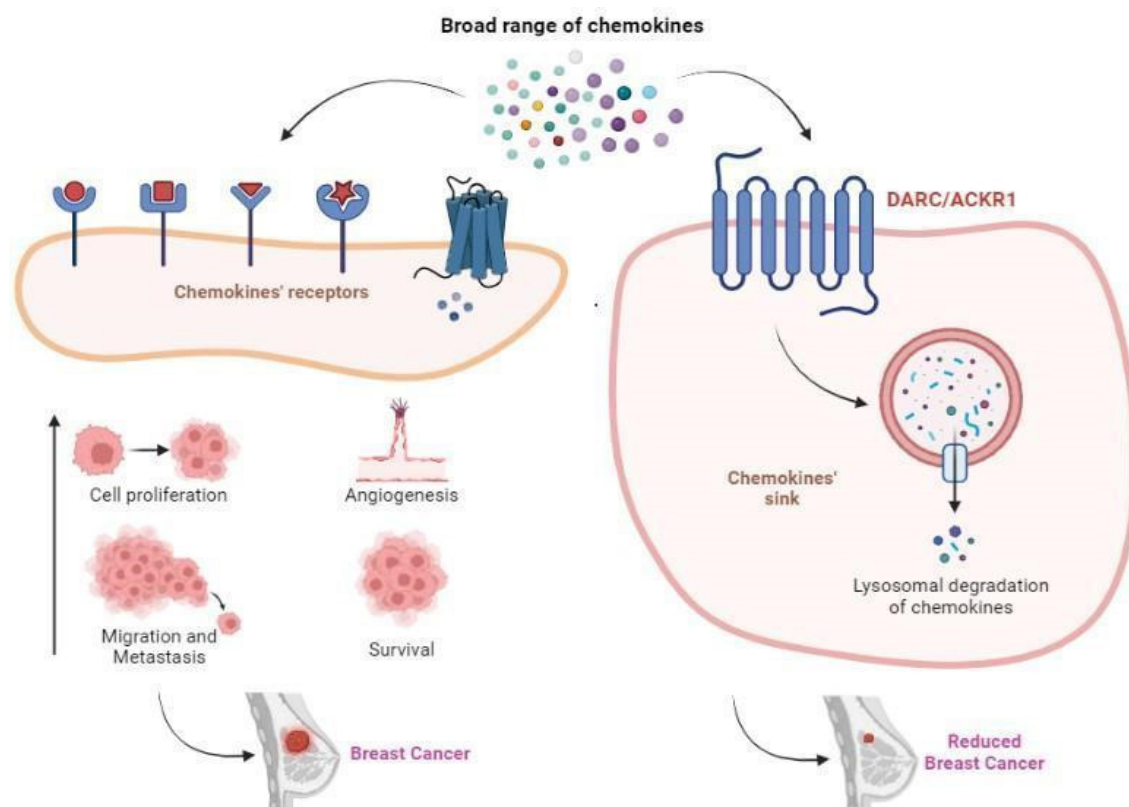


Figure 6. Role of ACKR1 in Breast Cancer, though the Same can be Extrapolated in Other Cancers as Well.

stimulate the release of matrix metalloproteinases like MMP-2 and MMP-9 [42]. Both of these events promote metastasis.

As described above, when ACKR1 is present on tumor cells, it protects against metastasis and angiogenesis by decreasing chemokines. Wang et al. demonstrated the inverse relationship between ACKR1 expression and metastatic potential [43]. Thus, levels of ACKR1 can be used to predict breast cancer metastasis.

Discussion

Breast cancer ranks among the most commonly diagnosed and life-threatening cancers in women. Managing the invasion and metastasis of breast cancer is challenging, and survival rates for patients with advanced stages are generally poor. Chemokines and their receptors are central to this issue. While extensive research has been done on chemokines in human and experimental tumors, chemokine receptors are much less studied. ACKR1 has previously been shown to modulate the biological functions of chemokines through three distinct mechanisms: scavenging, retention, and transportation. The enhancement or reconstitution of ACKR1-mediated protection can be a future therapy for breast and certain other cancers. When considering this, it is important to consider the various ways ACKR1 manipulation could impact chemokine biology and cell migration. Introducing ACKR1 in the appropriate cell types (using viral expression vectors, for example) is a therapeutic avenue to explore [44].

Several molecules such as proteins (i.e., Her2, ER,

and Ki67), mRNAs (i.e., ER α , ER β , and ERR γ), enzymes (i.e., CEA and TSGF), and microRNAs are currently used as diagnostic biomarkers for the detection and monitoring of breast cancer patients [45]. Appropriate biomarkers lead to a better understanding of cellular and molecular pathways involved in breast cancer pathogenesis. Hence, newer biomarkers are always needed to improve the sensitivity and specificity of the diagnosis. ACKR1 is a promising biomarker that can be used in combination with older biomarkers. Incorporating ACKR1 into prognostic models can enhance their accuracy and predictive power. Clinicians can use ACKR1 expression data alongside other clinical and molecular factors to better assess patient prognosis and make informed decisions regarding treatment options and follow-up care.

However, further studies investigating the effect of ACKR1 on the properties of tumor cells, such as proliferation, migration, and response to treatment, are needed. The binding interactions of various chemokines with ACKR1, as well as the mechanisms that regulate receptor expression and facilitate chemokine transport across cells, should be studied in depth. Comparisons with established biomarkers for TNBC, such as Ki-67 or BRCA mutations, could help determine whether ACKR1 provides additional predictive or prognostic information.

Evidence indicates that other atypical chemokine binders, such as D6 and CCX-CKR, may also play a significant role in suppressing the invasion and metastasis of cancer cells. However, their coexpression with ACKR1 in breast cancer has not been thoroughly characterized. Further study on the combined effect of ACKR1 and similar chemokine receptors, such as D6, is required [46].

In conclusion, the Duffy Antigen/ Receptor for Chemokine regulates chemokine levels via scavenging and transcytosis, influencing inflammation and tumor angiogenesis (Figure 6). In breast cancer, the expression of DARC correlates with improved prognosis, suggesting its potential as a biomarker and therapeutic target for managing metastasis and tumor progression.

Author Contribution Statement

VJ drafted the manuscript and figures. JT and PR assisted in manuscript writing. AS provided critical insights into the manuscript. RD and SK conceptualized and oversaw the whole work.

Acknowledgements

General

VJ wants to express gratitude to the Indian Council of Medical Research for the STS fellowship. SK acknowledges the Department of Biochemistry AIIMS Delhi for providing space and permission to carry out this work.

Availability of data

This article is based entirely on data already available in the public domain through published literature.

Scientific body approval

This review article is an independent work and is not part of an approved student thesis. However, the authors have previously conducted original research on the same topic under the Indian Council of Medical Research- Short Term Studentship (ICMR-STS) program, which was separately approved and completed.

Ethical consideration

As this article is a narrative review based on previously published literature, it did not involve human or animal participants and thus did not require approval of the Institute Ethics Committee.

Conflict of interest

The authors declare no conflict of interest.

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