

Chapter

Roles of Chemokines in Influencing Tumor Microenvironment in Breast Cancer

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Abstract

Chemokines regulate cell migration by binding to specific cell surface G protein-coupled receptors in development, physiology, and immune responses. Particularly in cancer, chemokines are involved in tumor cell growth, angiogenesis, cancer stem-like cell properties, metastasis, and directly and indirectly influencing tumor immunity and cancer progression. The chemokine signature in the tumor microenvironment affects immune contexture in tumor tissues and mutual communication between cells through the specific chemokine axis, contributing to cancer prognosis. The present chapter summarizes the role of chemokines in the tumor microenvironment in breast cancer, of which subtypes are classified as luminal A, luminal B, HER2-enriched, and basal-like, focusing on expression levels of chemokines and overall survivals in a chemokine-dependent manner and discovering the target chemokine axis. The outcome provides valuable information that improves the quality of life in patients with breast cancer by supporting the treatment options via the chemokine network in the tumor microenvironment.

Keywords: breast cancer, chemokines, tumor microenvironment, overall survivals, immune contexture

1. Introduction

Chemokines are chemoattractant cytokines that recruit immune cells into the tumor microenvironment through interactions between chemokines and their specific receptors [1], building an immune context that affects cancer progression and prognosis. Chemokines consist of four groups based on the number of amino acids between the first cysteine (C) motifs as follows: C (XCL1-2), CC (CCL1-28), CXC (CXCL1-17), and CX3C (CX3CL1). Each chemokine recognizes the specific chemokine receptors (XCR1, CCR1-10, CXCR1-8, and CX3CR1) to control angiogenesis, regulate the immune network, and change cellular functions (**Figure 1**), creating the unique chemokine axis [1] as shown in **Table 1**.

A fifth molecular subtype of breast cancer is defined in large part by expression levels of hormone receptors, such as estrogen receptor (ER) and progesterone receptor (PR), and HER2 as follows: luminal A (ER+/PR+/HER2–), luminal B (ER+/PR+/HER2+), HER2-enriched (ER–/PR–/HER2+), basal-like, (triple-negative, ER–/

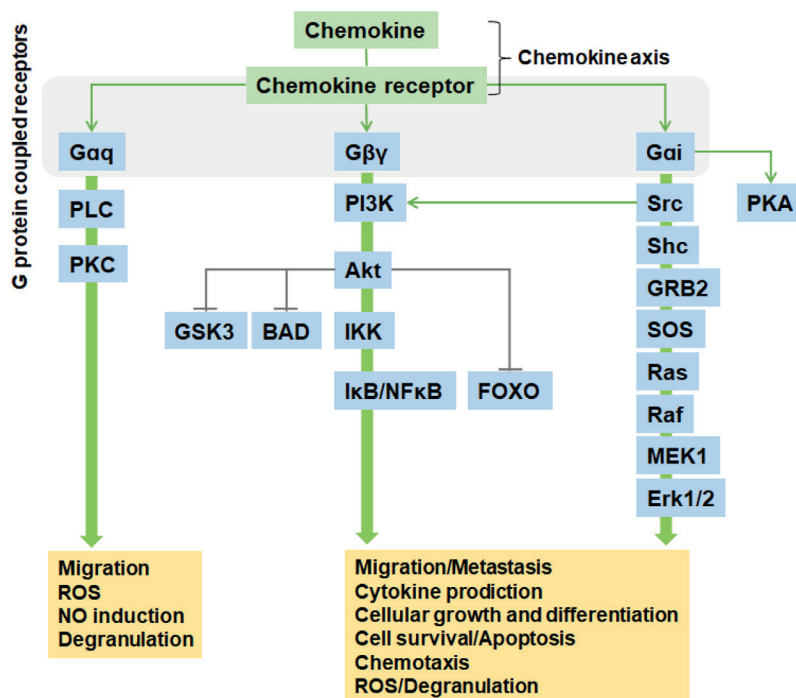


Figure 1.

Chemokine signaling pathway. Modified and simplified from the KEGG PATHWAY Database (<https://www.genome.jp/pathway/k004062>). The arrow (green) and block (gray) lines indicate positive and negative effects, respectively. PLC: phospholipase C; PKC: protein kinase C; PI3K: phosphoinositide 3-kinase; Akt: protein kinase B; GSK3: glycogen synthase kinase 3; BAD: BCL2 (B-cell leukemia/lymphoma 2) associated agonist of cell death; IKK: IκappaB kinase; IκB: inhibitor of nuclear factor kappa B; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; FOXO: forkhead box O; PKA: protein kinase A; SRC: proto-oncogene tyrosine-protein kinase Src; Shc: SHC adaptor protein; GRB2: growth factor receptor-bound protein 2; SOS: Son of sevenless; Ras: rat sarcoma virus; RAF: rapidly accelerated fibrosarcoma; MEK1: mitogen-activated protein kinase 1; Erk1/2: extracellular signal-regulated kinase 1/2.

PR–/HER2–), and normal breast-like (ER–/PR–/HER2–/CK5–/EGFR–). Chemokine signature in these subtypes was determined based on the expression module (PAM50 subtypes) provided by Breast Cancer Gene-Expression Miner v5.0 (bc-GenExMiner v5.0, <http://bcgenex.ico.unicancer.fr/BC-GEM/GEM-Accueil.php?js=1>) [2].

Chemokine signature between microarrays and RNA-seq shows a similar pattern except for CCL27 and CXCL4 expression levels (**Figure 2**). Generally, luminal subtypes have low expression levels of chemokines and chemokine receptors compared to other subtypes (**Figure 2**). In addition to chemokine signature in breast cancer subtypes, we have collected literature data on clinical aspects of chemokines in patients with breast cancer, excluding in vitro results of chemokines in breast cancer cell models and in vivo results of animal models for breast cancer. This chapter has described the functional roles of chemokine axes in breast cancer, focusing on chemokine signature in subtypes, overall survival, and clinicopathologic properties of chemokines in patients with breast cancer. Miner v5.0 (bc-GenExMiner v5.0, <http://bcgenex.ico.unicancer.fr/BC-GEM/GEM-Accueil.php?js=1>) was performed to determine the chemokine signature. Overall survivals in breast cancer were determined from a database provided by Kaplan-Meier Plotter (<http://kmplot.com/analysis/index.php?p=background>) [3].

Receptors	Chemokines
XCR1	XCL1, 2
CCR1	CCL3, 5, 7, 8, 14, 15, 16, 23
CCR2	CCL2, 7, 8, 13, 16
CCR3	CCL5, 7, 11, 13, 14, 15, 24, 26, 28
CCR4	CCL17, 22
CCR5	CCL3, 4, 5, 8, 11, 14, 16
CCR6	CCL20
CCR7	CCL19, 21
CCR8	CCL1, 16
CCR9	CCL25
CCR10	CCL27, 28
CXCR1	CXCL6, 7, 8
CXCR2	CXCL1, 2, 3, 5, 6, 7, 8
CXCR3A	CXCL9, 10, 11
CXCR3B	CXCL4, 9, 10, 11
CXCR4	CXCL12
CXCR5	CXCL13
CXCR6	CXCL16
CXCR7	CXCL11, 12
CXCR8	CXCL17
CX3CR1	CX3CL1

Orphan chemokines: CXCL14.
PITPNM3 is known as a receptor for CCL18.

Table 1.
Human chemokine network.

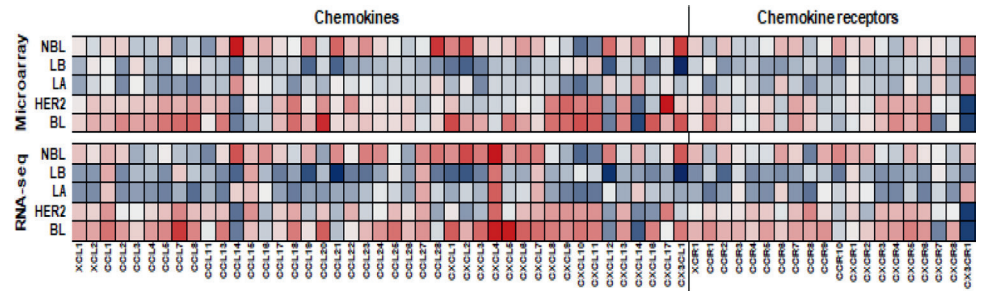


Figure 2.
Chemokine signature in breast cancer subtypes. Heatmaps from a database of microarrays and RNA-seq. Breast Cancer Gene-Expression. LA: luminal A (n = 3946; 1343); LB: luminal B (n = 1889; 966); HER2: HER2-enriched (n = 1414; 693); BL: basal-like (n = 1976; 783); NBL: normal breast-like (n = 1079; 602).

2. The XCL1/2-XCR axis

Luminal B and HER2 subtypes show high levels of XCL1, XCL2, and XCR1 compared to luminal subtypes (**Figure 2**). XCL1 shows better survival in all breast cancers,

Chemokines	ID	All		Basal-like		HER2		Luminal A		Luminal B		Normal	
		HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI
XCL1	206365_at	0.75	0.62-0.91	0.44	0.29-0.66	0.63	0.43-0.93			0.66	0.46-0.94		
	206366_x_at												
XCL2	214567_s_at	0.77	0.64-0.93	0.37	0.24-0.55	0.58	0.39-0.86			0.61	0.43-0.88		
CCL4	204103_at	0.73	0.61-0.89	0.58	0.39-0.86					0.66	0.46-0.95		
CCL5	204655_at	0.82	0.68-0.99	0.30	0.20-0.47	0.67	0.46-0.99			0.65	0.45-0.92		
	1405_i_at												
CCL8	214038_at			0.61	0.41-0.90								
CCL13	206407_s_at			0.66	0.45-0.96	0.63	0.43-0.93						
	216714_at												
CCL14	205392_s_at	0.74	0.61-0.89					0.94	0.62-1.44	1.51	1.06-2.14	2.78	0.96-8.07
CCL15	210390_s_at												
CCL18	209924_at			0.58	0.39-0.86								
	32128_at												
CCL19	210072_at	0.73	0.60-0.88	0.59	0.40-0.87								
CCL21	204606_at	0.76	0.63-0.92										
CCL22	207861_at	0.74	0.61-0.89	0.55	0.37-0.81	0.57	0.38-0.84						
CCL24	221463_at	1.21	1.00-1.46										
CCL25	206988_at											2.48	1.12-10.8
CCL28	238750_at											0.23	0.05-1.11
	224240_s_at												
CXCL8	202859_x_at	1.44	1.19-1.74										
	211506_s_at												

Chemokines	ID	All		Basal-like		HER2		Luminal A		Luminal B		Normal	
		HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
CXCL9	203915_at	0.77	0.64–0.93	0.34	0.22–0.52	0.65	0.44–0.96			0.65	0.45–0.92		
CXCL10	204533_at			0.43	0.28–0.64	0.68	0.46–1.01			0.62	0.43–0.88		
CXCL11	211122_s_at			0.39	0.26–0.59								
	210163_at												
CXCL12	203666_at	0.66	0.54–0.80										
	209687_at												
CXCL13	205242_at	0.61	0.50–0.74	0.31	0.20–0.48	0.63	0.42–0.92			0.58	0.40–0.83		
CXCL14	218002_s_at	0.71	0.59–0.86					0.59	0.38–0.91				
CCR2	206978_at	0.74	0.61–0.89	0.57	0.38–0.84								
	207794_at												
CCR5	206991_s_at	0.68	0.56–0.82	0.46	0.31–0.70	0.52	0.35–0.78			0.49	0.34–0.70		
CCR6	206983_at	0.69	0.57–0.84	0.64	0.43–0.94	0.60	0.40–0.89						
CXCR2	207008_at					0.58	0.39–0.86						
CXCR3	207681_at	0.74	0.61–0.90	0.55	0.37–0.81					0.59	0.41–0.85		
	217119_s_at												
CXCR4	209201_x_at			0.48	0.32–0.71			1.62	1.05–2.50				
	211919_s_at												
	217028_at												
CXCR6	206974_at	0.78	0.64–0.94	0.54	0.37–0.81	0.60	0.41–0.90			0.61	0.43–0.88		
	211469_s_at												
CXCR7	212977_at	1.37	1.13–1.65			1.83	1.23–2.72						
CXCR8	210264_at					1.67	1.12–2.49						

Chemokines	ID	All		Basal-like		HER2		Luminal A		Luminal B		Normal	
		HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
CX3CR1	205898_at	0.61	0.50–0.74					0.63	0.41–0.98				

Bold HR: $p < 0.05$ increase or decrease. Chemokines and chemokine receptors without statistical significance on overall survival are not described. Sample No. by PAM50 subtype: All ($n = 1879$), BL ($n = 431$), HER2 ($n = 431$), LA ($n = 596$), LB ($n = 439$), and NBL ($n = 51$).

Table 2.
Overall survivals based on expression levels of chemokines and chemokine receptors in breast cancer and its subtypes.

Chemokines	ID	BL1	BL2	IM	ME	MSL	LAR
		HR	95% CI	HR	95% CI	HR	95% CI
XCL1	206365_at						
	206366_x_at				0.42	0.21–0.84	0.28
CCL14	205392_s_at						0.54
CCL19	210072_at					0.22	0.07–0.71
CCL22	207861_at	0.43	0.19–0.97			0.28	0.09–0.84
CCL25	217706988_at		3.48	1.17–10.3			0.46
CCL26	223710_at					3.68	1.13–12.0
CCL28	238750_at						
	224240_s_at					0.31	0.10–0.96
CXCL2	209774_x_at		2.82	0.97–8.1			
CXCL3	207850_at		3.86	1.24–12.0			
CXCL0	206336_at					0.26	0.08–0.82
CXCL8	202859_x_at			2.83	1.18–6.80		
	211506_s_at						
CXCL9	203915_at	0.38	0.17–0.88		0.37	0.18–0.76	
CXCL10	204533_at				0.45	0.23–0.91	
CXCL13	205242_at	0.30	0.13–0.72	0.34	0.14–0.82	0.41	0.21–0.80
XCR1	221468_at					0.21	0.06–0.76
CCR2	206978_at				0.45	0.23–0.89	
	207794_at						
CCR4	208376_at						
	217970_s_at						0.50
	220671_at						0.26–0.93

Chemokines	ID	BL1		BL2		IM		ME		MSL		LAR	
		HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
CCR5	206991_s_at	0.40	0.17–0.92			0.29	0.12–0.73	0.48	0.24–0.97				
CCR7	206337_at							0.34	0.17–0.70				
CCR9	206887_at			3.13	1.01–9.71								
	207445_s_at												
CXCR3	207681_at												
	217119_s_at	0.30	0.13–0.72										
CXCR6	206974_at					0.42	0.18–0.97						
	211469_s_at												
CXCR8	210264_at											1.97	1.06–3.66
CX3CR1	205898_at					2.49	1.07–5.79						

Table 3. Overall survivals based on expression levels of chemokines and chemokine receptors in TNBC subtypes.
 Bold HR: $p < 0.05$ increase or decrease. Chemokines and chemokine receptors without statistical significance on overall survival are not described. Sample No. by Pietenpol TNBC subtype: BL1 (n = 103), BL2 (n = 58), IM (n = 149), ME (n = 114), MSL (n = 39), LAR (n = 116).

BL/HER2/LB subtypes (**Table 2**), and ME-/MEL-TNBC (**Table 3**). XCL2 has better survival in all breast cancers and BL/HER2/LB subtypes (**Table 2**). XCR1 alone has no effects on survival except for good survival in MSL-TNBC (**Table 3**). Studies on the XCL1/2 in human breast cancer samples are lacking. The XCL1/2-XCR axis shows a benefit for breast cancer, which extends overall survival and reduces tumor growth.

3. The CCL-CCR axis

3.1 The CCL3/5/7/8/14/15/16/23-CCR1 axis

Although CCL3 is highly expressed in the BL subtype compared to other types (**Figure 2**), it has no effects on survival. CCL3 shows high levels in breast cancers, inflammatory BC, ER-negative, and PR-negative subtypes, of which expression levels are related to tumor grade, and show increased Ki67 (a proliferation marker). A good survival rate of CCL3 is reported, but non-TNBC has a poor survival rate [4–9]. CCL5 is highly expressed in BL and HER2 subtypes compared to luminal subtypes (**Figure 2**) and shows better survival in all breast cancers and BL/HER2/LB subtypes (**Table 2**). CCL5 reduced the risks of breast cancer and LA/LB subtypes and had a good prognosis and survival, although poor survival in the HER2 subtype was reported [4–8]. CCL5 increased microvessel density and CD163+ Mφ infiltration [7, 10–19]. CCL7 is highly expressed in the BL subtype compared to other subtypes (**Figure 2**). CCL7 has no effects on survival from the database, although poor survival was reported [7, 10–19]. CCL7 is highly expressed in breast cancers, poorly differentiated cancers, TNBC, and African Americans. Expression levels of CCL7 are related to tumor grade and show the increased Ki67 [8, 12, 20]. CCL8 is highly expressed in BL and HER2 subtypes compared to other subtypes (**Figure 2**). CCL8 shows good survival in the BL subtype (**Table 2**) but is reported to have poor survival and prognosis, particularly in European Americans. CCL8 is highly expressed in ER-negative tumors, TNBC, and African Americans. Expression levels of CCL8 are related to tumor grade and show the increased Ki67 [8, 12, 21]. CCL14 is highly expressed in the NBL subtype compared to other subtypes (**Figure 2**). CCL14 has good survival in all breast cancers, the LA subtype, and LAR-TNBC, but shows poor survival in the NBL subtype (**Tables 2 and 3**). CCL14 is reported as an indicator of good survival and prognosis [10, 22]. CCL15 is similarly expressed between subtypes (**Figure 2**). CCL15 has poor survival in the LB subtype (**Table 2**) but is reported as an indicator of good survival and prognosis [6]. CCL16 is highly expressed in the NBL subtype compared to other subtypes (**Figure 2**). CCL16 has no effects on survivals from the database, although reports have shown an increased risk in the LA subtype and a decreased risk in TNBC [11]. CCL23 is highly expressed in the NBL subtype compared to other subtypes (**Figure 2**). Although CCL23 has no effects on survival, expression levels of CCL23 are related to tumor grade and good prognosis [8, 12]. CCR1 is highly expressed in the BL subtype compared to other subtypes (**Figure 2**) and has no effects on survival. Studies on CCR1 in patients with breast cancer are still lacking.

3.2 The CCL2/7/8/13/16-CCR2 axis

CCL2 is highly expressed in the BL subtype compared to luminal subtypes (**Figure 2**). CCL2 has no effects on survival from database, although it shows poor

survival in both tumoral and stromal CCL2-positive cancers have the worse survival in the order of BL > HER2 > LB > LA subtypes. CCL2 is highly expressed in breast cancers, lower differentiated cells, invasive ductal ER-negative breast cancers, PR-negative breast cancers, cancer-associated fibroblasts, BL subtype, claudin-low cancers, and advanced cancers. Expression levels of CCL2 are related to early relapse, postmenopausal status, lymph node involvement, tumor grade, tumor size, and nodal status, showing induced angiogenesis and increased Ki67. CCL2 induced CD3, CD20, and CD68 infiltration with increased or unchanged tumor-associated macrophage (TAM) in tumors [5, 8, 20, 23–39]. CCL7, CCL8, and CCL16 are described in section of the CCL3/5/7/8/14/15/16/23-CCR1 axis. CCL13 is highly expressed in the BL subtype compared to other subtypes (**Figure 2**) and shows better survivals in BL and HER2 subtypes (**Table 2**). CCL13 is highly expressed in the HER2 subtype and shows the increased Ki67 [8]. CCR2 is highly expressed in BL/HER2/NBL subtypes compared to luminal subtypes (**Figure 2**). CCR2 has good survival in all breast cancers, BL subtype, and ME-TNBC (**Tables 2 and 3**). CCR2 is highly expressed in invasive ductal breast cancer and shows good survival [33, 40, 41].

3.3 The CCL5/7/11/13/14/15/24/26/28-CCR3 axis

CCL5, CCL7, CCL13, CCL14, and CCL15 are described in sections of the CCL3/5/7/8/14/15/16/23-CCR1 axis and the CCL2/7/8/13/16-CCR2 axis. CCL11 is highly expressed in the HER2 subtype compared to other subtypes (**Figure 2**) and has no effects on survival. CCL11 is highly expressed in the HER2 subtype and shows a good prognosis [12]. CCL24 is highly expressed in BL and NBL subtypes compared to other subtypes (**Figure 2**) and has poor survival in all breast cancers (**Table 2**), as shown in patients with breast cancer [6, 10]. CCL26 is highly expressed in BL and HER2 subtypes compared to other subtypes (**Figure 2**) and has poor survival in MSL-TNBC (**Table 3**). CCL26 is highly expressed in inflammatory breast cancers [4]. CCL28 is highly expressed in the NBL subtype compared to other types (**Figure 2**) and has good survivals in the NBL subtype and MSL-TNBC (**Tables 2 and 3**). CCR3 is highly expressed in the BL subtype compared to luminal subtypes based on RNA-seq, but it has generally low expression levels based on microarray (**Figure 2**). CCR3 has no effect on survival. Studies on CCR3 in patients with breast cancer are lacking.

3.4 The CCL17/22-CCR4 axis

CCL17 is highly expressed in BL/HER2/NBL subtypes compared to luminal subtypes (**Figure 2**). Although CCL17 has no effects on survival from the database, it shows a poor prognosis and survival in patients with breast cancer, particularly African Americans. CCL17 is highly expressed in TNBC and African Americans and is related to the induced Ki67 [6, 8, 12]. CCL22 is highly expressed in the HER2 subtype compared to other subtypes (**Figure 2**). CCL22 has good survival in all breast cancers, BL/HER2 subtypes, BL1-TNBC, MSL-TNBC, and LAR-TNBC (**Tables 2 and 3**). CCL22 is highly expressed in breast cancers and HER2 subtypes and is related to low grade, showing a good prognosis and unchanged or good survival [6, 10, 12, 20, 42]. CCR4 is highly expressed in BL and HER2 subtypes compared to luminal subtypes (**Figure 2**) and has a good survival in LAR-TNBC (**Table 3**). Expression levels of CCR4 are related to lymph node metastasis and HER2 expression [40, 43], and yet there are controversial survivals among patients with breast cancer.

3.5 The CCL3/4/5/8/11/14/16-CCR5 axis

CCL3, CCL5, CCL8, CCL11, CCL14, and CCL16 are described in sections of the CCR1/CCR2/CCR3 axis. CCL4 is highly expressed in the BL subtype compared to other types (**Figure 2**) and has good survival in all breast cancers and BL/LB subtypes (**Table 2**), as shown in patients with breast cancer. CCL4 is highly expressed in inflammatory breast cancers and ER-negative cancers and is related to metastasis of LB subtype and grade [4, 6, 8, 10, 12, 44]. CCR5 is highly expressed in BL and HER2 subtypes, as shown in patients with breast cancer, compared to luminal subtypes (**Figure 2**) [17]. CCR5 has good survival rates in all breast cancers, including BL/HER2/LB subtypes, BL1-TNBC, IM-TNBC, and ME-TNBC (**Tables 2 and 3**).

3.6 Orphan ligand CCL18

Although P1TPNM3 is reported as a specific receptor for CCL18, further studies require clarifying the functional roles of chemokine receptors based on their similarity with CCR1-10. CCL18 is highly expressed in BL and HER2 subtypes compared to luminal subtypes (**Figure 2**) and shows good survival in the BL subtype (**Table 2**). CCL18 is highly expressed in breast cancers, advanced-stage cancers, and metastatic breast cancers and is related to metastasis and lymph node involvement. CCL18 shows a poor prognosis and survival in patients with breast cancer, particularly with higher CCL18-positive TAM [6, 20, 35, 45].

3.7 The CCL20-CCR6 axis

CCL20 is highly expressed in the BL subtype compared to other subtypes (**Figure 2**). Although CCL20 has no effects on survival from database, it shows poor survival in patients with breast cancer. CCL20 is highly expressed in TNBC, ER-negative cancers, and African Americans and is related to the induced Ki67 [8, 12, 46, 47]. CCR6 is highly expressed in LA and NBL subtypes compared to other subtypes (**Figure 2**) and has good survival in all breast cancers and BL/HER2 subtypes (**Table 2**). CCR6 is related to pleura metastasis and aggressive stage but has no effects on overall survival in patients with breast cancer [48, 49].

3.8 The CCL19/21-CCR7 axis

CCL19 is highly expressed in the NBL subtype compared to other subtypes (**Figure 2**) and shows better survival in all breast cancers, BL subtype, and MSL-TNBC (**Tables 2 and 3**). CCL19 is related to aggressive status and shows increased risks in the LA subtype but a good prognosis and survival in patients with breast cancer. Interestingly, patients with ER-positive cancers showed good survival with increased plasma levels of CCL19 but poor survival with tumoral levels of CCL19 [6, 10–12, 40, 49]. CCL21 is highly expressed in the NBL subtype compared to other subtypes (**Figure 2**) and shows better survival in all breast cancers (**Table 2**). CCL21 is highly expressed in metastatic breast cancers and has a good prognosis and survival [6, 10, 12, 22, 40, 50]. CCR7 is highly expressed in BL/HER2/NBL subtypes compared to luminal subtypes (**Figure 2**) and has good survival in ME-TNBC (**Table 3**). CCR7 is highly expressed in breast cancers, metastatic breast cancers, HER2 subtype, LB subtype, and TNBC and is related to lymph node metastasis in part, recurrence in part, TNM stage, grade, invasion, and aggressive status. CCR7 induced CD68 and

FOXP3 cell infiltration but had no change in CD8 and CD20 cell infiltration. There are controversial survivals, including good, no change, and poor survivals, among patients with breast cancer [48–60].

3.9 The CCL1/16-CCR8 axis

CCL1 is highly expressed in the BL subtype compared to other subtypes (**Figure 2**) and has no effects on survival. CCL1 is highly expressed in invasive cancers and ER-negative cancers and is related to tumor grade. CCL1 increased Treg infiltration and showed poor survival in patients with breast cancer [35, 42]. CCL16 is described in the section of the CCL3/5/7/8/14/15/16/23-CCR1 axis. CCR8 is highly expressed in BL and HER2 subtypes compared to luminal subtypes (**Figure 2**) and has no effects on survival. Studies on CCR8 in patients with breast cancer are lacking.

3.10 The CCL25-CCR9 axis

CCL25 is highly expressed in the BL subtype compared to other subtypes (**Figure 2**) and has poor survival in the NBL subtype and BL2-TNBC (**Tables 2 and 3**). CCL25 is highly expressed in TNBC in African Americans, and it shows poor survival, particularly in African Americans [12]. CCR9 is highly expressed in BL and NBL subtypes compared to other subtypes (**Figure 2**) and has poor survival in BL2-TNBC (**Table 3**). CCR9 is highly expressed in poorly differentiated breast cancers [61].

3.11 The CCL27/28-CCR10 axis

CCL28 is described in section of the CCL5/7/11/13/14/15/24/26/28-CCR3 axis. CCL27 is highly expressed in all breast cancer subtypes based on RNA-seq, but it generally has low expression levels based on microarray (**Figure 2**). CCL27 has no effect on survival. CCL27 is highly expressed in inflammatory breast cancers [4]. CCR10 is highly expressed in NBL subtypes compared to other subtypes (**Figure 2**) and has no effects on survival. Studies on CCR10 in patients with breast cancer are lacking.

4. The CXCL-CXCR axis

4.1 The CXCL6/7/8-CXCR1 axis

CXCL6 is highly expressed in BL/NBL subtypes compared to other subtypes (**Figure 2**) and has a good survival in MSL-TNBC (**Table 3**). CXCL6 is highly expressed in ER-negative breast cancers and is related to metastasis of breast cancers, showing unchanging or good survival [62, 63]. CXCL7 is highly expressed in BL/NBL subtypes compared to other subtypes (**Figure 2**) and has no effects on survival. CXCL7 is related to stage III breast cancers and has controversial survivals: good, unchanging, and poor [10, 62, 64–66]. CXCL8 is highly expressed in BL/HER2 subtypes compared to other subtypes (**Figure 2**) and has poor survival in all breast cancers and IM-TNBC (**Tables 2 and 3**). In human breast cancer samples, CXCL8 is highly expressed in breast cancers, inflammatory breast cancers, TNBC, advanced stage cancers, HER2/LA/LB subtypes, ER and PR-negative breast cancers, and cancer-associated fibroblasts (CAFs), and is related to metastasis of breast cancers

and lymph nodes and tumor grade and stage, showing induced angiogenesis and increased Ki67. CXCL8 induced CD68 infiltration and had a poor prognosis and survival, particularly in patients with CXCL8 (–251) A allele [4, 5, 8, 10, 20, 29, 44, 62–64, 67–76]. CXCR1 is a little bit highly expressed in HER2 and NBL subtypes compared to other subtypes (**Figure 2**) and has no effects on survival. CXCR1 is highly expressed in invasive breast cancers [41].

4.2 The CXCL1/2/3/5/6/7/8-CXCR2 axis

CXCL1 is highly expressed in the BL subtype compared to other subtypes (**Figure 2**) and has no effects on survivals. CXCL1 is highly expressed in breast cancers, TNBC, and ER-negative cancers and is related to metastasis of breast cancer and grade with increased Ki67. CXCL1 increased CD133 (stem cell marker) and CD68 (Mφ marker) cell infiltration and shows a poor prognosis and controversial survivals: poor, unchanging, and good [8, 63, 77–81]. CXCL2 is highly expressed in the NBL subtype compared to other subtypes (**Figure 2**) and has poor survival in BL2-TNBC (**Table 3**). CXCL2 is related to metastasis of breast cancer and shows a good prognosis and survival [62, 63, 65, 80]. CXCL3 is highly expressed in BL and NBL subtypes compared to other subtypes (**Figure 2**) and has poor survival in BL2-TNBC (**Table 3**). CXCL3 is highly expressed in aggressive breast cancers and is related to metastasis of breast cancer. CXCL3 shows a poor prognosis and controversial survivals: poor, unchanged, and good [62–65, 80, 82]. CXCL5 is highly expressed in the BL subtype compared to other subtypes (**Figure 2**) and has no effects on survivals. CXCL5 is highly expressed in breast cancers and ER-negative cancers and is related to low metastasis in the LB subtype. CXCL5 has no effects on survival [8, 23, 35, 44, 63]. CXCL6, CXCL7, and CXCL8 are described in a section of the CXCL6/7/8-CXCR1 axis. CXCR2 is highly expressed in BL and NBL subtypes compared to other subtypes (**Figure 2**) and has a good survival in the HER2 subtype (**Table 2**). CXCR2 is highly expressed in high-grade breast cancers, TNBC, ER and PR-negative breast cancers, and invasive breast cancers but shows low levels in relapse cases. CXCR2 enhanced tumoral TILs, CD3, CD8, PD-L1, and T/B-cell infiltration and showed good or poor survival in patients with breast cancers. Interestingly, CXCR2 C1208T variation increased the risk of breast cancer, leading to poor survival [41, 76, 83–86].

4.3 The CXCL4/9/10/11-CXCR3 axis

CXCL4 is highly expressed in all breast cancer subtypes based on RNA-seq compared to microarray (**Figure 2**). CXCL4 has no effect on survival. Studies on CXCL4 in human breast cancer samples are lacking. CXCL9 is highly expressed in BL and HER2 subtypes compared to other subtypes (**Figure 2**) and has a good survival in all breast cancers, BL/HER2/LB subtypes, and BL1–/ME-TNBC (**Tables 2 and 3**). CXCL9 is highly expressed in breast cancers, TNBC, low-proliferative cells, lymph node-negative breast cancers, HER2 subtype, and ER-negative cancers and is related to tumor grade with increased Ki67. CXCL9 has a good prognosis and both good and poor survivals, particularly showing good survivals in TNBC and luminal HER2 breast cancers [8, 10, 20, 22, 62, 64, 65, 80, 87]. CXCL10 is highly expressed in BL and HER2 subtypes compared to other subtypes (**Figure 2**) and has a good survival in BL/HER2/LB subtypes and

ME-TNBC (**Tables 2 and 3**). CXCL10 is highly expressed in breast cancers, poorly differentiated tumors, HER2 subtype, HR- and ER-negative cancers and is related to tumor grade and stage with increased Ki67 positive cells and TIL infiltration. CXCL10 has a good prognosis but no change in survival [8, 20, 62, 65, 80, 88–90]. CXCL11 is highly expressed in BL and HER2 subtypes compared to other subtypes (**Figure 2**) and has a good survival in the BL subtype (**Table 2**). CXCL11 is highly expressed in breast cancers, TNBC, HER2 subtype, and ER-negative cancers and is related to tumor grade with increased Ki67 positive cells, showing no change in survivals [8, 20, 80]. CXCR3 is highly expressed in BL and HER2 subtypes compared to other subtypes (**Figure 2**) and has a good survival in all breast cancers, BL/LB subtypes, and BL1-TNBC (**Tables 2 and 3**). CXCR3 is highly expressed in ER-negative breast cancers and is related to tumor grade and size. CXCR3 shows both good and poor survivals in breast cancers, particularly good survivals in BL subtype, ER-negative cancers, and LN-positive cancers [91–94].

4.4 The CXCL12-CXCR4 axis

CXCL12 is highly expressed in the NBL subtype compared to other subtypes (**Figure 2**) and has a good survival in all breast cancers (**Table 2**). CXCL12 is highly expressed in breast cancers and BL subtypes and is related to tumor stage, tumor grade, and lymph node metastasis with increased Treg infiltration. CXCL12 has a good prognosis and survival in patients with breast cancers [62, 64, 95], particularly in patients with high plasma levels of CXCL12 and CXCL12 isoforms. Some studies show no change in CXCL12 levels between subtypes and survivals [10, 22, 35, 62, 64, 65, 80, 95–102]. CXCR4 is highly expressed in BL and HER2 subtypes compared to other subtypes (**Figure 2**) and has good survival in the BL subtype but poor survival in the LA subtype (**Table 2**). CXCR4 is highly expressed in breast cancers, BL/HER2/LA/LB subtypes, locally advanced breast cancers, TNBC, ER and PR-negative cancers, atypical ductal hyperplasia, ductal carcinoma in situ, and invasive breast cancers. CXCR4 is related to the metastasis of TNBC, liver metastasis, lymph node metastasis, distant metastasis, recurrence in HER2 negative cancers and TNBC, tumor grade, and tumor size, and advanced TNM stage in TNBC, showing increased CXCR4 positive Treg infiltration in BL subtype compared to luminal subtypes. CXCR4 has controversial survivals for breast cancers as follows: good survivals, particularly in highly expressed CXCR4 fibroblasts, BL subtype, and ER-negative cancers; unchanged survivals; poor survivals, particularly in TNBC and patients with unmethylated CXCR4 or hypermethylated CXCL12/unmethylated CXCR4 [41, 48, 51, 54, 55, 59, 91, 92, 95–98, 100, 103–125].

4.5 The CXCL13-CXCR5 axis

CXCL13 is highly expressed in BL and HER2 subtypes compared to other subtypes (**Figure 2**) and has a good survival in all breast cancers, BL/HER2/LB subtypes, and BL1-/IM-/ME-TNBCs (**Tables 2 and 3**). CXCL13 is highly expressed in breast cancers, ER-negative cancers, and metastatic breast cancers and is related to lymph node metastasis with CXCR5 co-expression and increased Ki67. CXCL13 has a good prognosis and both unchanged and good survival in patients with breast cancers [10, 22, 35, 62, 64, 65, 80, 87, 126, 127]. CXCR5 is highly expressed in BL/HER2/NBL subtypes compared to luminal subtypes (**Figure 2**) and does not affect survival. CXCR5 is related to lymph node metastasis and tumor stage [75].

4.6 Orphan ligand CXCL14

CXCL14 is highly expressed in LA and NBL subtypes compared to other subtypes (**Figure 2**) and has a good survival in all breast cancers and LA subtypes (**Table 2**). CXCL14 is related to lymph node metastasis and has good survival in all breast cancers and BL/HER2/LA subtypes [10, 62, 64, 128, 129].

4.7 The CXCL16-CXCR6 axis

CXCL16 is highly expressed in the BL subtype compared to other subtypes (**Figure 2**) and has no change in survivals. CXCL16 increased the risk of cancer in the HER2 subtype [11]. CXCR6 is highly expressed in BL and HER2 subtypes compared to other subtypes (**Figure 2**) and has good survival in all breast cancers, BL/HER2/LB subtypes, and IM-TNBC (**Tables 2 and 3**). Studies on CXCR6 in human breast cancer samples are lacking.

4.8 The CXCL11/12-CXCR7 (ACKR3) axis

CXCL11 and CXCL12 are described in sections of the CXCL4/9/10/11-CXCR3 axis and the CXCL12-CXCR4 axis. CXCR7 is lowly expressed in the BL subtype compared to other subtypes (**Figure 2**) and has poor survival in all breast cancers and HER2 subtypes (**Table 2**). CXCR7 is highly expressed in TNBC, ER/PR-negative, or positive cancers and is related to TNM stage and tumor grade, showing poor survival [97, 130, 131].

4.9 The CXCL17-CXCR8 (GPR35) axis

CXCL17 is highly expressed in the HER2 subtype compared to other subtypes (**Figure 2**) and has no change in survivals. Studies on CXCL17 in human breast cancer samples are lacking. CXCR8 is highly expressed in LA and NBL subtypes compared to other subtypes (**Figure 2**) and has poor survivals in the HER2 subtype and LAR-TNBC (**Tables 2 and 3**). Studies on CXCR8 in human breast cancer samples are lacking.

5. The CX3CL1-CX3CR1 axis

CX3CL1 is highly expressed in BL and NBL subtypes compared to other subtypes (**Figure 2**) and has no change in survivals. CX3CL1 is highly expressed in inflammatory breast cancers, LB subtype, and PR-positive cancers and is related to tumor grade, tumor stage, tumor size, and lymph node metastasis with increased Ki67, stromal CD8, intratumoral DC, stromal NK, and TIL infiltration, showing both good and poor survivals [4, 8, 132, 133]. CX3CR1 is highly expressed in LA and NBL subtypes compared to other subtypes (**Figure 2**) and has good survival in all breast cancers and LA subtypes but poor survival in IM-TNBC (**Tables 2 and 3**). CX3CR1 is related to brain metastasis but has no change in survival [48].

6. Summary/conclusion

Chemokine axes are likely to prefer cell migration and invasion rather than cell proliferation, leading to changed immune contexture in the tumor microenvironment

followed by altered overall survivals. Accordingly, chemokines are likely to play a critical role in cancer cell metastasis and immune cell contexture, contributing to tumor size, grade, and stage. Some chemokines are related to tumor growth and angiogenesis through increased viability and angiogenic genes. Also, some chemokines are involved in cancer recurrence and chemoresistance, diminishing therapeutic effectiveness. Based on data obtained from human breast cancer samples, overall survivals are summarized by the chemokines-chemokine receptor axis (**Figure 3**). The XCL-XCR axis shows good survival. The CCL-CCR axis indicates various survivals as follows: good survivals in CC4, CCL5, CCL13, CCL14, CCL19, CCL21, CCL22, CCR5, and CCR6; poor survivals in CCL24 and CCL25; controversial survivals in CCL1, CCL2, CCL8, CCL15, CCL17, CCL20, CCR2, CCR4, CCR7, and CCR9; unchanged survivals in CCL3, CCL7, CCL11, CCL16, CCL23, CCL26, CCL27, CCL28, CCR1, CCR3, CCR8, and CCR10. The CXCL-CXCR axis also indicates various survivals as follows: good survivals in CXCL6, CXCL12, CXCL13, CXCR3, and CXCR6; poor survivals in CXCL8, CXCR7, and CXCR8; controversial survivals in CXCL1, CXCL2, CXCL3, CXCL7, CXCL9, CXCR2, and CXCR4; unchanged survivals in CXCL4, CXCL5, CXCL10, CXCL11, CXCL16, CXCL17, CXCR1, and CXCR5. Orphan chemokines CCL18 and CXCL14 have controversial and good survivals, respectively. The CX3CL1-CX3CR1 axis shows controversial survivals (**Figure 3**). There are differential chemokine signatures between tumor cells, stromal cells, immune cells, and adipocytes in

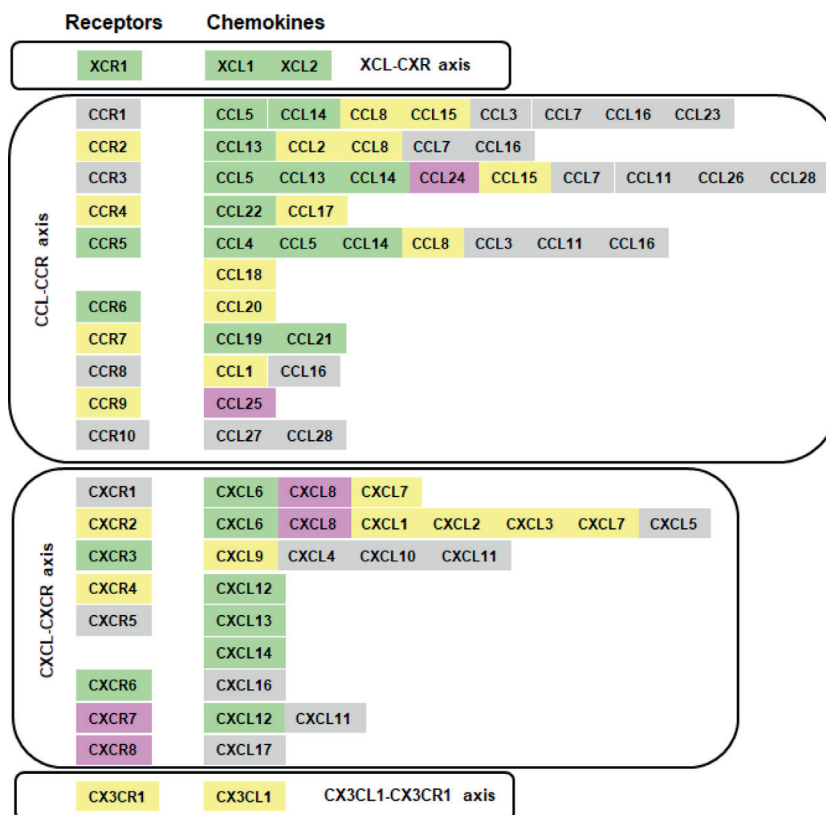


Figure 3. Impacts of chemokine axis on overall survivals in breast cancers. Green: good survivals; pink: poor survivals; yellow: controversial survivals; gray: unchanged survivals.

the breast tumor microenvironment. Therefore, cell-to-cell communication via the chemokine network is complex in the breast tumor microenvironment, which cannot be simply explained with one chemokine. Although CCL2, CXCL12, and CXCR4 have been studied extensively, there are still many chemokines that require clarification of their roles in breast cancers.

In conclusion, chemokines play a critical role in breast cancer progression, changing the breast tumor microenvironment through immune cell infiltration, cell-to-cell crosstalk, metastasis, chemoresistance, and tumor growth, followed by altered prognosis and survival.

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