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A narrative review: CXC chemokines influence immune surveillance in obesity and obesity-related diseases: Type 2 diabetes and nonalcoholic fatty liver disease

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Abstract

Adipose tissue develops lipids, aberrant adipokines, chemokines, and pro-inflammatory cytokines as a consequence of the low-grade systemic inflammation that characterizes obesity. This low-grade systemic inflammation can lead to insulin resistance (IR) and metabolic complications, such as type 2 diabetes (T2D) and nonalcoholic fatty liver disease (NAFLD). Although the CXC chemokines consists of numerous regulators of inflammation, cellular function, and cellular migration, it is still unknown that how CXC chemokines and chemokine receptors contribute to the development of metabolic diseases (such as T2D and NAFLD) during obesity. In light of recent research, the objective of this review is to provide an update on the linkage between the CXC chemokine, obesity, and obesity-related metabolic diseases (T2D and NAFLD). We explore the differential migratory and immunomodulatory potential of CXC chemokines and their mechanisms of action to better understand their role in clinical and laboratory contexts. Besides that, because CXC chemokine profiling is strongly linked to leukocyte recruitment, macrophage recruitment, and immunomodulatory potential, we hypothesize that it could be used to predict the therapeutic potential for obesity and obesity-related diseases (T2D and NAFLD).

Keywords Obesity · CXC chemokines · Type 2 diabetes · Nonalcoholic fatty liver disease · Therapeutic potential · Inflammation

Abbreviations

T2D	Type 2 diabetes
NAFLD	Nonalcoholic fatty liver disease
CVD	Cardiovascular diseases
NKT cells	Natural killer T cells
kDa	Kilodalton
ELR	Glutamic acid, leucine, and arginine motif
cAMP	Cyclic adenosine monophosphate
AC	Adenylate cyclase
PI	Phosphatidylinositol
PLC	Phospholipase C
PIP2	Phosphatidylinositol biphosphate
DG	Diacylglycerol
IP3	Inositol 1,4,5-triphosphate
PI3K	Phosphatidylinositol 3-kinase
MAPK	Mitogen-activated protein kinase
ASCs	Adipose stromal cells
Jak	Janus kinase
STAT	Signal transducers and activators of transcription
SOC	Suppressor of cytokine signaling protein
IR	Insulin resistance
TNF-α	Tumor necrosis factor alpha
NF-kB	Nuclear factor-kappa B
IL-6	Interleukin 6
IL-1 β	Interleukin-1 beta
IL-8	Interleukin 8
CRP	c-reactive protein
p-AKT	Phosphorylated serine/threonine kinase
ERK	Extra cellular signal-regulated kinase

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p38MAP	p38 mitogen-activated protein
BRAK	Breast and kidney chemokine
BMAC	B cell- and monocyte-activating chemokine
Mip-2γ	Macrophage inflammatory protein 2γ
HFD	High-fat diet
MCP-1	Monocyte chemoattractant protein
IL-7	Interleukin − 7
TLR-4	Toll-like receptor − 4
LPS	Lipo polysaccharide
ox-LDL	Oxidized low-density lipoprotein uptake
ADAM10	Disintegrin and Metalloproteinase
SS	Simple steatosis
NASH	Nonalcoholic steatohepatitis
HCC	Hepatocellular carcinoma
HSCs	Hepatic stellate cells
FFA	Free fatty acid
JNK	Jun N-terminal kinase
CDAA	Choline deficient amino acid-defined
MALAT1	Metastasis-associated lung adenocarcinoma transcript 1
DIAMOND	Diet-induced animal model of nonalcoholic fatty liver disease
GCP-2	Granulocyte chemotactic protein 2
TGF-β	Transforming growth factor-beta
EGFR	Epidermal growth factor receptor
mTOR	mammalian target of rapamycin
MAFLD	Metabolic-associated fatty liver disease
MLK3	Mixed lineage kinase 3
EVs	Extracellular vesicles
LPC	Lysophosphatidylcholine
DLX6-AS1	Distal-less homeobox 6 antisense 1
EMT	Epithelial-mesenchymal transition
Gro-α	Growth-regulated protein alpha
GROβ	Growth-regulated protein beta
GROγ	Growth-regulated protein gamma
PF4	Platelet factor 4
MIG	Interferon gamma
IP-10	Interferon gamma-induced protein 10
I-TAC	Interferon-inducible T cell alpha chemoattractant
SDF-1	Stromal cell-derived factor 1
SR-PSOX	Scavenger receptor for phosphatidylserine and oxidized lipoprotein
GPCRs	G protein-coupled receptors

1 Introduction

Obesity is increasing at an alarming rate around the world. Statistics from around the world show an epidemic rise in all age groups. Obesity affects one out of every six children aged 2 to 19, and the rate has more than tripled in the last 20 years. During this time, the prevalence of severe obesity nearly doubled, rising from 4.7 to 9.2% [1]. Moreover, obesity is a significant risk factor for several cancers, including insulin resistance (IR), type 2 diabetes (T2D), immune disorders, cardiovascular diseases (CVD), and nonalcoholic fatty liver disease (NAFLD). Overall, obesity is associated with a reduced life span, higher healthcare costs, and a reduced quality of life [2–6]. The overweight, obese individual has been found to have a spectrum of metabolic abnormalities, oxidative stress, mitochondrial dysfunction, immune dysfunction, and chronic low-grade inflammation [7, 8]. In addition, a recent review study reported that exercise prevented weight gain, weight loss, and maintenance of weight loss in obese individuals. Weight loss has been associated with improvements in the prevalence and severity of several obesity-associated comorbidities, such as IR, inflammation, dyslipidemia, hypertension, the metabolic syndrome, diabetes, pulmonary disease, and CVD [9].

Besides that, it has been shown that chemokines coordinate the recruitment of immune cells during obesity, T2D and CVD in both mice and humans which cause inflammation [10]. It has been suggested that adipocytes in obese adipose tissue recruit neutrophils, which then further promote inflammation. Adipocytes produce adipokines such as leptin and chemokine such as interleukin-8 (IL-8 or *CXCL8*). *CXCL8* is a potent chemoattractant for neutrophils. Once in the adipose tissue, neutrophils can recruit more blood neutrophils by releasing C–X–C motif chemokine ligand 2 (*CXCL2*), another important neutrophil chemoattractant. This study demonstrated that CXC chemokines play an important role in the inflammation during obesity [11].

There are currently 17 CXC chemokines in humans, most of which plays a role in obesity and obesity-related diseases [12–14]. During obesity, the proinflammatory effects of *CXCL1*, *CXCL5, CXCL8*, and *CXCL14* mainly lead to tumor cell growth and IR [15–20]. *CXCL16/CXCR6* axis plays an important role in the recruitment of NKT (Natural killer T) cell and induce inflammation in NALFD [21, 22]. Moreover, immune cell infiltration is stimulated by *CXCL9, CXCL10*, and *CXCL11* via *CXCR3* [23]; T lymphocyte and monocyte recruitment are mostly triggered by *CXCL12* and *CXCR4* [24]; and T cell recruitment is mainly promoted by *CXCL16/CXCR6* [25]. *CXCL17* also plays an important role in the development of NAFLD [26]. These molecules play proinflammatory and cytotoxic roles during obesity-induced diabetes. Furthermore, *CXCL13* is crucial for the chemotaxis and activation of leukocytes in diabetes [27]. Obesity and disorders related to obesity have been linked to CXC chemokines, which suggests that they play a vital role in the development of obesity-related disorders. As a consequence, CXC chemokines might be

prospective therapeutic targets for a number of obesity-related disorders. In this article, we provide an overview of the numerous functions of CXC chemokines ligands and chemokine receptors in obesity and the obesity-related disorders such as T2D and NAFLD.

2 Methods

This is a narrative review supported by a PubMed and Google Scholar literature search. The search was conducted from August 2022 to February 2023. Additional information is provided in Table 1.

3 CXC chemokine family

Chemokines are small peptide mediators composed of a group of small chemotactic cytokine proteins (15 kDa). Different cell types secret these proteins following induction, or they may be constitutively expressed [28]. Chemokines affect the migration, proliferation, angiogenesis, survival, and gene expression of numerous cell types in their respective microenvironments [28–30]. Chemokines can exert these effects via their respective G protein-coupled receptors (GPCRs).

Chemokines are classified into four subfamilies based on the location of the first two cysteines (C) in the main sequence, where "X" signifies an unconserved amino acid. CXC chemokines are further divided into ELR + and ELR- subtypes depending on whether the three-amino-acid motif ELR (glutamic acid, leucine, and arginine) is present or absent before the CXC sequence [31]. CXC chemokine ligands are related to trimeric G-proteins (Gαβγ), and the actions of four different types of Gα subunits determine activation effects inside cells [32–34].

$G\alpha_s$ and $G\alpha_i$ regulate cAMP levels by stimulating and inhibiting adenylate cyclase (AC), respectively; cAMP can further activate protein kinase PKA [34]. Gαq stimulates phosphatidylinositol (PI)-specific phospholipase C (PLC) and the hydrolysis of phosphatidylinositol biphosphate (PIP2), generating twosecond messengers, diacylglycerol (DG) and inositol 1,4,5-triphosphate (IP3); DG and IP3 can activate protein kinase PKC and stimulate intracellular calcium release [33]. $G_{\beta\gamma}$ complex has also been reported to trigger PLC activation. Gα12 exerts its functions primarily through other small monomeric G-proteins [33]. Further downstream of chemokine receptor pathways, phosphatidylinositol 3-kinase (PI3K), mitogen-activated protein kinase (MAPK), signal transducer and activator of transcription (STAT), and nuclear factor kB (NF-kB) cascades represent four major events promoting cell survival and chemotaxis [32].

The common receptor for ELR + CXC chemokines is *CXCR2*, except for *CXCL8*, which can also bind to *CXCR1*. There are three different growth-regulatory oncogenes: *CXCL1, CXCL2*, and *CXCL3*. The ELR- family chemokine *CXCL14* has been shown to have a high binding affinity for *CXCR4*, which lets it interact with the *CXCL12/CXCR4* axis [35]. Generally, *CXCR2*-binding ELR^+CXC chemokines can enhance angiogenesis by activating *CXCR2* on endothelial cells, but *CXCR3*-binding ELR^- CXC chemokines have the inverse effect [35]. The biological roles played by CXC chemokines in obesity and obesity-related disorders such as T2D and NAFLAD are discussed further below.

3.1 Role of CXC chemokines in the development of obesity

Previous research has shown that chemokines can aid in progression of morbid obesity by promoting inflammation in various obesity-related disorders. As shown in Table 2, diseases associated with obesity have significantly higher levels of CXC chemokines, which promote obesity and the pathologies linked to it.

3.2 *CXCL1* and *CXCL2*

In various adipose tissue depots, chemokines like *CXCL1, CXCL5, CXCL8*, and *CXCL10* are upregulated in obesity. Compared to lean individuals, obese people have

Table 1 The search strategy summary

Items	Specification
Date of search	August 2022 – February 2023
Databases and other sources searched	PubMed and Google Scholar
Search terms used	CXC chemokines (*CXCL1* to *CXCL17*), obesity, type 2 diabetes, nonalcoholic fatty liver diseases, simple steatosis, nonalcoholic steatohepatitis, cirrhosis, liver fibrosis, hepatocellular carcinoma,
Timeframe	1998–2023
Inclusion and exclusion criteria	English language only, original studies and reviews only
Selection process	West China Hospital Sichuan University
Any additional considerations, if applicable	We considered clinical/ preclinical studies, original studies, as well as data from previously published reviews.

Table 2 Studies on the upregulation of CXC-chemokines in obesity and obesity-related disorders

Family	Disease/indicators of obesity	Types of study	Abbreviations/ scientific name	Conclusion/effects	References
ELR+	Ovarian cancer, Prostate cancer and NAFLD	*In vitro*, *In vivo*	Gro-α/*CXCL1*	Angiogenesis in ovarian cancer cells. ↑ promotes prostate cancer progression. ↑ Promote systemic inflammation. ↑	[36, 15, 37, 38]
	Obese oocytes, Metabolic syndrome, Adipose tissue inflammation	*In vivo*	GROβ/*CXCL2*	Promote inflammation. ↑	[39–41]
	Obesity, Cervical cancer	*In vitro*, *In vivo*	GROγ/ *CXCL3*	Malignancy-associated capacities such as migration. ↑ Improvement obesity-related comorbidities. ↑ Promote systematic inflammation and insulin resistance. ↑	[42–44]
	Lymphatic vasculature dysfunction	*In vivo*	PF4/*CXCL4*	PF4 is a promising biomarker with lymphatic defects independent of the presence or absence of obesity. ↑	[45]
	Prostate Lung Colorectal and Ovarian cancer and Obesity	*In vivo*	GCP-2 /*CXCL6*	Worked out as an inflammatory biomarker. ↑	[46, 47]
	NAFLD, Obese obstructive sleep apnea and Metabolic inflammation at the maternal–fetal interface	*In vitro*, *In vivo*	IL -8 /*CXCL8*	Promote complex inflammation. ↑	[48–50, 51–54]
	NASH, Obesity and Psoriasis with obesity	*In vivo*	MIG/*CXCL9*	Promote Inflammation. ↑	[55–57]
ELR⁻	Obesity, Ovarian Inflammation, Diabetes, Diliary inflammation and NAFLD	*In vitro*, *In vivo*	IP-10/*CXCL10* and I-TAC/ *CXCL11*	Work as an Inhibitor of adipose tissue angiogenesis and promote inflammation. ↑	[58–62]
	Breast cancer and Obesity	*In vitro, In vivo*	SDF-1α/*CXCL12*	Regulating metastasis of breast cancer. ↑ Promote inflammation. ↑	[63, 64]
	Obesity models and Diabetes	*In vitro, In vivo*	BRAK/*CXCL14*	CXCL14 promotes the recruitment of M2-type macrophages. ↑ Promote inflammation. ↑ Regulator of glucose metabolism. ↑ Associated with inflammation or lipid metabolism. ↑	[65, 66, 19, 67–69]
	Obesity, Diabetes and Metabolic Syndrome in Psoriasis	*In vivo*	SR-PSOX/*CXCL16*	Accumulation and alterations in lipid metabolism. ↑ Associated with breast adipocyte hypertrophy in African American women. ↑ Innate lymphoid cells activation and tissue distribution in obese psoriatic patients. ↑	[70–72]

The ↑ symbol represented up-regulation of CXC-chemokines during obesity and obesity related disorders types 2 diabetes and nonalcoholic fatty liver diseases

significantly higher serum levels of these chemokines. Adipose stromal cells (ASCs) associated with obesity have higher levels of the chemokines *CXCL1* and *CXCL8*, as well as their receptors *CXCR1* and *CXCR2*, which regulate ASCs ($CD34^{bright}$ CD45-CD31-) trafficking and function in the tumor microenvironment (Fig. 1) [15, 16]. According to Hariharan et al., bladder-derived ASCs secrete *CXCL1*, which is crucial for migrating bladder cancer cells. Depleting *CXCL1* in an obese patient's conditioned media from ASCs prevented the migration of T24 bladder cancer cells [73]. A recent bioinformatics study found that the protein-protein interaction network in obese people is controlled by the hub genes *CXCL1, CXCL2, CXCL8*, and *CXCL12* [41]. A recent clinical study also found that the proinflammatory genes *CXCL1, CXCL12*, and *CXCL6* were significantly hypomethylated in the blood of obese individuals. This suggests that vascular dysfunction in obese adults may be caused by a systemic hypomethylation and increased expression of immune-related genes [47].

3.3 *CXCL5* and *CXCL8*

CXC Ligand 5 (*CXCL5*) is a chemokine that suppresses insulin action in muscles while also promoting IR. It is released by white adipose tissue during obesity [17]. In both mice and humans, circulating *CXCL5* and its receptor *CXCR2* are significantly increased during obesity [17, 74]. *CXCL5* encodes one of the chemokines involved in the recruitment of immune cells. In this context, the adipose tissue of obese patients secretes free chemokines that enhance monocyte chemotaxis and macrophage infiltration [75]. In addition, *CXCL5* blocks insulin action in muscle via stimulating the Janus kinase/signal transducers and activators of transcription/ suppressor of cytokine signaling protein (Jak/STAT/SOC) signaling pathway, suggesting its ability to cause in IR. IR patients have a higher *CXCL5* concentration than non-IR obese patients. Furthermore, *CXCL5* is directly regulated by tumor necrosis factor alpha (TNF-α) in adipose tissue and macrophages via NF-kB activation, indicating that *CXCL5* mediates the effects of TNF-α on IR. Significantly inhibition of signaling from *CXCR2*, the *CXCL5* receptor, by injection of a neutralizing anti-*CXCL5* antibody or a selective antagonist to *CXCR2* improves insulin sensitivity and glucose clearance in insulin-resistant obese mice. Thus, these findings show that *CXCL5* promotes IR, and its suppression and/or elimination may be considered as a therapeutic strategy for treating metabolic syndrome (Fig. 2) [17, 74].

Cytokines (i.e. TNF- α, Interleukin 6 (IL-6) and Interleukin-1 beta (IL-1 β) cause inflammation. They are already known to be released by white adipose tissue [76] also several chemokines, including *CXCL8* also known Interleukin 8 (IL-8) and *CCL2* [77, 78]. Recent studies have found elevated levels of *CXCL8* in obese individuals [54, 79–81]. *CXCL8* represents the α and β chemokines, respectively, and may contribute to the adipose tissue inflammation via chemotaxis of inflammatory cells such as monocytes/macrophages, neutrophils and mast cells. *CXCL8* is secreted by adipocytes, monocytes, macrophages, T-lymphocytes, and endothelial cells [80–82]. Furthermore, references reported that the level of *CXCL8* in the medium and *CXCL8* mRNA

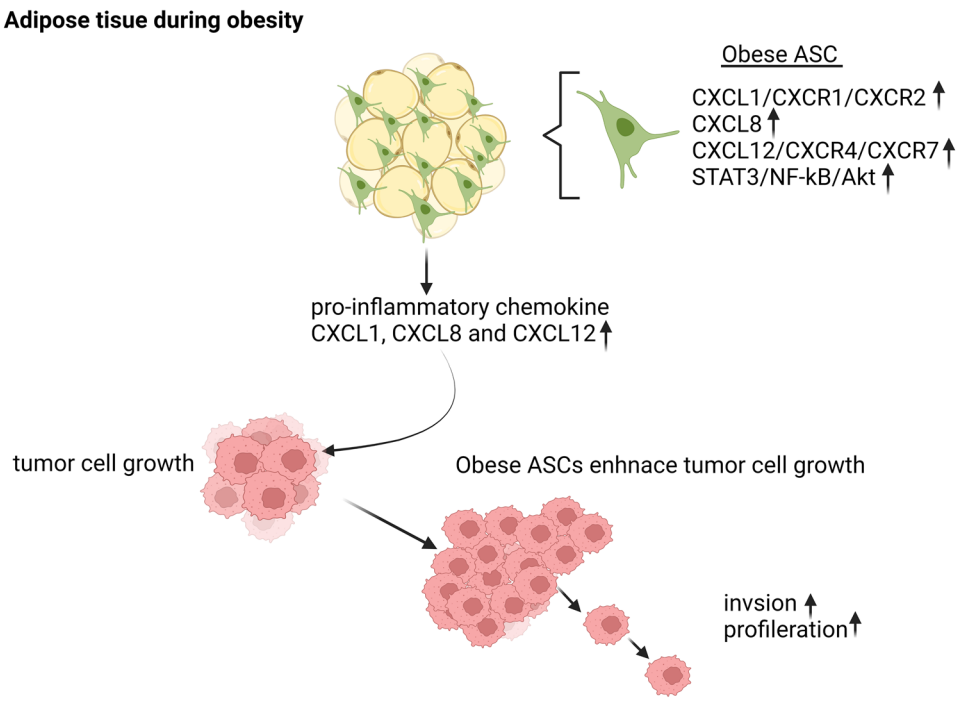

Fig. 1 The effect of ***CXCL1, CXCL8*** and ***CXCL12*** in obesity on adipose-derived stromal cells and their impact on the tumor cell growth environment. During obesity, pro-inflammatory chemokines *CXCL1, CXCL8* and receptors *CXCR1* and *CXCR2*, as well as chemokine *CXCL12* signaling via receptors *CXCR4* and *CXCR7*, activate tumor cell growth and invasion pathways (STAT3, NF-kB, and AKT) in adipose stromal cells. Created with BioRender.com

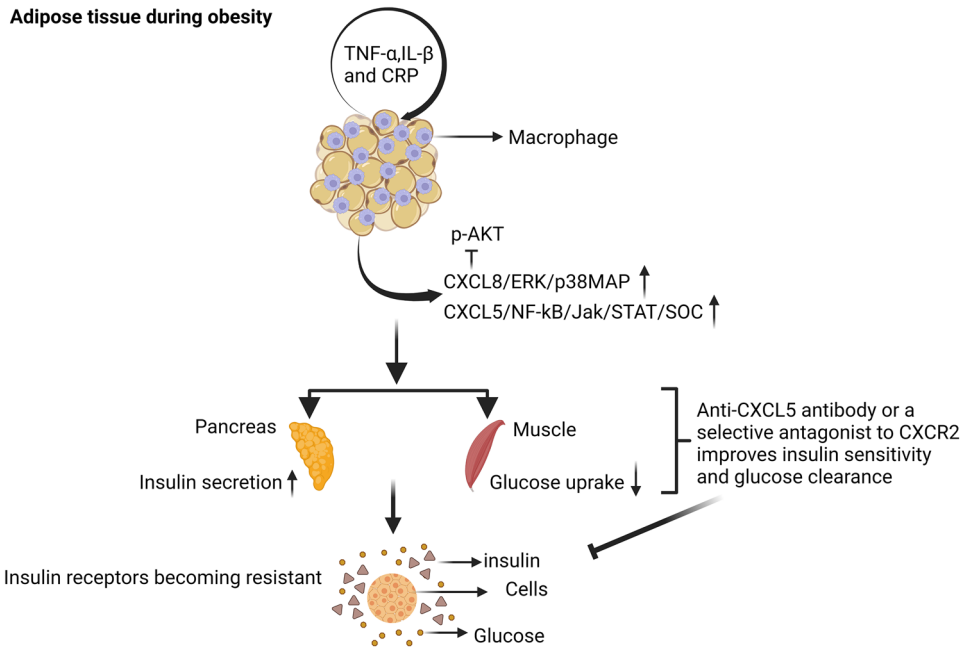

Fig. 2 Effect of ***CXCL5*** and ***CXCL8*** on insulin resistance associated with obesity. *CXCL5* is produced in response to TNF-α by adipose tissue-resident macrophages. Adipose tissue-resident macrophages also produce *CXCL8* in response to TNF-α, IL-β, and CRP. *CXCL5* activates the NF/kB/Jak/STAT/SOC signaling pathways and *CXCL8* activates the ERK/p38MAP signaling pathways, which shows that *CXCL5* and *CXCL8* can induce insulin resistance inhibition of the insulin-induced p-Akt pathway. Inhibition of signaling from *CXCR2*, by injection of a neutralizing anti-*CXCL5* antibody or a selective antagonist to *CXCR2* improves both insulin sensitivity and glucose clearance in insulin-resistant obese mice. Created with BioRender.com

expression were significantly increased in human adipocytes after stimulation with TNF-α, IL-1β, or c-reactive protein (CRP) [18, 83]. CXCL8 is a key adipocytokine that leads to IR in adipocytes by blocking the insulin signal phosphorylates a serine/threonine protein kinase (p-AKT) pathway through the extracellular signal-regulated kinase (ERK) and p38 mitogen-activated protein (p38MAP) kinase pathways during obesity (Fig. 2) [18]. Stimulation of *CXCL8* action could be a target for obesity intervention strategies and complications.

3.4 *CXCL12* and *CXCL14*

A recent study found that the chemokine *CXCL12*, which activates tumor cell growth and invasion pathways (STAT3, NF-kB, and AKT) in ASCs obtained from white adipose tissue of obese HiMyc mice via receptors *CXCR4* and *CXCR7*, is responsible for accelerated prostate tumor growth in obesity (Fig. 1) [84]. Also, Su et al. found that *CXCL12* signaling in the prostate epithelium from ASCs promotes prostate cancer in obese individuals [85]. Numerous studies have shown that *CXCL12* is highly expressed in adipose tissue during obesity, indicating that *CXCL12* and its receptors (*CXCR4/CXCR7*) play a significant role in obesity [41, 47, 85]. *CXCL12* has also been identified as an adipokine that stimulates systemic IR, obesity-related inflammation, and macrophage recruitment to adipose tissue (Fig. 3A) [86].

CXCL14 (also known as BRAK, BMAC, or Mip-2γ) is found in skeletal muscle, white adipose tissue, and brown adipose tissue, implying that it may be involved in myogenesis, adipogenesis, and metabolic regulation. *CXCL14* attracts activated tissue macrophages and dendritic progenitor cells as a chemoattractant [87–93]. *CXCL14* promotes visceral obesity and adipose tissue inflammation in animals, leading to an increase in hepatic gluconeogenesis and the development of IR [19, 65, 94–96]. In addition, the obesity-induced upregulation of *CXCL14* in white adipose tissue promotes macrophage infiltration and subsequent inflammatory responses. Increased *CXCL14* production in high-fat diet (HFD) fed mice modulates the expression of adipokines, including adiponectin, retinol-binding protein-4, and IL-6, thereby promoting gluconeogenesis in the liver and inhibiting glucose uptake in skeletal muscle. It is susceptible that the dramatic increase in macrophages in white adipose tissue and the direct action of *CXCL14* on skeletal muscle play significant roles in this diabetic cascade. *CXCL14* also indirectly contributes to the fatty liver formation, which significantly affects glucose metabolism (Fig. 3B) [19, 20]. In regards to simply recruiting inflammatory cells to visceral white adipose tissue, these studies demonstrated that CXC chemokines play essential roles in obesity-induced IR and impaired glucose metabolism.

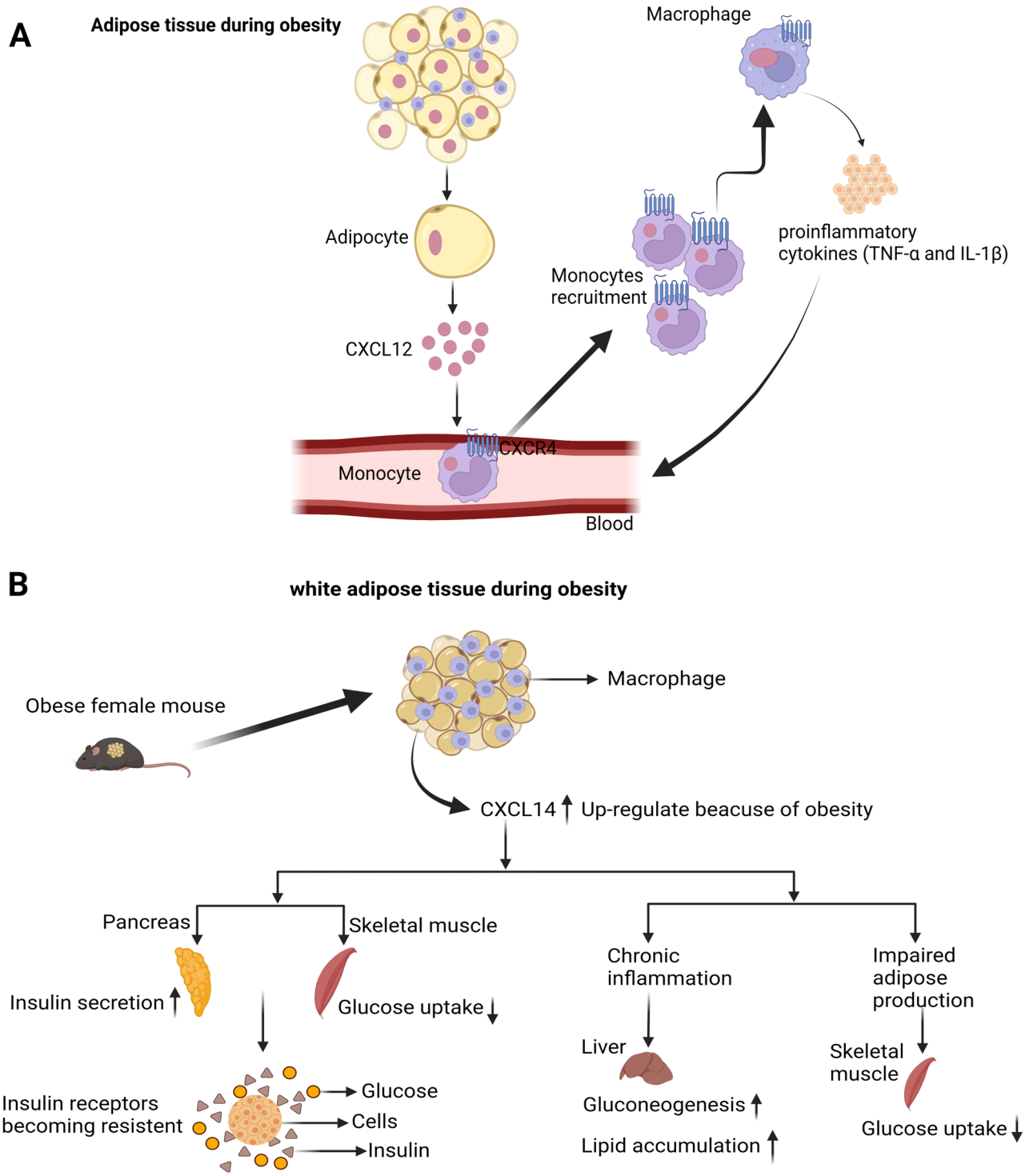

Fig. 3 ***CXCL12***-derived macrophage recruitment in adipose tissue and ***CXCL14***'s metabolic regulator functions. **A** Adipocytes secrete *CXCL12* during obesity, which recruits monocytes into adipose tissue via its receptor *CXCR4*. Mature macrophages, which have been differentiated from monocytes, secrete proinflammatory mediators, which may lead to systemic insulin resistance. **B** On the basis of the phenotypic abnormalities of *CXCL14*-deficient female mice fed an HFD, *CXCL14* is implicated in obesity-induced insulin resistance. Organs and consequences of *CXCL14* action are illustrated schematically. Created with BioRender.com. ↑ arrow symbol shows up-regulated while ↓ arrow show downregulated

4 CXC chemokines and T2D

Obesity is associated with higher levels of low-grade chronic inflammation, which predisposes humans to a broad spectrum of comorbidities such as T2D, dyslipidemia, CVD, and NAFLD [97, 98]. T2D, also known as non-insulin-dependent diabetes mellitus, is distinguished by IR and pancreatic-cell (β cells) dysfunction attributable to hyperglycemia [99, 100]. IR impacts the entire diabetes pathophysiology. IR can pursue in the liver, muscles, and adipose tissue. Islet *β* cells produce more insulin to compensate for IR, which may exceed their maximum capacity and result in *β* cell failure [101].

Chronic, low-grade inflammation of adipose tissue in regard to obesity and IR is crucial to the development of T2D. Popov et al. reported that inflammation is associated with impairment of oxidative status, carbohydrate and lipid metabolism in T2D complicated by NAFLD [102]. Many studies have been conducted in both humans and mice on the role of inflammation's involvement in the development of T2D. In human and mouse adipocytes, multiple pro-inflammatory mediators, such as *CXCL1, CXCL10*, and monocyte chemoattractant protein (MCP)-1, induce IR [103, 104]. The biological role of CXC chemokines in T2D development is addressed further below.

4.1 *CXCL1* and *CXCL2*

According to previous studies, T2D patients exhibited the most significant increases in *CXCL1* and *CXCL5* levels [105–107]. Craig and colleagues demonstrated that *CXCL1* and *CXCL5* are up-regulated in obese diabetic mice (db/db) compared to control mice (non-diabetic/non-obese) [108]. *CXCL1* is highly expressed in diabetic wounds in rats and humans via the interleukin 17 (IL-17) pathway. In the same study, interleukin (IL-7) inhibitors (Huangbai liniment and berberine) significantly reduced IL-17 expression and its downstream targets, including *CXCL1*, in diabetic wounds [109]. Similarly, another study demonstrated that *CXCL1* and *CXCL2* are up-regulated in diabetic wound mice, whereas Cryptotanshinone (inhibitor) significantly decreased *CXCL1* and *CXCL2* chemokine in Cryptotanshinone mice relative to vehicle mice [110]. In addition, Anuradha et al. found that the number of chemokines found in the plasma of T2D patients increased. These chemokines include *CXCL1, CXCL2, CXCL8, CXCL9, CXCL10*, and *CXCL11*. This finding suggests that the chemokine network plays a significant role in the progression of T2D [111]. The bioinformatics analysis of endothelial precursor cells isolated from T2D patients also revealed that *CXCL1* chemokine is up-regulated, implying that *CXCL1* may play an essential role in the pathophysiology of endothelial precursor cells during T2D and stimulate an inflammatory response, which may be critical for the reduced number and hypofunction of endothelial precursor cells isolated from T2D patients [112]. Moreover, prior studies have demonstrated that the serine-phosphorylated STAT1 and NF-kB (IkKB) pathways, which control the transcription of *CXCL1* and *CXCL2*, are significant contributors to the inflammatory response in β cells associated with islet β cell death in T2D. In both humans and animals with T2D, the *CXCL1* and *CXCL2* genes are regulated, encoding proteins that promote neutrophils and other CXCR2 + cells to migrate toward secreting tissue [113–115]. Single-cell RNA analysis has demonstrated that in diabetic macular edema, through boosting the production of the pro-inflammatory chemokines *CXCL2* and *CXCL8*, $CD14^{++}$ monocytes predominate in inducing inflammation. These highly expressed genes for inflammation suggest that immune cells in the blood of diabetic macular edema patients were in a proinflammatory state. This may have led to the destruction of vascular endothelial cells and retinopathy [116]. Nevertheless, the skin tissue from mice with a T2D-like phenotype displayed an up-regulation of the inflammatory gene *CXCL2*. These results indicate that *CXCL2* is strongly associated with inflammation of tissues in mouse models of T2D [117]. In contrast, a transcriptome study found that *CXCL2, CXCL3, CXCL5*, and *CXCL8* are down-regulated in T2D patients' neutrophils compared to healthy controls, whereas *CXCR1* and *CXCR2* genes are significantly upregulated in T2D patients' neutrophils compared to healthy controls. This work demonstrates that circulating neutrophils from T2D patients exhibit aberrant activation at the transcriptome level and that these neutrophils may also have reduced motility due to downregulated chemotaxis, which may help to explain why certain T2D patients have higher infection rates [118].

4.2 *CXCL8*

Previous research indicates that toll-like receptor (TLR)-4 signaling is one of the key pro-inflammatory pathways induced via endogenous or exogenous molecules related to risk or infections. Circulation levels of the classical TLR4 ligand lipopolysaccharide (LPS), which has been recently designated "metabolic endotoxmia", are high in obese and T2D patients. This situation is also found in obesity/ diabetes model of rodents. [119, 120]. Isolated human islets were stimulated to produce IL-1, *CXCL8*, and TNF by LPS in a TLR4-dependent manner, whereas β cell viability and function were substantially compromised. *CXCL8*, which was specifically detected in β cells, stimulated monocyte recruitment, which was completely prevented by *CXCL8* neutralization. TLR4 is extremely pathogenic in human islets, causing a complicated multi-cellular inflammatory response that includes β cell failure, chemokine secretion,

and macrophages infiltration. The highly elevated TLR4 response in obesity may exacerbate β cell damage and hasten diabetes progression [48].

Cimini and colleagues found that T2D patients had higher *CXCL8* levels than non-diabetic subjects, and that *CXCL8* concentration correlated with higher IL-6, TNF-α, fasting blood glucose, glycosylated hemoglobin, low-density lipoprotein cholesterol, lower adiponectin, and 25(OH) vitamin concentrations, indicating that T2D patients have a marked elevation of circulating *CXCL8*, which identifies subjects with worse inflammatory, glycometabolic and lipid profile and lower vitamin D levels [121]. Moreover, reference showed that *CXCL8* recruits' neutrophils and stimulates tissue inflammation through binding to *CXCR1* and *CXCR2*. In both *in vitro* and *in vivo* diabetes models, *CXCL8* suppression inhibits the activation of *CXCR1* and *CXCR2*, as well as their downstream JAK2/STAT3 and ERK1/2 pathways [122].

4.3 *CXCL9, CXCL10*, and *CXCL11*

Numerous studies have shown that *CXCL9, CXCL10*, and *CXCL11* and their receptor *CXCR3* are up-regulated in T2D patients [123–125]. Blocking the *CXCL10/CXCR3* system is considered to be a promising therapeutic target due to the extensive research on the *CXCL10/CXCR3* axis role in the immunopathogenesis of diabetes [105]. Additionally, high glucose levels activate the p38 MAP kinase signaling pathway, which in turn induces *CXCR3* in $CD8^+$ T cells. Likewise, high glucose levels induced *CXCL9,CXCL10*, and *CXCL11* expression, which promoted and infiltrated $CD8^+$ T cells into the peripheral tissue of diabetics and increased cytotoxicity [123, 126].

4.4 *CXCL12* and *CXCL13*

SDF-1 alpha (*CXCL12*) is a stromal cell-derived factor that has a role in the activation of T lymphocytes and monocytes but not neutrophils. It induces a rapid and transient dramatic increase in intracellular calcium ions and further chemotaxis by activating the receptor *CXCR4*, which acts as its receptor. *CXCL12* can also bind to another receptor, *CXCR7*, activating the beta-arrestin pathway [105, 127]. Patients with T2D who have the heterozygous SDF-1 3′A genotype (801G/A in the 3′ untranslated region) have higher levels of insulin-dependent adult progenitor cell mobilization, which is known to be involved in angiogenesis and vascular repair. On the other hand, homing of progenitor cells is a factor in the vascular complications of diabetes. This is because patients with the SDF-1 3′A genotype have higher levels of *CXCL12* mRNA in their peripheral blood mononuclear cells. Variations in the *CXCL12* gene's genetic makeup may impact the movement of inflammatory cells or defective precursors, which might increase the risk of diabetes disease [128, 129]. Moreover, karimabad et al. reported that injured duct, red blood cells, δ-cells, β cells, and α cells display higher amounts of *CXCL12* during T2D and that bone marrow and secondary lymphoid organs recruit immune cells to the blood via the *CXCR4* receptor. Together, *CXCL12* and *CXCR4* contribute to the development of T2D, potentially by increasing B-cell mortality, glomerulonephritis, and microangiopathy [129]. Elevated *CXCL12* is associated with disease in the systemic compartment and can be used as a blood biomarker to identify individuals with T2D [130, 131].

CXCL13/CXCR5 has a considerable proinflammatory consequence by itself. *CXCL13/CXCR5* signaling is a crucial upstream mediator driving p-ERK, p-AKT, and p-STAT3 cell signaling pathways as well as stimulating the production of inflammatory cytokines TNF- α and IL-6. The chemokine *CXCL13* and its receptor *CXCR5* in the spinal cord contribute to the pathogenesis of painful diabetic neuropathy [132]. Surprisingly, Jiang et al. reported that *CXCL13* promoted bone marrow stromal cell proliferation in high glucose environments, promoting the healing of fractures in diabetic rats [133]. Furthermore, previous studies have showed increased levels of *CXCL13* in T2D patients, and this protein has been speculated to be responsible for triggering leukocyte chemotaxis and activation [27, 82, 134].

4.5 *CXCL14*

Obesity affects the majority of T2D patients. Matsushita et al. found that serum *CXCL14* levels were independently associated with serum C-peptide and fatty liver index in T2D patients. A high serum C-peptide concentration may reflect IR rather than β cell function in these patients, because *CXCL14* displayed simple correlations with obesity-related factors. These findings suggested that serum *CXCL14* levels in T2D patients could be used to predict elevated serum C-peptide and hepatic steatosis [66]. Although *CXCL14*'s cellular receptor and signaling pathway are still unknown, it is postulated to have chemotactic activity toward a wide range of inflammatory mononuclear cells, such as monocytes, neutrophils, dendritic cells, and natural killer cells [135]. In this outcome, the serum *CXCL14* concentration in T2D individuals involved has been reported to be elevated in correlation with IR and hepatic steatosis. It is believed that *CXCL14* plays an important role in both the immune response and inflammation. This chemokine could be a new biomarker or therapeutic target for IR, hepatic steatosis, and T2D linked to obesity.

4.6 *CXCL16*

CXCL16 is a protein that combines the functions of a scavenger receptor with those of an inflammatory chemokine. This transmembrane protein is composed of an extracellular chemokine domain and a transmembrane mucin stalk [136]. This chemokine domain functions as a recruiter for cells expressing the *CXCR6* receptor as well as a scavenger, facilitating oxidized low-density lipoprotein uptake (ox-LDL). Pro-inflammatory stimuli increase *CXCL16* expression, which increases ox-LDL uptake and hastens foam cell formation in the vascular endothelium [137]. *CXCL16* is a remarkable chemokine that is available in two forms: Soluble *CXCL16* links to immune cells that express the *CXCR6* receptor and leads them to the site of inflammation [138] and ox-LDL is subsequently internalized by the cell membrane receptor form [139]. According to previous studies, the pancreatic β cell's autophagy and transcription factor activation in diabetes could be induced by the activation of the *CXCL16*/ox-LDL pathway in β cells [140, 141]. Similar, Gutwein et al. reported that high levels of oxLDL were associated by increased glomerular *CXCL16* expression in diabetic nephropathy [142]. This evidence confirms that oxLDL and *CXCL16* have a link during diabetes. Moreover, the membranous *CXCL16* can be cleaved to its soluble form by a Disintegrin and Metalloproteinase (ADAM10) [143]. Recent research indicates that ADAM10/*CXCL16* upregulation in the pancreatic islets of diabetic mice results in an accumulation of T-cells via an increased NF-kB pathway. Consequently, in diabetic mice, cleaved *CXCL16* promoted T-cell recruitment into β cells and enhanced oxidative stress, inflammatory response, and mortality [140]. In addition, recent study demonstrated the processing enzyme ADAM10 and the *CXCL16/CXCR6* receptor have a role in the development and progression of proliferative diabetic retinopathy. The researcher accepted that proliferative diabetic retinopathy is mediated by elevated levels of retinal NF-kB, vascular endothelial growth factor, and intercellular adhesion molecule 1 [144]. In a recent study by Tawfik et al. discovered that patients with T2D had much higher levels of *CXCL16* in their blood than healthy patients [145]. Likewise, *CXCL16* serum levels were elevated in T2D patients with or without coronary artery disease compared to healthy patients [146]. Moreover, patients with diabetes mellitus, with or without gestational diabetes mellitus disease, had elevated blood *CXCL16* levels [141, 147]. These studies confirmed that the chemokine *CXCL16* is a key part of inflammation and may contribute to the development and progression of T2D. In T2D, serum *CXCL16* might be used to monitor inflammation. Figure 4 displays the recent evidence regarding the role of CXC chemokines in the development of T2D and their blockade as a potential therapeutic approach.

5 CXC chemokines and NAFLD

The metabolic syndrome, which includes obesity, dyslipidemia, hyperinsulinemia, and IR, is characterized by NAFLD, which is its hepatic manifestation [148, 149]. Because of this, NAFLD is often considered a hepatic manifestation of metabolic syndrome [150]. NAFLD represents a wide range of liver disorders, from simple steatosis (SS) to nonalcoholic steatohepatitis (NASH) [151] ; It is well known that the latter increases the risk of liver cirrhosis and hepatocellular carcinoma (HCC) [152]. SS patients rarely suffer sever disease, but nearly 20% of NASH patients progress to the end-stages of liver disease [153, 154]. The risk of developing cirrhosis and hepatocellular carcinoma is higher in individuals with NASH than in individuals with SS, implying that NASH is a more severe form of liver injury [154–156].

Furthermore, adults with diagnosed NAFLD tend to follow dietary patterns including high fat and sodium with suboptimal micronutrient intake and low physical activity [157]. Abdallah et al. reported that anti-inflammatory dietary patterns showed benefits to NAFLD risk factors, severity markers and inflammatory markers compared to the control diet [158]. These studies demonstrated that NAFLD could be prevented through dietary patterns.

5.1 *CXCL1* and *CXCL2*

Regarding the development of NAFLD, a number of reference articles provide a comprehensive summary of key chemokines and their receptors. Chemokine pathophysiological involvement in the development of NAFLD have been widely explored in NAFLD humans and animal models [159–161]. *CXCL1* was among the most significantly active genes in the livers of mice following a 3-month HFD with binge ethanol exposure (30-fold in the liver and 5-fold in epididymal adipose tissue) [162]. *CXCL1* expression increased significantly in hepatocytes, hepatic stellate cells (HSCs), and liver sinusoidal endothelial cells in the liver [162]. The regulation of *CXCL1* by an HFD-plus-ethanol binge is thought to be associated with elevated levels of free fatty acid (FFA) in the liver, which stimulate *CXCL1* in hepatocytes via ERK1/2, Jun N-terminal kinase (JNK), and NF-kB. While *CXCL1* overexpression exacerbated steatohepatitis in 3-month HFD-fed mice, *CXCL1* inhibition with a neutralizing antibody or *CXCL1* gene disruption decreased hepatic neutrophil infiltration and injury following an HFD plus ethanol binge [162]. Moreover, In the choline deficient amino acid-defined (CDAA) diet-induced animal NASH model, *CXCL1* mRNA levels are enhanced in a TLR4-MyD88-dependent manner, resulting in increased neutrophil infiltration related to hepatic inflammation and fibrosis [163].

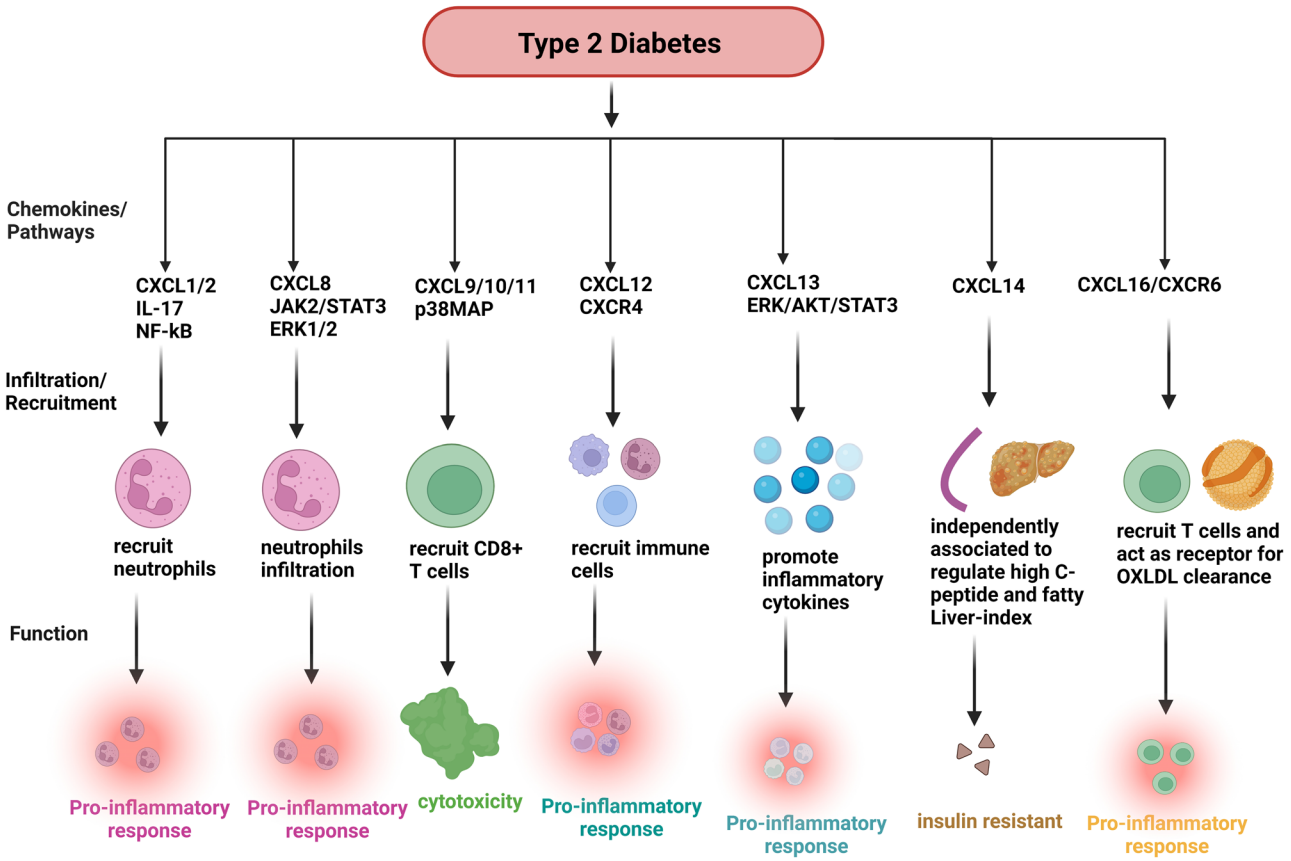

Fig. 4 The functions of CXC chemokines in T2D. Chemokines mainly control the migration of neutrophils, monocytes, T cells, and leukocytes in T2D. *CXCL1* and *CXCL2* recruit neutrophils through the IL-17/NF-kB pathway and play a pro-inflammatory role. *CXCL8* recruits neutrophiles via the JAK2/STAT3/ERK1/2 pathways to induces pro-inflammatory response. *CXCL9, CXCL10*, and *CXCL11* recruits CD8 + T cells through the p38MAP pathway, which plays an important role in cytotoxicity. *CXCL12/CXCR4* axis recruits immune cells, which creates inflammation. *CXCL13* recruits promote inflammatory cytokines with the help of ERK/AKT/STAT3 pathways and induces inflammation. In addition, *CXCL14* independently associated with serum C-peptide and fatty liver index which induce insulin resistance. *CXCL16/CXCR6*/ADAM10 recruits T cells via NF-kB pathway and acts as a receptor for oxLDL clearance. Created with BioRender.com

In addition, In HFD-fed animals, adenoviral overexpression of *CXCL1* induces hepatic neutrophil infiltration, oxidative stress, and hepatocyte mortality, increasing progression from SS to steatohepatitis [37]. Mueller et al. reported that *CXCL1* is up-regulated in Ldlr-/-. Leiden mice enhanced hepatic inflammation, but treatment with the multicomponent pharmaceutical product (HC-24) inhibits the development of free cholesterol and has anti-inflammatory actions at the molecular and cellular levels in the liver [38]. Recently, bioinformatic studies of human and animal also demonstrated that *CXCL1* and *CXCL2* is highly expressed in the NALFD disorder which indicated that *CXCL1* and *CXCL2* play important role in the live inflammation in human and mice [164, 165]. Moreover, a study demonstrated that *CXCL2* activates the TLR4 pathway to recruit neutrophil and macrophage infiltrations in the palmitate-induced fibrosis mouse model [166]. Saiman et al. found that increased hepatic levels of *CXCL1* and *CXCL2* trigger the recruitment of neutrophils from the periphery after hepatic injury in humans [167]. These data indicate that *CXCL1* and *CXCL2* have a role in neutrophil recruitment and infiltration as a consequence of hepatic cell dysfunction in the liver, which leads to the development of chronic inflammation in NAFLD.

5.2 *CXCL5*

Previous reports indicated that *CXCL5* is essential for neutrophil recruitment and activation via the *CXCR2* receptor, as well as hepatocyte proliferation [168, 169]. *CXCL5* is linked to neutrophil infiltration and a poor prognosis in HCC. It is considered a therapeutic target in the disease, as treatment with small-interfering RNAs or antibodies against *CXCL5* can inhibit tumor growth, proliferation, migration, and invasion [170]. Xu et al. found that *CXCL5* was over-expressed in HCC with high metastatic potential, and that *CXCL5* could increase HCC migration and invasion, most frequently via

autocrine and paracrine mechanisms. Evidence also suggests that the *CXCL5*-*CXCR2*-ERK1/2/JNK/p38MAPK pathways may play important roles in HCC migration and invasion, and neutrophil and macrophage recruitment [171]. *CXCL5* was identified as a gene target of metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) in liver cells, and increased levels of *CXCL5* transcript and protein were found in fibrotic liver and activated hepatic stellate cells. Previous research demonstrated that MALAT1 expression increases in activated hepatic stellate cells and is regulated by hyperglycemia and insulin *in vitro*. In addition, MALAT1 expression was found to increase in activated hepatic stellate cells [172]. A recent study showed that *CXCL5* activation of the NF-kB pathway in human hepatocyte-derived spheroids and primary rat hepatocytes caused NASH, while livogrit, a *CXCL5* inhibitor, showed promise as a haptic therapeutic formulation that could reduce CXCL5 levels in the development of NASH [173]. In Longitudinal studies, *CXCL5* chemokine is evaluated in the diet-induced progression of NAFLD to HCC in diet-induced animal model of nonalcoholic fatty liver disease (DIAMOND) [174].

5.3 *CXCL6*

Chemokine *CXCL6* (GCP-2) is an essential component of inflammatory cells. It is expressed in the liver and plays a role in the pathogenesis of multiple inflammatory responses and liver fibrosis [175]. *CXCL6* dysregulation was closely associated with the activation of liver-infiltrating lymphocytes in the initial stage of hepatitis C-induced fibrosis [176]. Cai et al. showed that activated Kupffer cells (or stellate macrophages) are the source of *CXCL6* in fibrotic livers, and that *CXCL6* secreted by these macrophages promotes the release of transforming growth factor-beta (TGF-β) by Kupffer cells via the *CXCR1/2* epidermal growth factor receptor (EGFR) pathway, which promotes HSCs activation [175]. Moreover, a recent study found that mRNA expression levels of *CXCL6*, and *CXCR1* were high in SS during the pathogenesis of NAFLD via the pro-inflammatory NF-kB pathway [177].

5.4 *CXCL8* and *CXCL9*

As evidenced by experimental findings, *CXCL8* is a CXC chemokine with capabilities that are simultaneously pro-inflammatory and pro-angiogenesis [178]. Macrophages are an essential element of NAFL and NASH, and research has demonstrated that liver-activated macrophages can create higher levels of *CXCL8*, hence inducing *CXCL8*/mir-17 clusters. *CXCL8* may enhance neutrophil recruitment in NASH by triggering the AKT/mTOR/STAT signaling pathway. The intrahepatic expression of *CXCL8* was also elevated in the blood and liver of NAFL patients. These findings revealed that *CXCL8*, with the highest ranking in the NAFL stage, may play a significant role in both the NAFL and NASH stages [178, 179]. In addition, inflammatory neutrophil infiltration is distinguished by upregulation of *CXCL8*, and *CXCR1/2*, which recruit neutrophils into the liver to produce reactive oxygen species and proteases, resulting in hepatocyte damage [180–182]. For instance, studies have demonstrated that patients with NAFLD have increasing levels of the inflammatory chemokine *CXCL8* [49, 179, 183–185] and these recent research suggests that *CXCL8* plays a role in the pathophysiology of NAFLD and could be a potential treatment target for NAFLD.

The gene *CXCL9* is a member of the chemokine superfamily, which produces secreted proteins that are involved in immune regulation, inflammation, and T cell trafficking. The encoded protein attracts lymphocytes but not neutrophils when it binds to the *CXCL3*. According to studies, *CXCL9* plays a role in a number of pathological processes, including the growth of tumors, immunity, and inflammation [186, 187]. The liver tissues of NASH patients have higher levels of *CXCL9* expression. *CXCL9* mRNA was discovered to be overexpressed in both NASH and SS mice models, and hepatocytes and sinusoid endothelial cells that released *CXCL9* protein were detected in regions where inflammatory cells had infiltrated [188]. In a high-risk cohort of obese adults with NASH without fibrosis, the expression of *CXCL9* was upregulated [55]. Another cohort research found that the effects of liver fibrosis were positively connected with blood *CXCL9* concentrations in patients with chronic liver disease, which were considerably greater than in healthy control individuals [189]. Patients with chronic hepatitis C virus infection also had higher levels of *CXCL9* expression, which was associated with liver fibrosis [190]. In mouse models, the interaction from NAFLD to HCC in male mice was associated with a chronic trend of increased *CXCL9* levels [174, 191]. Furthermore, a recent study found that *CXCL9* disrupts the Treg/Th17 balance in a mouse model of metabolic-associated fatty liver disease (MAFLD) by activating the p-JNK pathway [192]. Moreover, bioinformatics analysis also demonstrated that *CXCL9* is up-regulated in both humans and animals NAFL and NASH disorders [193–195]. *CXCL9* is a key factor in chronic liver inflammation, according to these findings; nevertheless, its expression and involvement in NAFLD require additional exploration.

5.5 *CXCL10* and *CXCL12*

CXCL10 is produced by a number of cells, including macrophages, monocytes, hepatocytes, hepatic stellate cells, and endothelial cells [196]. In a well-designed and comprehensive study, Ibrahim et al. may have identified the central link between lipotoxicity, and recruitment of macrophages, which promotes inflammatory processes in NASH. The

researchers examined the chemokine *CXCL10* and mixed lineage kinase 3 (MLK3) in hepatocytes stimulated by palmitic acid or lysophosphatidylcholine (LPC), as well as in an *in vivo* model of NASH [197]. *CXCL10*-containing extracellular vesicles (EVs) were increased in treated cells and mice fed a high-calorie (saturated fat, cholesterol, and fructose; FFC) diet. *In vitro*, *CXCL10* bound to EVs exerted a stronger chemotactic effect on macrophages than *CXCL10* unbound to EVs. Two significant pathways controlled by MLK3 were discovered by MLK3 deletion or pharmacological inhibition. First, inhibiting MLK3 reduces LPC-induced *CXCL10* production, most probably via a p38/signal transducer and activator of transcription 1-dependent pathway; second, MLK3 inhibition diminished *CXCL10* trafficking into EVs (with increased intracellular *CXCL10* levels in hepatocytes) and LPC-induced EV release, which may be dependent on JNK activation. In conclusion, MLK3-dependent hepatocyte production of *CXCL10*-containing EVs may represent a crucial interface between lipotoxicity and inflammation generated by macrophages recruited into the liver [197]. Finally, these findings not only emphasize the importance of *CXCL10* in driving hepatic inflammation in NASH, but it also suggests the role of EVs in hepatic inflammation, which is a novel field of cell biology that requires further investigation [197]. Furthermore, several studies on *CXC10* chemokine and NAFLD indicate that *CXCL10* has been recommended as a potential therapeutic target for NAFLD treatment [198–200].

CXCL12 is abundantly expressed in numerous tissues, including the liver, where biliary cells express it [201]. *CXCL12* as well as its receptor *CXCR4* have aberrant expression that has been linked to NAFLD. *CXCR4* regulates cell localization, chemotaxis, activation, migration, division, and differentiation when it binds to its ligand, *CXCL12* [202, 203]. *CXCL12* is widely generated by sinusoidal endothelial cells in the liver and enhances hematopoietic stem cell migration following chronic liver injury [202]. NASH developments include elevated *CXCR4* and *CXCL12* protein levels as well as aberrant $CD4^+$ T- cell responses to *CXCL12* [202, 204]. During immune surveillance and liver inflammation, liver sinusoidal endothelial cells promote $CD4^+$ T cell recruitment by upregulating peri-vascular *CXCL12* production and activating *CXCL12/CXCR4*-dependent intracellular transport pathways [24]. Moreover, Activation of the *CXCL12/CXCR4* axis increased collagen I synthesis and hematopoietic stem cell proliferation in an animal model of CCL4-induced hepatic fibrosis [205].

5.6 *CXCL16*

Prior research has found that *CXCL16* is substantially expressed in the livers of patients who suffer from metabolic and inflammatory liver disorders [206, 207] and that *CXCL16* inhibition reduced steatohepatitis and liver macrophage infiltration in chronic hepatic damage [208]. In addition, *CXCL16* is considered to be a survival and maturation regulator for hepatic NKT cells [209].

In experimental NAFLD, *CXCR6* promotes liver inflammation by enhancing the invasion of hepatic NKT cells and inflammatory macrophages [208, 210, 211]. The *CXCL16/CXCR6* axis stimulates hepatic NKT cell migration, promoting CCl4-induced liver fibrosis [21, 22]. Indeed, injured hepatocytes exhibited increased *CXCL16/CXCR6* axis expression, showing that the *CXCL16/CXCR6* interplay is involved in the pathogenesis of NAFLD [208, 212–214].

5.7 *CXCL17*

CXCL17 is a newly identified 119-amino acid CXC chemokine; its recently identified receptor, *GPR35/CXCR8*, is a GPCR involved in metabolic processes [215–217]. It stimulates monocytes, macrophages, dendritic cells, and immature myeloid-derived cells as a chemoattractant [217]. Autophagy inhibition was also associated with increased levels of *CXCL17*, which enhances cell proliferation and migration in human HCC tissues. Its suppression induces autophagy via nuclear translocation of liver kinase B1, which phosphorylates and activates AMPK, leading to an increase in tumor size and proliferation reduction [218]. In addition, an indicator that can predict the patient's prognosis in liver cancer is lncRNA called distal-less homeobox 6 antisense 1 (DLX6-AS1) [219], whose down-regulation hinders cancer cells' tendency to proliferate [220]. Likewise, silencing DLX6-AS1 effectively suppresses the bioactivities of HCC cells [221]. MicroRNAs (miRNAs), such as miR-15a-5p, are also crucial in the development of liver cancer. Interestingly, miR-15a-5p levels that are higher can inhibit the proliferation of liver cancer cells as well as other tumor-promoting features [222, 223]. There have been some studies on the roles of HCC-derived exosomes in human cancers. For instance, in HCC cells co-cultured with HCC-derived exosomes, increased migration, invasion, and epithelial-mesenchymal transition (EMT), as well as decreased E-cadherin and elevated vimentin levels, have been observed [224]. The M2-polarized macrophages and the miR-15a-5p/*CXCL17* axis make it possible for DLX6-AS1 in HCC-derived exosomes to induce cancer. DLX6-AS1 suppresses miR-15a-5p, which stimulates the polarization of M2 macrophages and the invasion and metastasis of HCC. The silencing of *CXCL17* can inhibit migration, invasion, and EMT. Finally, DLX6-AS1 in HCC-derived exosomes modulates *CXCL17* by binding to miR-15a-5p in a competitive fashion. This induces M2 macrophage polarization, which in turn promotes HCC migration, invasion, and EMT [26]. Furthermore, Li et al. demonstrated that *CXCL17* may positively regulate $CD68^+$ macrophage accumulation while negatively regulating $CD4^+$ T cell infiltration in HCC tumors, suggesting that *CXCL17* production is connected

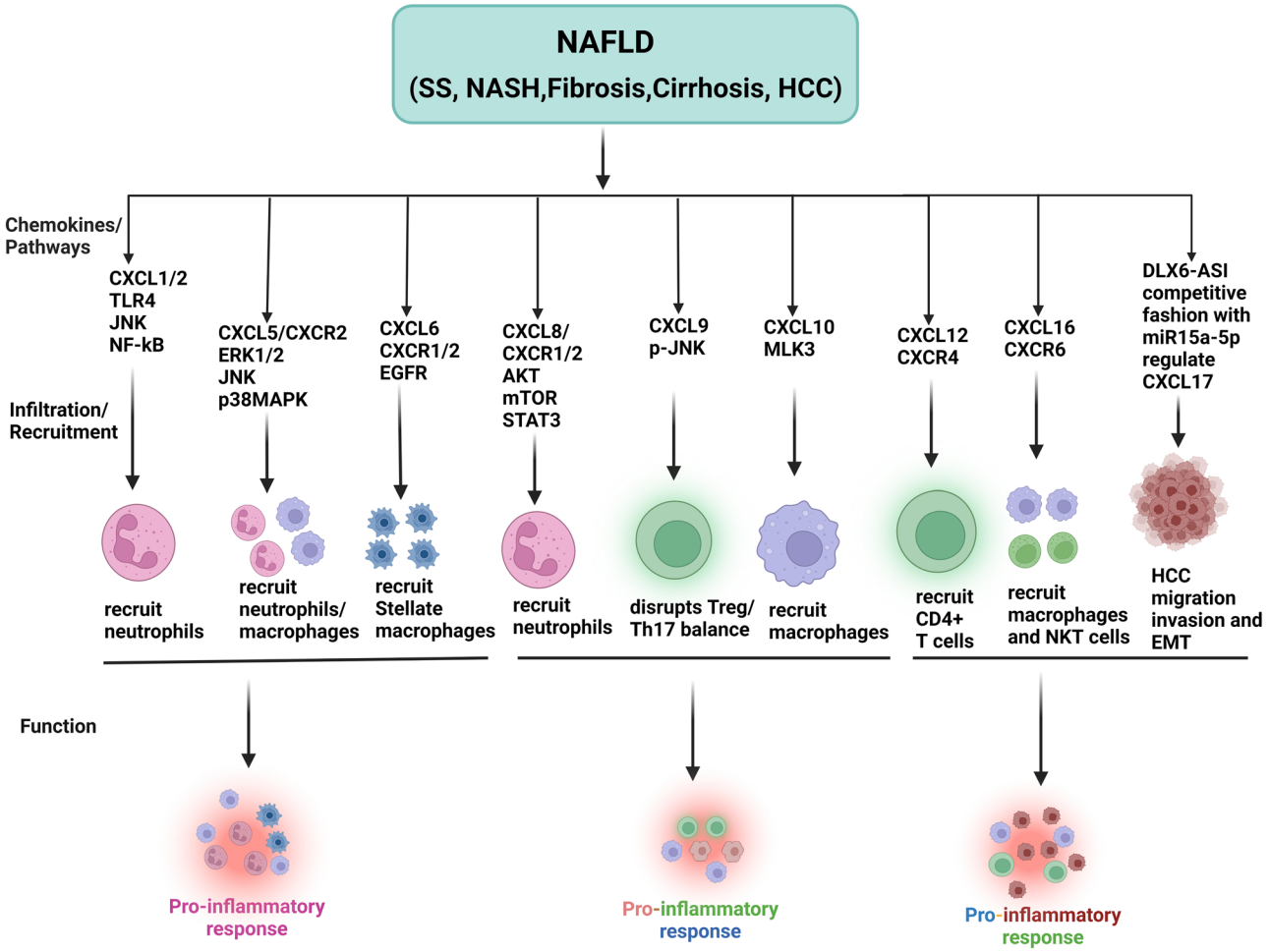

Fig. 5 The role of CXC chemokines in the NAFLD. *CXCL1* and *CXCL2* recruit neutrophils via TLR- 4, JNK and NF-kB signaling, which induce inflammation. *CXCL5* recruits neutrophiles through the ERK1/2/JNK and p38MAPK pathways, which plays an important role in the pro-inflammatory process. *CXCL6* and receptor *CXCR1* and *CXCR2* recruits stellate macrophages by EGFR mechanism as a result pro-inflammatory response occur, *CXCL8* and its receptors, *CXCR1* and *CXCR2*, recruit neutrophils through the AKT/mTOR/STAT3 pathways, causing hepatocyte injury and inflammation. *CXCL9* disrupts the Treg/Th17 via the p-JNK pathway, which acts as a pro-inflammatory signal. *CXCL10* recruits the macrophage chemotaxis via MLK3 mechanism and produces a pro-inflammatory response. *CXCL12* and its receptor *CXCR4* recruit $CD4^+$ T cells in the results of liver injury. *CXCL6* and its receptor, *CXCR6/CXCR6* axis, primarily recruit macrophages and NKT cells and produce pro-inflammatory response. DLX6-AS1 in HCC-derived exosomes modulates *CXCL17* by binding to miR-15a-5p in a competitive fashion, which in turn promotes HCC migration, invasion, and EMT. Created with BioRender.com

with adverse immune infiltration and may be a key target for anti-HCC therapy [225]. Figure 5 illustrates the recent evidence regarding the role of CXC chemokines in the pathogenesis of NAFLD and their blockade as a potential therapeutic approach.

6 Conclusions and future perspectives

We attempted to explain the expression, molecular mechanisms, sources, and key functions of CXC chemokines in obesity and disorders associated with obesity, such as T2D and NAFLD. In particular, suppressing the *CXCR2* pathway prevents the development of IR and inflammation, which may help to improve the prognosis of disorders associated with obesity and inflammation. CXC chemokines suppression in an obese patient's conditioned media from ASCs prevented cancer cell migration. Moreover, the CXC chemokines linkage may contribute to the immunopathogenesis of diabetes. On the other side, this axis' suppression can decrease the risk of immunological rejection. This could be a possible therapeutic target for diabetes patients. Inhibition of the CXC chemokines can inhibit tumor growth, proliferation, migration, and invasion during HCC, making it a potential target for therapeutic intervention.

Nevertheless, our understanding of the complex communication system between CXC chemokines and their receptors is still inadequate, which could hinder the creation of innovative therapeutics for obesity, T2D, and NAFLD. If possible, the role of each CXC chemokine and chemokine receptor should be adequately and instantly addressed to ensure translation into potential clinical implications. As a result, further clinical and pre-clinical studies are required to investigate the molecular mechanism and ascertain whether an anti-inflammatory strategic approach targeting specific CXC chemokines and chemokine receptors could be a promising therapeutic approach to prevent the progression of obesity, T2D, and NAFLD.

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Author contributions All authors contributed to the conception, drafting, illustration, and final revision of the work. Each author has reviewed and approved the final manuscript.

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Declarations

Conflict of interest The authors say that they have no commercial or financial ties that could be seen as a conflict of interest in the study we did. Because of this, there were no conflicts of interest in the study.

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