

Review Article

Chemokine Ligand-Receptor Axes for Therapeutic Targeting During Skin Regeneration

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Abstract

Chemokines and their cognate receptor interactions regulate the balance between pro-inflammatory and anti-inflammatory signals to support the physiological functions of the skin. Chemokines also regulate the process of angiogenesis, epithelialization and collagen deposition. A severely dysregulated chemokine ligand-receptor network has been observed in chronic non-healing wounds and skin diseases. Evaluation of the chemokine signaling pathways in pathological skin conditions is essential for the development of targeted therapeutic interventions that can enhance skin regeneration. Although chemokines and their receptors serve as attractive targets for drug discovery, clinical trials to date have seen limited success, especially in skin regeneration. Repurposing of the already established drugs can overcome the limitations. Therefore, we identified a set of chemokines and chemokine receptors that are expressed during skin regeneration. Further, we provided a network of existing drugs targeting these chemokines and chemokine receptors that can be repurposed for enhancing skin regeneration in chronic wounds and skin diseases. This review underscores the pivotal role of chemokine ligand-receptors axes in complex wounds and skin diseases and highlights the preclinical and clinical breakthroughs targeting these networks for skin regeneration.

Keywords: Chemokines; Chemokine Receptors; Complex Wounds; Skin Diseases; Drug-Gene Interaction; Drug Repurposing

Introduction

Chemokines are a group of short positively charged chemotactic cytokines that regulate cell-cell communication. They are classified into four sub-families according to the positioning and number of the conserved cysteine residues- C, CC, CXC and CX3C. The C-family chemokines have only two cysteine residues instead of four, CC chemokines have two juxtaposed cysteine residues near the N-terminus, the CXC chemokines have a variable amino acid separating the two N-terminal cysteines and the CX3C chemokines have three amino acids between the cysteines [1,2]. They bind to the N-terminus of G-protein coupled receptors which are hepta-helical transmembrane receptors that mediate their signaling via heterotrimeric G-proteins [3]. Chemokines/chemokine receptors show a promiscuous binding pattern, i.e., some chemokine receptors bind to multiple chemokines (ligands) while some chemokines bind to more than one receptor [3]. Functionally, chemokines can be either homeostatic, which is constitutively expressed or inflammatory, which is expressed during an inflammatory response [4].

Chemokines regulate inflammatory and reparative events during cutaneous wound healing [5]. The skin is known to express many chemokines including the CC and CXC chemokines [6]. Temporal expression patterns of chemokines during the sequential stages of normal wound healing control the processes of leukocyte trafficking, angiogenesis and epithelialization. However, the balance between basal and inflammatory chemokines gets severely disrupted in pathological conditions such as diabetes or

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ischemia, resulting in prolonged non-healing chronic wounds e.g., venous ulcers, pressure ulcers or Diabetic Foot Ulcers (DFUs) [7,8]. Current therapeutic strategies including stem cell transplantation therapy often do not accelerate wound closure or promote scarless healing due to the reduced efficacy of the transplanted cells in the harsh injury microenvironment [9]. Since chemokines play a pivotal role in regulating the process of wound healing, understanding the mechanisms of chemokine ligand-receptor interactions in normal and pathological skin conditions is crucial for the therapeutic targeting of chemokines and chemokine receptors. This review focuses on the expression pattern of chemokines and chemokine receptors in different stages of wound healing. Further, it highlights the changes in chemokines ligand-receptor interactions in acute and chronic wounds and skin diseases. It also discusses the preclinical and clinical chemokine-targeted therapeutic strategies to accelerate wound closure.

Chemokine Ligand-Receptor Interactions During Wound Healing

Wound healing is a multistep process that involves various cell types and signaling molecules. The process of normal wound healing can be subdivided into four well-coordinated overlapping phases: hemostasis, inflammation, proliferation, and remodeling [10]. Chemokines are secreted by the wound resident T-cells to regulate all the phases of wound healing but are most predominant during the inflammation and proliferation phases (Fig. 1).

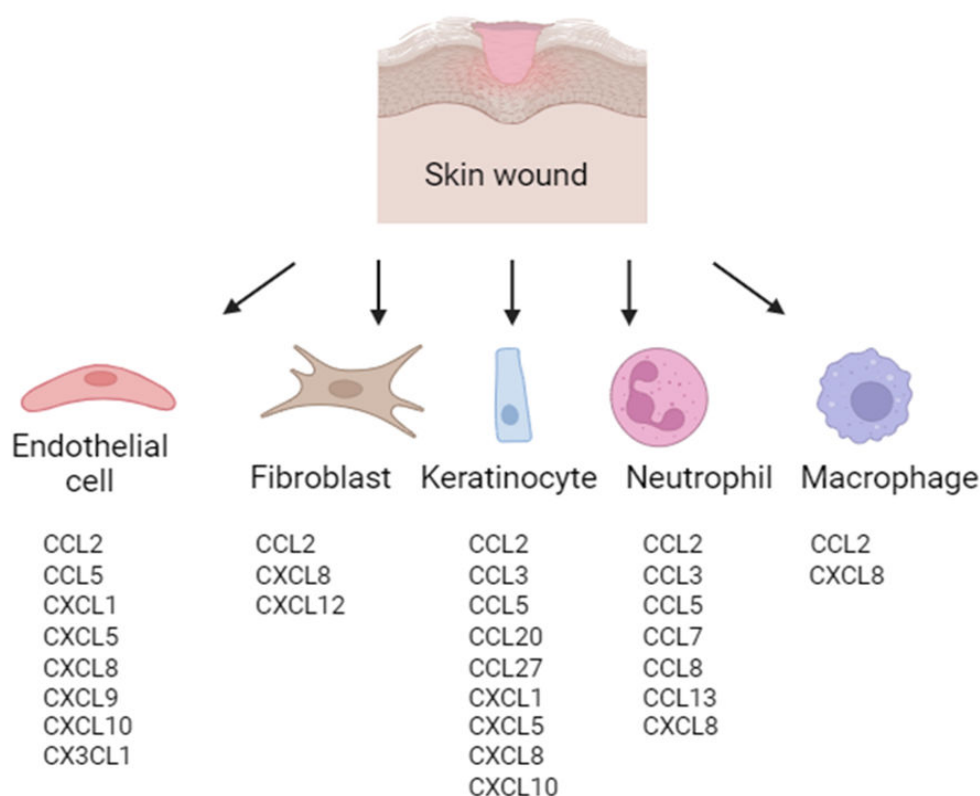


Figure 1: Chemokines are released by different types of skin cells. Skin is composed of different types of cells such as keratinocytes, fibroblasts, endothelial cells, and immune cells (neutrophils and macrophages). During the process of wound healing, these cells secrete CC and CXC chemokines and regulate the stages of wound healing via autocrine and/or paracrine regulation. Often these chemokines are dysregulated in the chronic non-healing wounds that cause prolonged inflammation, which in turn hinders the skin regeneration.

Hemostasis

Hemostasis is the first phase of wound healing that occurs immediately post-injury. During this stage, a variety of CC and CXC chemokines such as CCL2, CCL3, CCL5, CXCL1, CXCL4, CXCL5, CXCL7 and CXCL8, are released due to the degranulation of platelet α -granules [11]. The coagulation cascade gets activated resulting in fibrin clot formation to prevent blood loss from the injury site.

CXCL4 (Platelet factor 4, PF4), the predominant chemokine at this stage, was initially described as angiostatic. It also regulates several other biological processes like coagulation, neutrophil adhesion to endothelium and inhibition of hematopoiesis and megakaryopoiesis [12]. The binding of CXCL4 to CXCR3-B (a variant of CXCR3) upregulates the apoptosis of human microvascular endothelial cells, which demonstrates the angiostatic effect by activating the p38 MAPK pathway [13]. Platelet degranulation also activates mast cells, macrophages, keratinocytes, and fibroblasts at the wound site which in turn produce the proinflammatory chemokines CXCL8 (interleukin 8, IL8) and CCL2 (monocyte chemoattractant protein-1, MCP-1) [14]. These chemokines promote the directional migration of inflammatory and endothelial cells toward the injury site to start the next stage of wound healing.

Inflammation

During this stage, an influx of inflammatory cells such as macrophages, monocytes and neutrophils cleanses the wound debris and infection [15]. The first wave of inflammation is characterized by the release of chemokines CXCL8, CXCL1 and CXCL2 by the wound resident platelet α -granules. The chemokine receptor CXCR2 is expressed by neutrophils which are recruited in response to its cognate ligand CXCL8, which is a potent proinflammatory chemokine. The neutrophils that are recruited at the wound site secrete CXCL8 along with the CC chemokines CCL2, CCL3, CCL5, CCL7, CCL8 and CCL13 which further recruit neutrophils and monocytes via paracrine signaling. CXCL8 also activates the receptors CXCR1 and CXCR2 in the microvascular endothelial cells that stimulate vascular permeability [16]. The wound resident keratinocytes and endothelial cells also secrete the chemokines CXCL1, CXCL5 and CXCL8 which bind to the receptor CXCR2 and ease further neutrophil recruitment [17]. The platelets at the wound site release the growth factors TGF- β 1 and PDGFs that activate the Mesenchymal Stem Cells (MSCs), neutrophils and macrophages. During normal wound healing, the level of neutrophils markedly reduces post-day 1 - 3 of wounding [18]. At this stage, macrophages become the inflammatory cells at the wound site. As the process of wound healing progresses, the macrophages switch from the M1 phenotype, which is pro-inflammatory, to the M2 phenotype which is pro-repair. This phenotype switch promotes the reduction of inflammation and the release of cytokines and growth factors like VEGF, bFGF, TNF- α and IFN- γ that stimulate angiogenesis and start the proliferation phase [19].

Proliferation

Proliferation begins on day 3 - 10 post-wounding and is characterized by enhanced collagen deposition due to an increased number of fibroblasts contributing to a temporary Extracellular Matrix (ECM) generation and an increased number of endothelial cells and keratinocytes promoting neovascularization and re-epithelialization, respectively [20]. The chemokine CCL2 (MCP-1) increases the expression of TGF- β , TIMP-1 and MMP-1, in fibroblasts and induces collagen deposition [11]. CXCL12 enhances bone marrow-derived stem cell recruitment at the wound site. The activation of the CXCL12-CXCR4 axis also promotes the mobilization and homing of endothelial progenitor cells [21]. Further, during this stage, CXCL11 is also crucial for regulating dermal-epidermal interactions [22]. Neovascularization is governed by the proangiogenic chemokines CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, CXCL7 and CXCL8, which bind to and activate their cognate receptors CXCR2 and CXCR1 on the endothelial cells [23]. The chemokines CXCL11 and CXCL10, secreted by basal keratinocytes, promote re-epithelialization via their cognate receptor CXCR3, expressed by keratinocytes, thereby regulating in an autocrine fashion [24]. Additionally, the chemokine CCL27 secreted by keratinocytes promotes the migration of keratinocyte stem cells toward the wound area through its receptor CCR10, helping the re-epithelialization process [25].

Remodeling

Remodeling is the longest and the last phase which persists for a few months following wound healing [26]. ECM turnover during wound maturation and remodeling is accompanied by a reduction in cellularity, reorganization, crosslinking of disorganized collagen fibers and neo-vasculature regression. Fibroblasts and myofibroblasts release metalloproteinases that digest nascent matrix and promote matrix maturation in addition to producing mature connective tissue [27]. CCL2 stimulates the expression of TIMP-1 and MMP-1 in fibroblasts, thus regulating matrix synthesis and remodeling. The CXC chemokines CXCL11, CXCL10 and CXCL9 facilitate the processes of dermis and epidermis maturation and regression of neo-vasculature [26,27].

Chemokines in Complex Acute and Non-Healing Chronic Wounds

Chronic wounds are non-healing wounds that show impairment in the normal wound healing progression and occur either due to a metabolic disorder like diabetes or advanced age [28]. These wounds are often characterized by a prolonged inflammatory stage, increased levels of Reactive Oxygen Species (ROS), proteases and senescent cells, persistent infection, and dysfunctional endogenous stem cell populations. Complex acute wounds such as severe burn wounds are also characterized by increased levels of pro-inflammatory chemokines leading to a prolonged non-healing state.

Diabetic Wounds

Diabetes Mellitus (DM) is a rapidly increasing health concern that affects millions of patients worldwide. Prolonged hyperglycemia and associated complications predispose patients to DFUs. Approximately 30% of diabetic patients develop DFUs in their lifetime [29]. The existing treatment protocols often fail resulting in lower-limb amputations, which is a key factor in diabetic patient morbidity and mortality [29].

Preclinically, the use of transgenic mice db/db serves as a standard model of type 2 diabetes (DM). This mouse has mutations in the leptin receptor long isoform encoding gene, resulting in a lack of hypothalamic leptin signaling. This leads to persistent hyperphagia, obesity and high insulin levels [30]. Sustained expression of the chemokines CXCL2 and CCL2 was observed in db/db transgenic mice which resulted in an increased number of neutrophils and macrophages in late-stage wounds [31]. Further, db/db mice also express low levels of CXCL12, which facilitates angiogenesis and granulation tissue formation in normal wounds [32].

A study by Bekeschus, et al., compared wound exudates from diabetic patients and large acute wounds. A significant reduction in the concentration of CXCL10, CXCL11 and CCL5 and increased CXCL8 were observed in the wound exudates of diabetic patients as compared to the acute wounds [33]. Reduction in the levels of CXCL10 and CXCL11, which are expressed by basal keratinocytes, indicate impaired proliferation and remodeling stages of wound healing [34]. The upregulation of CXCL8 leads to a sustained inflammatory response in diabetic wounds due to the increased chemotaxis of neutrophils [33].

Advanced Age-Related Wounds

With increasing age, normal skin functions such as thermoregulation, protection against microorganisms, physical and chemical insults, regulation of water loss and sensory functions deteriorate [35]. The age-related morphological and structural changes include reduced keratinocyte proliferation and vascularity, decreased melanocytes, Langerhans cells, fibroblasts, macrophages and flattened dermal-epidermal junctions [35]. These alterations make the skin more susceptible to wounds and affect the normal wound-healing process. Patients suffering from advanced chronic diseases develop non-healing wounds like pressure ulcers, venous leg ulcers and chronic limb ischemia-related lower extremity wounds [35]. There is a marked reduction in the inflammatory response post-initial wounding in aged wounds. Preclinical studies with aged mouse wound models have reported a marked reduction in neutrophil and macrophage infiltration despite the elevated levels of CXCL1, CXCL2 and CCL2 [36]. Furthermore, aged mice wounds also demonstrated reduced CXCL12 levels as compared to young mice wounds which correlated with a reduction in angiogenesis and reduced granulation tissue formation [37].

Burn Wounds

Burn wounds are characterized by increased inflammation, persistent vasodilation, edema, and capillary permeability. The levels of CCL2, CCL3, CCL11 and CXCL1 were significantly higher in mice at post-burn injury day 1 as compared with unwounded controls. This results in a marked increase in acute macrophage inflammatory response at post-burn injury day 3. Further, elevated CXCL1 levels result in neutrophil recruitment at the burn wounds on day 7 [38]. Burn wound patients showed elevated levels of inflammatory mediators such as interleukin (IL)-6, CXCL8, CCL2, CCL4 and CCL20 which resulted in reduced keratinocyte proliferation and delayed re-epithelialization [39]. Interestingly, the levels of CCL20 decreased post-burn injury day 4 and CCL27 decreased post-burn injury days 1-4 [40]. Additionally, increased concentrations of CCL2, CCL3 and CCL7 in burn wounds have also been shown to promote macrophage immune response [41].

Chemokines in Skin Diseases

Chemokines regulate the recruitment and activation of immune cells like macrophages, T lymphocytes and neutrophils towards

the site of inflammation. Thus, chemokines play a crucial role in the pathogenesis of skin disorders like psoriasis, atopic dermatitis and epidermolysis bullosa. They serve as important biomarkers for disease severity and have also been identified as potential therapeutic targets for the treatment of inflammatory skin diseases.

Psoriasis

Psoriasis is a chronic inflammatory skin disorder characterized by scaly erythematous skin lesions. Scaly plaques are developed due to the hyperproliferation and impaired maturation of keratinocytes which is caused by Th1 and Th17 lymphocytes and the release of IL-12, IL-17, IL-23 and TNF- α . The skin of psoriatic patients is infiltrated by various immune cells such as neutrophils, macrophages, masT-cells, CD4+ and CD8+ T lymphocytes and dendritic cells. The peripheral blood levels of the chemokines CCL2, CCL3 and CCL4 are higher in psoriasis patients which correlates with disease severity [42]. Additionally, CCL20, CXCL8, CXCL2 and its receptor CXCR2 are also highly expressed in psoriatic skin lesions. The chemokine CX3CL1 and its receptor CX3CR1, which regulate leucocyte extravasation, are known as “psoriasis susceptibility genes” due to their high expression in psoriatic plaques and location in the genomic regions linked to psoriasis [43]. A significantly higher expression of CXCL12/SDF-1 has been observed in the psoriatic lesions, predominantly in the dermal cells and dermal-epidermal junction as compared with the skin of healthy volunteers⁴⁴. Mechanistically, SDF-1 binds to its receptor CXCR4 which leads to increased proliferation of keratinocytes via the activation of the ERK signaling [44].

Atopic Dermatitis

Atopic Dermatitis (AD) is another chronic inflammatory skin condition characterized by enhanced inflammatory cell infiltration and thickening of the epidermis. Keratinocytes of AD patients secrete inflammatory cytokines such as IL-1 β , IL-6, IL-8, IL-18, IL-13, IL-17A, IL-18 and IL-25 and chemokines such as CCL22, CCL20, CXCL9, CXCL10, CXCL11 [45,46]. A high serum concentration of CCL17 and CCL27 has been reported in pediatric AD patients [47]. During the acute phase of AD, there is an increase in the number of TNF- α producing Langerhans cells and an influx of Th-2 lymphocytes that secrete IL-4, IL-5 and IL-13. In contrast, the chronic phase of AD involves the activation of Th-1 lymphocytes which produce IFN- γ , TNF- α , IL-8 and IL-12. IL-1 and TNF- α induce the keratinocytes to produce CCL27, a skin-specific chemokine that enhances CLA+ (cutaneous lymphocyte-associated antigen), CCR10+ and CCR4+ lymphocyte recruitment to the skin [48]. CCL17-CCR4 signaling activation also increases the migration of CLA+ T-cells [47]. These lymphocytes secrete the cytokines IL-4, IL-13 and IFN- γ , which in turn induce the production of chemokines CCL11 and CCL26 by the keratinocytes, endothelial cells, and T-cells. Additionally, enhanced levels of CCL2, CCL3, CCL4, RANTES and eotaxin have been observed during AD pathogenesis [49].

Epidermolysis Bullosa

Epidermolysis Bullosa (EB) includes a group of rare heterogeneous inherited skin fragility disorders that are characterized by mechanical stimulation-induced skin blisters that can lead to skin and mucous membrane ulcers. It is classified into four subtypes- junctional epidermolysis bullosa, epidermolysis bullosa simplex, Kindler syndrome and dystrophic epidermolysis bullosa. Ujiie et al reported a significant increase in the levels of CXCL12 and HMGB1 in the sera of EB patients with a concomitant increase in the affected body surface area. Further, the serum level of CCL21 was significantly lower in EB patients as compared with the control samples. In contrast, the tissue samples from EB patients showed higher expression of CCL21 suggesting the presence of a concentration gradient between the skin tissue and blood vessels of EB patients [50]. Additionally, elevated levels of CCL2, CCL4, CCL5, CCL15, CCL24 and CCL27 and CXCL1, CXCL2, CXCL3, CXCL7, CXCL8 and CXCL10 were detected in the blister fluid from EB patients. The presence of these chemokines helps the recruitment of inflammatory cells which express their cognate receptors, contributing to EB pathology [51].

Modulation of Chemokines to Potentiate Skin Regeneration: Preclinical to Clinical Developments

Chemokines play a crucial role in regulating the normal process of wound healing as well as in the pathogenesis of skin diseases and chronic wounds. Targeting chemokines therapeutically to modulate the chemokine ligand-receptor axis signaling can improve wound healing outcomes in complex skin wounds. Chemokine ligands and receptors have been therapeutically targeted for the development of agonists, antagonists, or neutralizing antibodies to manipulate the chemokine ligand/chemokine receptor signaling. Additionally, the chemokine ligand/receptor-based gene therapy approach has also been used to accelerate wound tissue regeneration and promote scarless healing.

Several chemokines such as CCL2, CXCL12, CXCL16 and their receptors have been targeted to accelerate wound healing in preclinical models. Diabetic wounds show reduced expression of the chemokine CCL2 during early stages of wound healing which results in delayed macrophage response. CCL2 administration in murine diabetic wounds accelerated macrophage infiltration and enhanced wound healing [52]. Administration of CXCL12 entrapped hydrogels activated the CXCL12-CXCR4 axis, which is known to promote neo-vascularization and re-epithelialization has been efficiently utilized for the trafficking of bone marrow-derived stem cells at the wound sites [53]. Similarly, transplantation of MSC overexpressing CXCL12 [54] accelerated cutaneous wound healing. Topical administration of genetically modified *Lactobacilli* with a plasmid encoding CXCL12, enhanced wound closure in mice by sustained production of CXCL12 [55]. Interestingly, enhanced wound healing in diabetic mice was also achieved by topical administration of CXCR4 antagonist AMD3100 [56]. AMD3100 treatment enhanced the expression of PDGF-BB at the wound site which in turn stimulated the recruitment of macrophages and fibroblasts. Chemokine ligand/receptor axes have also been modulated to enhance the migratory potential of transplanted MSCs toward the wound area. Intravenous injection of CCR2 overexpressed MSCs accelerated wound healing in db/db mice due to targeted migration in response to increased level of CCL2 in diabetic wounds [57]. A high expression of the chemokine CXCL16 in the mice wound bed post-surgery days 0 through 10 led to bioengineering of MSC with overexpression of its cognate receptor CXCR6. This bioengineered MSC overexpressing CXCR6 when therapeutically transplanted intravenously led to enhanced migration and engraftment at the wound site which accelerated skin regeneration. Transplantation of CXCR6-bioengineered MSCs also accelerated wound closure in chronic non-healing diabetic wounds via enhanced neo-angiogenesis and re-epithelialization at wound site [58].

Although chemokine ligand-receptor interactions have been extensively studied pre-clinically, therapeutic targeting of chemokines and their receptors in clinical settings has not yet been explored for skin regeneration in chronic diabetic and burn wounds. Chemokine receptor inhibitors and neutralizing antibodies against chemokine ligands such as T487 (small molecule inhibitor of CXCR3), SCH51125 (CCR5 inhibitor) and ABX-IL8 (monoclonal CXCL8 neutralizing antibody) have been used in clinical trials for psoriasis [59-61]. However, these trials were discontinued as they failed to yield significant patient benefits. RPT193, a small molecule inhibitor of CCR4 that blocks the recruitment of Th2 cells, has shown promising results in a randomized placebo-controlled phase I clinical trial with AD patients and is currently being explored for the safety and efficacy of a single dose in AD and asthma patients under phase II trial [NCT05399368, ClinicalTrials.gov].

Predicted Drug-Gene Interactions of Chemokines and Chemokine Receptors

Chemokines and their receptors have been used as therapeutic targets for several diseases like multiple sclerosis, rheumatoid arthritis, and asthma [62]. Most of the research has focused on developing small-molecule inhibitors against chemokine receptors. However, only a few of these drugs such as Maraviroc (CCR5 inhibitor) and Plerixafor (CXCR4 inhibitor) have been successful through the clinical trials for HIV and hematopoietic stem cell mobilization, respectively have reached the market [62]. The failures in the clinical trials have been attributed to incorrect target selection, insufficient dosing, small molecule toxicity or poor trial design. Our review of the literature identified 14 chemokines and 12 chemokine receptors that are involved in skin regeneration. Furthermore, the drug-gene interaction database (DGIdb) analysis revealed potential drugs that can target these chemokine ligand-receptor genes [63]. The database predicted 81 plausible drugs targeting six chemokines (Table 1) and 55 probable drugs targeting seven chemokine receptors (Table 2).

Chemokines	Drug	Interaction Type	Sources
CCL2	CARLUMAB	Inhibitor	ChEMBLInteractions/TTD
	RISPERIDONE	ND	PharmGKB
	BINDARIT	ND	TTD
CCL3	INFLIXIMAB	ND	NCI
	NAGRESTIPEN	ND	TTD

CCL20	GSK-3050002	ND	TTD
CXCL8	ABX-IL8	Inhibitor	ChemblInteractions/TTD
	HUMAX-IL8	Inhibitor	ChemblInteractions
	LEFLUNOMIDE	ND	NCI
	YANGONIN	ND	DTC
	E319	ND	DTC
	FOSCARNET	ND	NCI
	NAPROXEN	ND	NCI
	ALDRIN	ND	DTC
	COLCHICINE	ND	DTC
	MIDAZOLAM	ND	NCI
	FENTANYL	ND	NCI
	ACETAMINOPHEN	ND	NCI
	CORONOPILIN	ND	DTC
	DIPYRIDAMOLE	ND	NCI
	IBUPROFEN	ND	TTD
	IONOMYCIN	ND	NCI
	CHLORDANE DANAZOL	ND	DTC
	CHEMBL1902074	ND	NCI
	OMEPRazole	ND	DTC
	DINITRO CRESOL	ND	NCI
	QUESTIOMYCIN B	ND	DTC
	FENRETINIDE	ND	DTC
	HEPTACHLOR	ND	NCI
	PYROGALLOL	ND	DTC
	CANERTINIB	ND	DTC

	HYDROQUINONE	ND	NCI
	ENDOSULFAN	ND	DTC/NCI
	EMODIN	ND	DTC
	LANSOPRAZOLE	ND	DTC
	RETINAL	ND	NCI
	HARMINE HYDROCHLORIDE	ND	DTC
	PACLITAXEL	ND	DTC
	BEVACIZUMAB	ND	NCI
	PAMIDRONIC ACID	ND	PharmGKB
	TALC	ND	NCI
	TRETINOIN	ND	NCI
	SUNITINIB	ND	NCI
	CETUXIMAB	ND	PharmGKB
	CHEMBL1579130	ND	NCI
	ALPRAZOLAM	ND	DTC
	METHIMAZOLE	ND	NCI
	RETINOL	ND	DTC
	RIBAVIRIN	ND	DTC
	TERFENADINE	ND	NCI
	DICYCLOHEXYLCARBODIIMIDE	ND	DTC
	CEFTRIAZONE	ND	NCI
	ASPIRIN	ND	NCI
	CLARITHROMYCIN	ND	NCI
	DACARBAZINE	ND	DTC
	PENTOXIFYLLINE	ND	NCI
	CIDOFOVIR	ND	NCI
	BROXURIDINE	ND	DTC

	TROGLITAZONE	ND	NCI
	DICHLORVOS	ND	DTC
	VERAPAMIL	ND	NCI
CXCL10	NI-0801	Inhibitor	ChemblInteractions/TTD
	REGAMOSTIM	ND	NCI
	METHYLPREDNISOLONE	ND	NCI
	ANTIBIOTIC	ND	NCI
	RITONAVIR	ND	NCI
	STAVUDINE	ND	NCI
	ATORVASTATIN	ND	NCI
	ATROPINE	ND	NCI
	TESTOSTERONE	ND	NCI
	OXALIPLATIN	ND	NCI
	ELDELUMAB	ND	TdgClinicalTrial/TTD
	ZIDOVUDINE	ND	NCI
CXCL12	VINCRIStINE	ND	PharmGKB
	ALEMTUZUMAB	ND	PharmGKB
	CHLORAMBUCIL	ND	PharmGKB
	FLUDARABINE	ND	PharmGKB
	CYCLOPHOSPHAMIDE	ND	PharmGKB
	PREDNISONE	ND	PharmGKB
	RITUXIMAB	ND	PharmGKB

Table 1: List of drugs that can be potentially repurposed against chemokines. Candidate drugs identified from the DGIdb database that are presently used to treat various diseases but can target chemokines secreted during wound healing [63]. ND: Not Determined; TTD: Therapeutic Target Database; NCI: NCI (National Cancer Institute) Cancer Gene Index; DTC: Drug Target Commons.

Chemokine Receptor	Drug	Interaction Type	Sources
CCR1	AZD4818	Antagonist	ChemblInteractions
	BMS-817399	Antagonist	TTD
	CCX354	Antagonist	TdgClinicalTrial/ ChemblInteractions/ TTD
	TERPYRIDINE	ND	DTC
	CHEMBL2205805	ND	DTC
CCR2	AZD2423	Antagonist/allosteric modulator	ChemblInteractions/ TTD
	PF-04634817	Antagonist	ChemblInteractions
	CCX140	Antagonist	TdgClinicalTrial/ ChemblInteractions/ TTD
	PLOZALIZUMAB	Antibody/antagonist	TdgClinicalTrial/ ChemblInteractions
	CHEMBL41275	Antagonist	DTC
	CENICRIVIROC	Antagonist	ChemblInteractions/ TTD
	MK-0812	ND	TTD
	PLERIXAFOR	ND	DTC
	SIMVASTATIN	ND	NCI
	MORPHINE	ND	NCI
	PIMAGEDINE	ND	TTD
CCR5	MARAVIROC	Antagonist	DTC/TdgClinicalTrial/ChemblInteractions/ TEND/PharmGKB/ TTD
	LERONLIMAB	Antagonist/antibody	ChemblInteractions/ TTD
	INCB-9471	Antagonist	ChemblInteractions/ TTD
	CENICRIVIROC	Antagonist	TdgClinicalTrial/ ChemblInteractions/ TTD
	APLAVIROC HYDROCHLORIDE	Antagonist	ChemblInteractions
	VICRIVIROC MALEATE	Antagonist	ChemblInteractions

	PF-04634817	Antagonist	ChemblInteractions
	VICRIVIROC	Antagonist	TdgClinicalTrial/TTD
	AZD5672	Antagonist	ChemblInteractions
	CHEMBL207004	Antagonist	DTC/TTD
	PF-232798	ND	TTD
CCR6	CHEMBL592124	ND	DTC
	CHEMBL114544	ND	DTC
CXCR1	LADARIXIN	Modulator	ChemblInteractions
	REPARIXIN	Allosteric modulator/ modulator	ChemblInteractions/ TTD
	NAVARIXIN	Antagonist	TdgClinicalTrial/TTD/ ChemblInteractions
	IBUPROFEN	ND	TTD
CXCR2	REPARIXIN	Allosteric modulator/modulator	ChemblInteractions/ TTD
	NAVARIXIN	Antagonist	ChemblInteractions/ DTC/TdgClinicalTrial/ChemblInteractions/ TTD
	DANIRIXIN	Antagonist	ChemblInteractions/ TTD
	LADARIXIN	Modulator	ChemblInteractions
	ELUBRIXIN	Antagonist	ChemblInteractions/ TTD
	ACETYLCYSTEINE	ND	NCI
	GENISTEIN	ND	NCI
	IBUPROFEN	ND	TTD
	VITAMIN E	ND	NCI
	CLOTRIMAZOLE	ND	TTD
	BKT140	Antagonist	TdgClinicalTrial/ ChemblInteractions/ TTD
	PLERIXAFOR	Antagonist/partial agonist	DTC/TdgClinicalTrial/ ChemblInteractions/ NCI/TEND/TTD

CXCR4	MSX-122	Antagonist	TdgClinicalTrial/ ChEMBLInteractions/ TTD
	POL6326	Antagonist	ChEMBLInteractions/ TTD
	ULOCUPLUMAB	Antibody	TTD
	MAVORIXAFOR	Antagonist	DTC/TdgClinicalTrial/ TTD
	CTCE-9908	Antagonist	ChEMBLInteractions/ TTD
	BURIXAFOR	Antagonist	TdgClinicalTrial/ ChEMBLInteractions/ TTD
	USL-311	ND	TTD
	BALIXAFORTIDE	ND	TTD
	PF-06747143	ND	TTD
	CHEMBL1221944	ND	DTC
	CHEMBL2062277	ND	DTC
	BEVACIZUMAB	ND	PharmGKB
	CHEMBL1242210	ND	DTC
	CHEMBL2347632	ND	DTC
	CISPLATIN	ND	CIViC
	CHEMBL2347631	ND	DTC
	CHEMBL2347633	ND	DTC
	CHEMBL2347630	ND	DTC

Table 2: List of drugs that can be potentially repurposed against chemokine receptors. Candidate drugs identified from DGIdb database that are presently used to treat various diseases but can target chemokines secreted during wound healing. ND: Not Determined; TTD: Therapeutic Target Database; NCI: NCI (National Cancer Institute) Cancer Gene Index; DTC: Drug Target Commons; TEND: Trends in the exploitation of Novel Drug targets; CIViC: Clinical Interpretations of Variants in Cancer.

By using the STITCH plugin of Cytoscape (version 3.10.0), we constructed networks of the candidate drugs that showed direct association with the chemokines (Fig. 2) and chemokine receptors (Fig. 3) [64]. Although there are existing clinical trials based on these drugs, very few of them have been explored for skin disorders and chronic wounds. Drug repurposing strategy, which identifies novel therapeutic applications of the existing approved drugs, can be a promising tool to identify candidate drugs targeting chemokine-chemokine receptor axes for treating chronic wounds and skin diseases. This approach is faster than the traditional drug discovery process and overcomes limitations such as high cost and risk of failure [65].

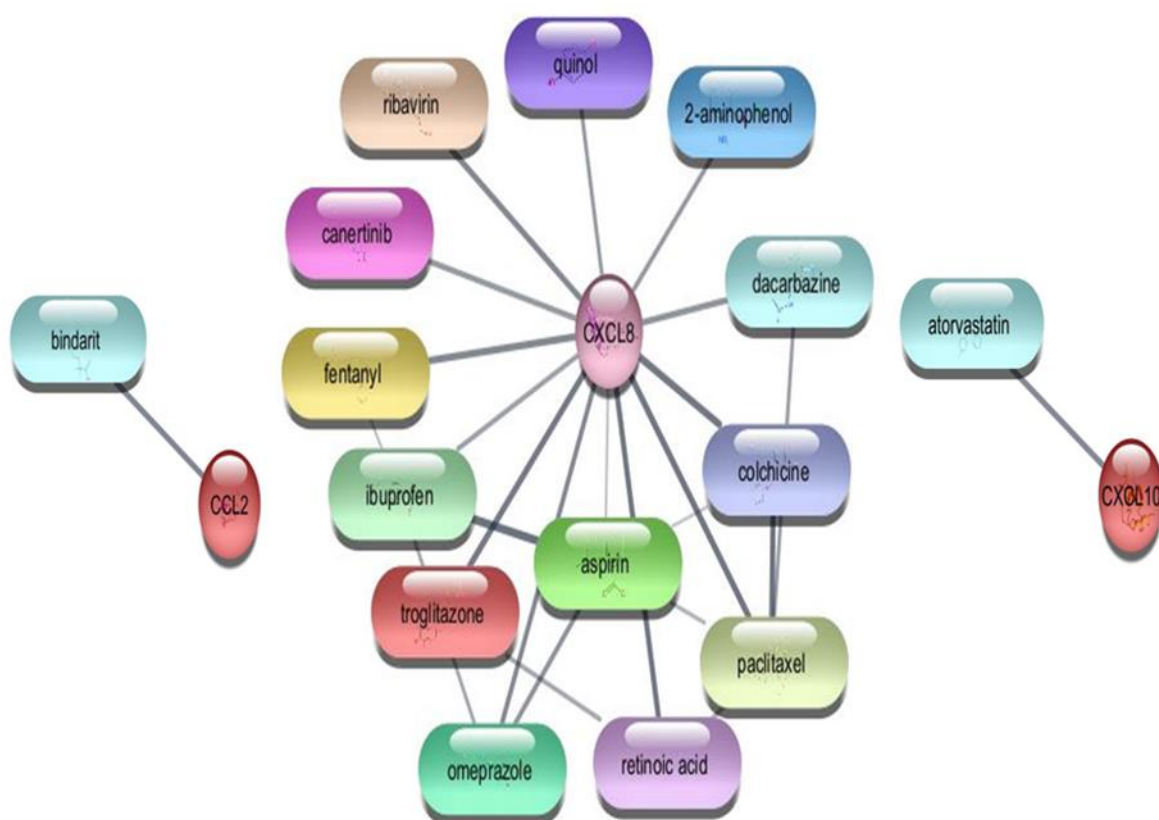


Figure 2: Network of candidate drugs targeting chemokines. Predicted drug-gene interaction network of the identified drugs from DGIdb database that have direct association with the chemokines, CCL2, CXCL8 and CXCL10 which are secreted at the wound microenvironment during skin regeneration. The interaction network was generated using Cytoscape v3.10.0: STITCH plugin.

In the present study, drug-gene interaction analysis revealed three chemokines and six chemokine receptors showing direct interaction with one or more drugs. The chemokine receptor CCR1 showed a direct association with the drug AZD4818 (identified as L-685,818 in STITCH) which is an antagonist and has been used for the treatment of COPD [66]. CCR2 showed a direct association with five drugs, MK-0812, Pimagedine (identified as Aminoguanidine in STITCH), Ceniviroc, CHEMBL41275 (identified as TAK-779 in STITCH) and Plerixafor. Ceniviroc and CHEMBL41275 were identified as antagonists of CCR2 and used in clinical trials for HIV infection and non-alcoholic steatohepatitis (NASH) [67,68]. CCR5 showed a direct association with five antagonists, Maraviroc, Vicriviroc, Aplaviroc, CHEMBL207004 (identified as TAK-220 in STITCH) and Ceniviroc, which are primarily used for HIV-1 infection [67,69-72]. The CXC chemokine receptor CXCR1 showed direct interaction with the drug Navarixin, which is an antagonist used for the treatment of COPD (NCT01006616) and prostate, lung and colorectal cancer (NCT03473925). Similarly, CXCR2 showed direct interaction with the antagonist Elubrixin which is used for the treatment of cystic fibrosis, ulcerative and obstructive pulmonary disease, and colitis [73]. Additionally, both CXCR1 and CXCR2 showed a direct association with Reparixin and the interaction type was identified as allosteric modulation. Reparixin has been used for the treatment of COVID-19 pneumonia [NCT04878055], breast cancer [NCT02370238], primary myelofibrosis [NCT05835466] and preventing graft dysfunction in pancreatic islet transplantation [NCT01967888]. CXCR4 showed a direct association with the antagonists CTCE-9908 and MSX-122 which are anti-inflammatory and anti-metastatic [74,75]. These chemokine receptors bind to the pro-inflammatory chemokines such as CCL2, CCL3, CCL4, CCL5, CCL7, CXCL8 (IL8) and CXCL12 that are secreted by the skin keratinocytes, fibroblasts and endothelial cells and immune cells such as neutrophils and

macrophages [2,5,6]. The levels of these chemokines increase during skin pathologies leading to a prolonged inflammatory phase. Thus, targeting these chemokine-receptor axes can provide an effective therapeutic strategy for the treatment of cutaneous pathological conditions.

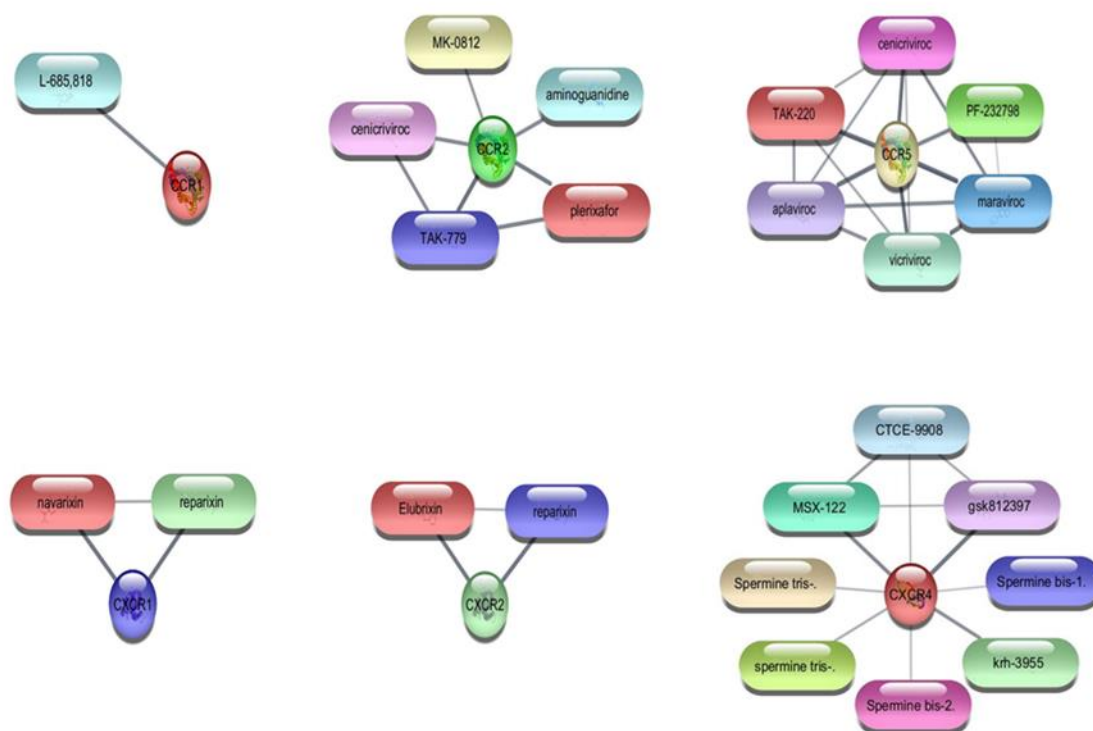


Figure 3: Chemokine receptor targeted by network of candidate drugs. The predicted drug-gene interaction network of the identified drugs from DGIdb database revealed the direct association of one or more drugs with chemokine receptors that are expressed during skin regeneration. (Generated using Cytoscape v3.10.0: STITCH plugin).

Conclusion and Future Perspectives

Skin wound healing is one of the most complex physiological processes involving the temporal and spatial synchronization of multiple chemokines, growth factors and cytokines. Chemokines are a group of chemotactic cytokines that regulate the cellular events in all the phases of skin wound healing, especially the inflammatory and proliferation phases. During the hemostasis phase, platelet degranulation results in the release of various CXC and CC chemokines which help the process of fibrin clot formation and migration of inflammatory and endothelial cells, leading to the inflammatory phase of wound healing characterized by the release of neutrophil and monocyte-attracting chemokines. Next, chemokines regulate neovascularization, collagen deposition and re-epithelialization during the later proliferation and remodeling phases. The normal process of wound healing gets severely disrupted in complex and chronic non-healing wounds such as DFUs, age-related wounds and critical burn wounds. These wounds are characterized by a sustained inflammatory response due to a marked increase in the pro-inflammatory chemokines. Dysregulated chemokine ligand-receptor interactions also contribute to the pathogenesis of various skin diseases like atopic dermatitis, psoriasis and epidermolysis bullosa. Preclinical investigations targeting chemokines and chemokine receptors for accelerated skin regeneration have shown promising results. However, the successful transition from preclinical studies to clinical applications requires a deeper understanding of the chemokine network in different patient populations such as individuals with chronic diseases like diabetes, inflammatory skin diseases like psoriasis and atopic dermatitis or elderly individuals. In the present study, we have provided a list of drugs targeting chemokines and chemokine receptors that are involved in skin regeneration. Some of these drugs have already been explored for other diseases. Since multiple chemokine-chemokine receptor pathways are involved in skin pathologies, targeting these drugs can be a potential

therapeutic strategy to accelerate skin tissue regeneration. Future clinical trials should also focus on confirming the safety and efficacy of chemokine-based therapies. A combinatorial approach that can integrate chemokine-based therapies with tissue engineering and gene therapy approaches can significantly enhance skin regeneration and improve clinical outcomes.

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Conflict of Interest

The authors have no conflict of interest to declare.

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