A Review of CXCL1 in Cardiac Fibrosis

Cheng-Long Wu, Ran Yin, Su-Nan Wang and Ru Ying*

Department of Cardiology, The First Affiliated Hospital of Nanchang University, Nanchang, China

Chemokine C-X-C motif ligand-1 (CXCL1), principally expressed in neutrophils, macrophages and epithelial cells, is a valid pro-inflammatory factor which performs an important role in mediating the infiltration of neutrophils and monocytes/macrophages. Elevated serum level of CXCL1 is considered a pro-inflammatory reaction by the organism. CXCL1 is also related to diverse organs fibrosis according to relevant studies. A growing body of evidence suggests that CXCL1 promotes the process of cardiac remodeling and fibrosis. Here, we review structure and physiological functions of CXCL1 and recent progress on the effects and mechanisms of CXCL1 in cardiac fibrosis. In addition, we explore the role of CXCL1 in the fibrosis of other organs. Besides, we probe the possibility that CXCL1 can be a therapeutic target for the treatment of cardiac fibrosis in cardiovascular diseases.

Keywords: chemokine C-X-C motif ligand-1, cardiac remodeling, cardiac fibrosis, inflammation, atrial fibrillation

HIGHLIGHTS
- In this review, we have retrospectively analyzed the role of CXCL1 in the pathological process of cardiac fibrosis.
- CXCL1 may be a potential target for the treatment of cardiac fibrosis.

INTRODUCTION

The morbidity of heart failure (HF) is at a high level. Cardiac remodeling is a clinical process of HF, and could finally evolve into cardiac fibrosis. Cardiac fibrosis usually appears when myocardium is constantly at the stage of ischemia and hypoxia (1). It is proposed that chemokine C-X-C motif ligand-1 (CXCL1) presents significant effect during HF and ischemic cardiomyopathy (2). CXCL1 is a member of chemokines family which mediates the directional immigration of inflammatory cells, and is critical in recruiting neutrophils and monocytes/macrophages into the target position such as injured myocardium and arterial wall in CVD (2). Previous studies show that the inhibition of CXCL1 improves adverse cardiac remodeling and myocardial fibrosis thereby protects cardiac function (2, 3). Therefore, novel therapeutic method could be applied based on interference of CXCL1 to improve cardiac fibrosis. CXCL1 is also active in inflammation in other organs as a major neutrophil chemoattractant to mediate tissue injury (4, 5). However, the regulation and the mechanism of CXCL1 remain complex and obscure. More research is demanded to clarify CXCL1 and its function in CVD.
Structure and Physiological Functions of CXCL1

CXCL1 is widely known as a strong neutrophil chemotactant which participates in inflammation of multiple tissues (2, 6–8). It is a member of CXC superfamily which is one category of chemokines (2, 9). Chemokines are small chemotactant molecules which recruit and activate leukocytes via specific seven-transmembrane receptors (7). They are classified into four categories according to the sequence of aminoacids related to the first 2 cysteine residues, namely CC, CXC, C, and CX3C families (7, 9, 10). The CXC family is further divided based on presence or absence of Glu-Leu-Arg sequence (ELR motif) adjacent to CXC motif (9, 11). CXCL1 is about 8 kDa (12, 13), also called growth-regulated oncogene-α (GRO-α) and keratinocyte-derived chemokine (KC) (Figure 1) (7, 11), and usually expressed in neutrophils, macrophages, and epithelial cells. CXCL1 produces its effect via its receptor CXCR2 which is mainly expressed on neutrophils and other types of cells (2).

CXCL1 exists in various tissues and produces multiple effects. As a pro-inflammatory chemokine, CXCL1 mediates acute and chronic inflammation in diverse organs thereby promotes the progress of fibrosis. The major physiology function of CXCL1 is mediating leukocyte recruitment and activation to promote inflammation and aggravate tissue injury. ELR-chemokines are valid neutrophil chemoattractants acting on G protein-coupled receptors (11). CXCL1 processes the Glu-Leu-Arg sequence and attracts neutrophils when inflammation occurs (14). Excluding inflammation, CXCL1 is also active in angiogenesis, wound healing as well as tumorigenesis depending on interaction with leukocytes, endothelial cells, and fibroblasts (7, 15). CXCL1 is related to angiogenesis during tissue remodeling (9, 16, 17). Interestingly, ELR-chemokines such as CXCL1 and CXCL2 promote vascular remodeling, whereas non-ELR CXC ligand such as CXCL4 and CXCL9 serve opposite effect (9). Besides, numerous studies indicate CXCL1 is important in tumorigenesis and progress of tumor, and CXCL1 is a promoter in evolvement of some kinds of tumor. In addition, CXCL1 widely participates in wound healing, mitosis and ischemia-reperfusion injury (18, 19).

The Role of CXCL1 in the Development of Cardiac Fibrosis

It is believed that the main pathological characteristics of CVD are cardiac inflammation and fibrosis (20). The pathological characteristics of cardiac fibrosis could be concluded as increased interstitial fibrosis, myocyte death, and cardiac contractile dysfunction (21). Current study indicates that HF could be improved with the depression of cardiac inflammation tends to be closely relevant to the dysfunction of heart. As previously described, CXCL1 is active in mediating the infiltration of neutrophils and monocytes/macrophages into the impaired tissues including injured myocardium and arteries. It is indicated that CXCL1 may aggravate cardiac fibrosis via pro-inflammatory effect (22). It is found that CXCL1 inhibition protects heart from Ang II-induced inflammation, hypertrophy and fibrosis (2). Mice treated with CXCL1 neutralizing antibody tend to have better cardiac function, lower level of brain natriuretic peptide and less degree of hypertrophy compared with control group. Similarly, cardiac remodeling and fibrosis are apparently alleviated through application of CXCR2 specific inhibitor. In HF patients with hypertension, the serum level of CXCL1 is obviously increased in patient with cardiac remodeling and fibrosis (2, 23). It could be concluded that CXCL1 promotes the inflammation in heart thereby accelerates the process of cardiac remodeling and myocardial fibrosis. Atrial fibrosis is the basis of atrial fibrillation (AF). Current study indicates CXCR-2 knockout mice had significantly attenuated atrial fibrillation inducibility, atrial diameter, fibrosis, and infiltration of macrophages compared with saline-treated wild-type mice (24). Moreover, circulating blood CXCL-1 levels were higher and associated with AF in human patients compared with sinus rhythm controls (24). Besides, CXCL1 is also considered to mediate the irradiated rat cardiac fibrosis by miR-21 (25).

In sum, CXCL1 may aggravate cardiac fibrosis induced by hypertension, atrial fibrillation, post-ischemia/reperfusion and so on.

Mechanisms of CXCL1 in Cardiac Fibrosis

CXCL1 Mediates Leukocyte Recruitment

There is growing evidence to support an important role of inflammatory cells especially monocytes/macrophages in the pathophysiology of HF (26). CXCL1 has been reported to exert a critical role in HF by regulating the recruitment of neutrophils, T lymphocytes and monocytes, especially regulating CXCR2+ monocytes into the heart tissues leading to cardiac remodeling and initiating and developing AF (2, 24). CXCL1 produces its effect via its receptor CXCR2 which is mainly expressed on neutrophils. CXCR2 activation plays critical roles in the recruitment of leucocytes and neutrophils, which are involved in the pathogenesis of atherosclerosis and cardiac fibrosis. In cardiovascular diseases, it is cognized that CXCL1 is vital in enlisting neutrophils and monocytes/macrophages into the impaired myocardium and artery to mediate atherosclerosis and cardiac remodeling (2). Obvious neutrophil influx mediated by CXCL1 is discovered in inflammatory sites (27).

CXCL1 Mediates Inflammation

The inflammation in plasma and tissue is accompanied with risen level of CXCL1 in relevant studies (28). Some researches demonstrated that the CXCL1-CXCR2 axis mediates the infiltration of monocytes into heart tissues, leading to cardiac fibrosis. CXCL1 is also active in inflammation in other organs as a major neutrophil chemoattractant to mediate tissue injury. CXCL1 may mediates inflammation by NF-κB (nuclear factor-κB) signaling, a key regulator of pro-inflammatory mediators and NOX (nicotinamide adenine dinucleotide phosphate oxidase)-2 subunit. CXCR-2 deletion reduced the activation of NF-κB signaling (24). However, whether CXCL1 transcription is regulated by NF-κB needs further study.

Abbreviations: CVD, cardiovascular disease; HF, heart failure; Ang, angiotensin; IL, Interleukin; HSCs, hepatic stellate cells; IHD, ischemic heart disease; RAAS, renin-angiotensin-aldosterone system; MMP-12, matrix metallopeptidase 12; LPS, lipopolysaccharide; CCL, C-C Motif Chemokine Ligand.
The Effect of CXCR2 on Cardiomyocyte (CM) Hypertrophy
CXCR2 was reported to promote CM hypertrophy. CXCR2 KO macrophages were co-cultured with WT neonatal rat cardiac myocytes (CMs) or fibroblasts (CFs), respectively. After 24 h of Ang II treatment, co-culture of CMs with CXCR2 KO macrophages had a significant reduction in CM size, the expression of the protein levels of p-AKT, p-ERK1/2, p-STAT3 and CaNA compared with co-culture of CMs with WT macrophages (2). Therefore, AKT, ERK1/2, STAT3 and CaNA may be the important mediators of cardiomyocyte hypertrophy.

CXCL1 in Cardiovascular Angiogenesis
Excluding inflammation and fibrosis, CXCL1 is also active in angiogenesis. In chronic ischemic heart disease (IHD) patients, the formation of coronary collateralization is notable. In chronic IHD, myocardial ischemia may stimulate the secretion of angiogenic chemokines such as CXCL1 to mediate the formation of coronary collateralization (9). Coronary collateralization tends to result in better cardiac function, less arrhythmias, less complications and higher survival (9). It is indicated that CXC chemokines play a vital role in the presence of coronary collaterals (9). ELR motif is structurally decisive for the physiological functions of CXC chemokines (9). The level of ELR-chemokines including CXCL1 is risen in vascular remodeling and angiogenesis. Conversely, CXC chemokines without ELR motif inhibit the progress of angiogenesis. Therefore, CXCL1 is a potent promoter of angiogenesis.

The Effect of CXCL1 on TGF-Smad2/3 Signaling
TGF (transforming growth factor)-Smad2/3 are the key signaling mediators of cardiac fibrosis. These researches investigated that TGF-β1, p-Smad2/3 were suppressed in CXCR-2 knockout mice, and α-SMA and collagen I also decreased (2, 24). Therefore, CXCL1 may induce cardiac fibrosis by TGF-Smad2/3 signaling.

Several Factors Influence the Level of CXCL1 in Cardiac Fibrosis
Many factors are known to have an impact on the serum level of CXCL1. Renin-angiotensin-aldosterone system (RAAS) is a major aspect. Angiotensin (Ang) II promotes the expression of CXCL1 (2). The inhibition of the activity of RAAS contributes to cardiac remodeling and fibrosis (2, 3). TRAF3IP2 (TRAF3 interacting protein 2T) is known as a signaling intermediate of aldosterone/salt-induced cardiac remodeling and myocardial fibrosis (3). It is discovered that the deletion of TRAF3IP2 gene significantly attenuated expression of CXCL1 (3). Meanwhile, CXCL1 mRNA level increases obviously in aldosterone-treated mice (3). Oppositely, it is indicated that Ang II modulates smoke- induced lung fibrosis and suppresses the increasing of CXCL1 (29).

IL-17 is thought a factor of adverse cardiac remodeling and fibrosis (30), and a key downstream mediator of TGF-β which is an important promote-fibrosis cytokine. It is indicated that IL-17 promotes the mRNA expression of CXCL1 and CXCL1 is a downstream gene of IL-17 (30, 31). With the neutralization of IL-17, there is a downward trend of expression of CXCL1 (30).
Knockout of IL-17 gene also markedly down-regulates the level of CXCL1 in liver fibrosis (32).

Bmal1 (aryl hydrocarbon receptor nuclear translocator-like protein 1) is the gene of aryl hydrocarbon receptor nuclear translocator-like protein 1 in cardiomyocyte (33). It is presented that cardiomyocyte-specific deletion of Bmal1 significantly upgrades the transcript level of CXCL1, triggers diastolic dysfunction, extracellular matrix response, and impaired resolution of inflammation (33).

Besides, a proteolytic enzyme named MMP-9 is known to have the ability of decomposing CXCL1 (34). MMP-12 which is produced by macrophages is also related to the serum level of CXCL1 (35, 36). It is known for its function of degrading extracellular matrix, but MMP12 has several other functions. The mRNA level of CXCL1 is much higher in MMP12−/− mice in infarct area of heart compared with wild type group (35). It is suggested that MMP12 inhibits infiltration of neutrophils by depression of CXCL1/CXCL2/CXCL5- CXCR2 axis (35). However, in other study, the silence of MMP12 leads to decline of CXCL1 and MMP12 is thought a contributor of secretion of CXCL1 (36). This is a contradiction we should pay attention to.

In addition to the above, a chemokine-binding protein called “Evasins” is demonstrated to have the ability of inhibiting both CC and CXC chemokine (37). Evasin-4 is proved to be relevant to the decreasing of the serum level of CXCL1 (37). CCL5 (C-C Motif Chemokine Ligand 5) is proved important in the synthesis of CXCL1 and it could be blocked by Evasin-4 (37). In addition, chemokines CC-chemokine ligand 2 (Ccl2) was related to the expression of CXCL1 in HSCs (38). In this research, Tnfr1−/− /Mdr2−/− mice expressed high levels of CCL2, showed significantly up-regulated hepatic gene expression of CXCL1 compared to wild type.

**Signaling Pathway Regulating CXCL1 Expression**

In addition to neutrophils, macrophages, and epithelial cells, activated hepatic stellate cells (HSCs) also release CXCL1. CD147 promotes CXCL1 expression in HSCs and CXCL1 promoted HSCs activation through autocrine (39). CD147 can bind to integrin and activates the downstream FAK/PI3K signaling pathway. CD147 overexpression induced the AKT phosphorylation; however, treating with FAK/PI3K inhibitor LY294002, CD147-induced AKT phosphorylation and CXCL1 expression were significantly inhibited. Taken together, CD147 regulates CXCL1 release in HSCs by phosphatidylinositol 3 kinase(PI3K)/protein kinase B(AKT) signaling. Therefore, PI3K/AKT signaling may be one mechanism of CXCL1 expression. A working model is illustrated in Figure 1.

MMP12 (matrix metalloproteinase 12) is proved relevant to several inflammatory diseases. Increased expression of MMP12 leads to proliferation of macrophages (36). CXCL1 is regulated by MMP12 as a pro-inflammatory chemokine (36). Knockdown of MMP12 gene reduces the expression of multiple types of cytokines including CXCL1 in animal models (36). Notably, MMP12 silencing significantly down-regulate the expression of mitogen-activated protein kinase p38(P38) and extracellular regulated kinase 1/2 (ERK1/2) and their phosphorylation (36). It is hard to say the role of the ERK/P38 MAPK signaling pathway in pro-inflammatory chemokine CXCL1 during inflammation, but it provides a new mentality to figure out CXCL1 and its regulation.

### CXCL1 in the Fibrosis of Other ORGANS

#### Lung Fibrosis

CXCL1 is connected with fibrosis of other organs in extensive research. Lung fibrosis is known as a progressive disease characterized by inflammatory infiltration and interstitial fibrosis (40, 41). Neutrophils mediate lung injury via recruitment and activation (42, 43). Neutrophil influx correlated with CXCL1 plays an important role in pulmonary fibrosis (27, 28). Inhibition of the genetic synthesis of extracellular matrix protein is accompanied with reduced level of CXCL1 (44, 45). It is suggested that IL-17 inducing chemokines promote the progress of pulmonary fibrosis (46). CXCL1 is recognized as the downstream gene regulated by IL-17 and is at a higher level in fibrosis model (46–48). IL-9 is similar to IL-17 in some experiments (49, 50). In bleomycin-induced lung fibrosis model, the release of CXCL1 is promoted by bleomycin (51, 52). Besides, CXCL1 is a novel marker for evaluating the severity of chronic obstructive pulmonary disease (28, 53). CXCL1 is also involved in airway remodeling, asthma and cystic fibrosis in lung (54–56).

#### Hepatic Fibrosis

CXCL1 is also related to hepatic fibrosis. Similar to pulmonary fibrosis, liver fibrosis also has an accumulation of extracellular matrix proteins in structure (57–59). Fibrosis in liver is usually a consequence of chronic inflammation caused by alcohol, diet and virus infections (39, 60). Neutrophils play an important role in liver injury (61). Cholestatic liver injury is accompanied with infiltration of neutrophils and upregulated expression of CXCL1 (62, 63). Decreased level of CXCL1 is observed in treatment of non-alcoholic steatohepatitis and hepatic fibrosis. Hepatic stellate cells (HSCs) are considered as a precursor of myofibroblasts in the liver and correlate with the production of extracellular matrix (64–66). CXCL1 could be secreted by HSCs in liver and CXCL1 promotes the activation of HSCs at the same time (39). HSCs stimulated by CXCL1 increase the expression of collagen type I and α-SMA (39). Therefore, CXCL1 is considered to be a promoter of hepatic fibrosis (67). Reduced expression CXCL1 is able to accelerate HSCs apoptosis thereby ameliorating liver fibrosis (68). In addition, CXCL1 performs a vital role in hepatic fibrosis induced by high cholesterol and alcohol. Blockade of CXCL1 by specific antibody reduced hepatic neutrophil infiltration and liver fibrosis in relevant study (66). Besides, M2-type macrophage mediated by CXCL1 is significantly upregulated in cirrhosis patients (69). CXCL1 could also be regulated by IL-17 in liver (70). Extracellular vesicles-derived miR-150-5p secreted by adipose-derived mesenchymal stem cells inhibits CXCL1 expression to attenuate hepatic fibrosis (3). Surprisingly, some studies suggest that CXCL1 has a protective effect against liver fibrosis and the expression of CXCL1 suppress fibrosis (58). The effect of CXCL1 in hepatic fibrosis remains further research.
Renal Fibrosis

All progressive chronic kidney diseases including obstructive nephropathy could result to renal fibrosis with impaired renal function (71, 72). CXCL1 acts an important role in chronic renal inflammation including obstruction as a neutrophil chemoattractant (73–75). Increased expression of CXCL1 exacerbates kidney damage in animal model (4, 76). The expression of CXCL1 gene could be controlled by NF-κB in kidney, and NF-κB is known as an indirect pro-fibrogenic factor (77). Blockade of CXCL1-CXCR2 axis efficiently alleviated renal inflammation. In addition, previous studies indicated that renal fibrosis is prompted by increased level of receptor CXCR2 (78). Macrophages mediated by CXCL1 are correlated with collagen formation, extracellular matrix deposition and the degree of renal dysfunction in experimental animal models (79). CXCL1 is also relevant to the fibrosis of intra-allograft in some cases (80).

Other Organs

CXCL1 is also related to the fibrosis in pancreas and biliary atresia (81, 82). What’s more, fibrosis after autoimmune thyroiditis is also supposed to related to CXCL1 (83).

CONCLUSION

CXCL1 is a potent neutrophil chemoattractant, which could be secreted by macrophages, fibroblasts, keratinocytes, and epithelial cells (84). It is involved in diverse tissue inflammations, fibrosis, tumor, angiogenesis in various tissues. In CVD, CXCL1 plays an important role in cardiac fibrosis especially induced by hypertension, atrial fibrillation, post-irradiation. Therefore, CXCL1 is a promising target and antagonism of CXCL1 or CXCR2 is a novel therapy for treatment of cardiac fibrosis. However, whether cardiac fibrosis induced by other causes (such as lone AF, aortic coarctation and myocardial infarction) is associated with CXCL1 is not clear. Hence, more researches need to conduct to ascertain the roles and relevant mechanisms of CXCL1 in these cardiac fibrosis. Actually, we have been doing related research, and we found that the oxidative stress related pathway might contribute to the effect of CXCL1 in cardiac fibrosis. However, we need more research. With the aid of further researches of CXCL1, it will help cardiologists devise more reasonable therapeutic plans and improve the prognosis of CVD patients.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

C-LW: the main writer. RYin: reference collection and screening. S-NW: typography and format modification. RYing: manuscript design, modification, and submission. All authors contributed to the article and approved the submitted version.

FUNDING

This research work was financially supported by grants: the National Natural Science Foundation of China (81960093), Science and Technology Program of Jiangxi Province (No. 20171BB215003), Science and Technology Plan of Health Commission of Jiangxi Province (202130208), and Science and Technology Project of Education Department of Jiangxi Province (GJJ180044).

REFERENCES

1. Lafuse WP, Wozniak DJ, Rajaram M. Role of cardiac macrophages on cardiac inflammation, fibrosis and tissue repair. Cells. (2020) 10:51. doi: 10.3390/cells10010051
2. Wang L, Zhang YL, Lin QY, Liu Y, Guan XM, Liu Y, et al. CXCL1-CXCR2 axis mediates angiotensin II-induced cardiac hypertrophy and remodelling through regulation of monocyte infiltration. Eur Heart J. (2018) 39:1818–31. doi: 10.1093/eurheartj/ehy085
3. Sakamuri SS, Valente AJ, Siddesha JM, Delafontaine P, Siebenlist U, Gardner JD, et al. TRAF3IP2 mediates aldosterone/salt-induced cardiac hypertrophy and fibrosis. Mol Cell Endocrinol. (2016) 429:84–92. doi: 10.1016/j.mce.2016.03.038
4. Hermert D, Martin IV, Reiss LK, Liu X, Breitkopf DM, Reimer KC, et al. The nucleic acid binding protein YB-1–controlled expression of CXCL1 in these cardiac fibrosis. Actually, we have been doing related research, and we found that the oxidative stress related pathway might contribute to the effect of CXCL1 in cardiac fibrosis. However, we need more research. With the aid of further researches of CXCL1, it will help cardiologists devise more reasonable therapeutic plans and improve the prognosis of CVD patients.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

C-LW: the main writer. RYin: reference collection and screening. S-NW: typography and format modification. RYing: manuscript design, modification, and submission. All authors contributed to the article and approved the submitted version.

FUNDING

This research work was financially supported by grants: the National Natural Science Foundation of China (81960093), Science and Technology Program of Jiangxi Province (No. 20171BB215003), Science and Technology Plan of Health Commission of Jiangxi Province (202130208), and Science and Technology Project of Education Department of Jiangxi Province (GJJ180044).

REFERENCES

1. Lafuse WP, Wozniak DJ, Rajaram M. Role of cardiac macrophages on cardiac inflammation, fibrosis and tissue repair. Cells. (2020) 10:51. doi: 10.3390/cells10010051
2. Wang L, Zhang YL, Lin QY, Liu Y, Guan XM, Liu Y, et al. CXCL1-CXCR2 axis mediates angiotensin II-induced cardiac hypertrophy and remodelling through regulation of monocyte infiltration. Eur Heart J. (2018) 39:1818–31. doi: 10.1093/eurheartj/ehy085
3. Sakamuri SS, Valente AJ, Siddesha JM, Delafontaine P, Siebenlist U, Gardner JD, et al. TRAF3IP2 mediates aldosterone/salt-induced cardiac hypertrophy and fibrosis. Mol Cell Endocrinol. (2016) 429:84–92. doi: 10.1016/j.mce.2016.03.038
4. Hermert D, Martin IV, Reiss LK, Liu X, Breitkopf DM, Reimer KC, et al. The nucleic acid binding protein YB-1–controlled expression of CXCL1 in these cardiac fibrosis. Actually, we have been doing related research, and we found that the oxidative stress related pathway might contribute to the effect of CXCL1 in cardiac fibrosis. However, we need more research. With the aid of further researches of CXCL1, it will help cardiologists devise more reasonable therapeutic plans and improve the prognosis of CVD patients.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

C-LW: the main writer. RYin: reference collection and screening. S-NW: typography and format modification. RYing: manuscript design, modification, and submission. All authors contributed to the article and approved the submitted version.

FUNDING

This research work was financially supported by grants: the National Natural Science Foundation of China (81960093), Science and Technology Program of Jiangxi Province (No. 20171BB215003), Science and Technology Plan of Health Commission of Jiangxi Province (202130208), and Science and Technology Project of Education Department of Jiangxi Province (GJJ180044).
normal mucoa of healthy controls. *Inflamm Bowel Dis.* (2017) 23:1098–108. doi: 10.1097/MIB.0000000000001066

13. Ye MY, Chen MY, Chang YH, Huang JS, Huang TT, Wong TY, et al. Growth-regulated oncogene α from oral submucous fibrosis fibroblasts promotes malignant transformation of oral precancerous cells. *J Oral Pathol Med.* (2018) 47:890–6. doi: 10.1111/jop.2018.03.016

14. Konishi T, Schuster RM, Goetzman HS, Caldwell CC, Lentsch AB. Cell-specific regulatory effects of CXCR2 on cholestatic liver injury. *Am J Physiogastrointest Liver Physiol.* (2019) 317:G773–83. doi: 10.1152/ajpgi.00080.2019

15. Wilson CL, Jurk D, Fullard N, Banks P, Page A, Luli S, et al. NFκB1 is a suppressor of neutrophil-driven hepatocellular carcinoma. *Nat Commun.* (2015) 6:6818. doi: 10.1038/ncomms7818

16. Tsai Y, Hao S, Chen C, Lin BJ, Wu W. Involvement of B2 receptor in bradykinin-induced proliferation and proinflammatory effects in human nasal mucosa-derived fibroblasts isolated from chronic rhinosinusitis patients. *PLoS ONE.* (2015) 10:e0126853. doi: 10.1371/journal.pone.0126853

17. Kang J, Hur J, Kang JA, Lee HS, Jung H, Choi JI, et al. Priming mobilized peripheral blood mononuclear cells with the “activated platelet supernatant” enhances the efficacy of cell therapy for myocardial infarction of rats. *Cardiovasc Ther.* (2016) 34:245–53. doi: 10.1002/tox.22759

18. Amrouche L, Desbuissons G, Rabant M, Sauvaget V, Nguyen C, Benon A, et al. MicroRNA-146a in human and experimental ischemic AKI: CXCL8-dependent mechanism of action. *J Am Soc Nephrol.* (2017) 28:479–93. doi: 10.1681/ASN.2016010045

19. Perrault DP, Lee GK, Bouz A, Sung C, Yu R, Pourmousa AI, et al. Ischemia and reperfusion injury in superficial inferior epigastric artery-based vascularized lymph node flaps. *PLoS ONE.* (2020) 15:e0227599. doi: 10.1371/journal.pone.0227599

20. Jin Y, Wu Z, Wang N, Duan S, Wu Y, Wang J, et al. Association of EGF receptor and NLRs signaling with cardiac inflammation and fibrosis in mice exposed to fine particulate matter. *J Immunol.* (2016) 203:3107–11. doi: 10.4049/jimmunol.1900890

21. Zhang Y, Geng C, Yang J, Fang J, Yan X, Li P, et al. Chronic inhibition of chemokine receptor CXCR2 attenuates cardiac remodeling and dysfunction in spontaneously hypertensive rats. *Biochim Biophys Acta.* (2019) 1865:165551. doi: 10.1016/j.bbadis.2019.165551

22. Ferreira JP, Pizard A, Machu J, Bresso E, Rocca HB, Girend N, et al. Plasma protein biomarkers and their association with mutually exclusive cardiovascular phenotypes: the FIBRO-TARGETS case-control analyses. *Clin Res Cardiol.* (2010) 109:22–33. doi: 10.1007/s00392-010-01480-4

23. Mikolaiczky TP, Szczepaniak P, Vidler F, Maffia P, Graham GJ, Guzik TJ. Role of constitutive inflammation in hepatocellular carcinoma. *Pharmacol Therap.* (2021) 233:107799. doi: 10.1016/j.pharmthera.2020.107799

24. Zhang Y, Cao H, Han X, Xie Y, Chen C, Yang J, et al. Chemokine receptor CXCR-2 initiates arterial fibrillation by triggering monocyte mobilization in mice. *Hypertension.* (2020) 76:381–92. doi: 10.1161/HYPERTENSIONAHA.120.14698

25. Guo H, Zhao X, Su H, Ma C, Liu K, Kong S, et al. miR-21 is upregulated, and induces fibrosis in nasal mucosa-derived fibroblasts isolated from chronic rhinosinusitis patients. *Am J Physiogastrointest Liver Physiol.* (2019) 317:H581–96. doi: 10.1152/ajpgi.00080.2015

26. Ilatovskaya DV, Potts C, Clayton J, Domondon M, Troncoso M, Pippin S, et al. CD8+ T-cells negatively regulate inflammation post-myocardial infarction. *Am J Physiol Heart Circ Physiol.* (2019) 371:H581–96. doi: 10.1152/ajpheart.00012.2019

27. Kubota A, Suto A, Suzuki K, Kobayashi Y, Nakajima H. Matrix metalloproteinase-12 produced by Ly6Clow macrophages prolongs the survival after myocardial infarction by preventing neutrophil influx. *J Mol Cell Cardiol.* (2019) 131:41–52. doi: 10.1016/j.yjmcc.2019.04.007

28. Guan C, Xiao Y, Li K, Wang T, Liang Y, Liao G. MMP-12 regulates proliferation of mouse macrophages via the ERK/P38 MAPK pathways during inflammation. *Exp Cell Res.* (2019) 378:182–90. doi: 10.1016/j.yexcr.2019.03.018

29. Braunseretheur V, Montecucco F, Pelli G, Galan K, Proudfoot AE, Belin A, et al. Treatment with the CC chemokine-binding protein Evasin-4 improves post-infarction myocardial injury and survival in mice. *Thromb Haemost.* (2011) 110:807. doi: 10.1016/THRX.00289R

30. Berkholz L, Barilkin R, Schiller R, Ravichandran G, Krech T, Neumann K, et al. Deletion of tumour necrosis factor α receptor 1 elicits an increased TH17 immune response in the chronically inflamed liver. *Sci Rep.* (2019) 9:4232. doi: 10.1038/s41598-019-40324-z

31. Shi W, Ju D, Li H, Yuan L, Cui J, Luo D, et al. CD147 promotes CXCL1 expression and modulates liver fibrogenesis. *Int J Mol Sci.* (2018) 19:1145. doi: 10.3390/ijms19041145

32. Brochetti RA, Leal MP, Rodrigues R, Da Palma RK, de Oliveira LVF, Horliana ACRT, et al. Photobiomodulation therapy improves both inflammatory and fibrotic parameters in experimental model of lung fibrosis in mice. *Lasers Med Sci.* (2017) 32:1825–34. doi: 10.1007/s11181-017-2281-7

33. Nakazawa Y, Ohtsuka S, Nakahashi-Oda C, Shibuya A. Cutting edge: involvement of the immunoreceptor CD300c2 on alveolar macrophages in bleomycin-induced lung fibrosis. *J Immunol.* (2019) 203:3107–11. doi: 10.4049/jimmunol.1900889

34. Mo Y, Jiang M, Zhang Y, Wan R, Li J, Zhong CJ, et al. Comparative mouse lung injury by nickel nanoparticles with differential surface modification. *J Nanobiotechnol.* (2019) 17:2. doi: 10.1186/s12951-018-0436-0

35. Wan R, Mo Y, Zhang Z, Jiang M, Tang S, Zhang Q. Cobalt nanoparticles induce lung injury, DNA damage and mutations in mice. *Part Fibre Toxicol.* (2017) 14:38. doi: 10.1186/s12989-017-0219-x

36. Liu G, Guoelli MA, Jarnicki AG, Hsu AC, Nair PM, Haw TJ, et al. Fibulin-1 regulates the pathogenesis of tissue remodeling in respiratory diseases. *ICI Insight.* (2016) 1e:86380. doi: 10.1172/inci.2016.86380

37. Liu G, Guoelli MA, Nair PM, Donovan C, Hsu AC, Jarnicki AG, et al. Airway remodelling and inflammation in asthma are dependent on the extracellular matrix protein fibulin-1c. *J Pathol.* (2017) 243:510–23. doi: 10.1002/path.4979

38. Cipolla E, Fisher AJ, Gu H, Mickler EA, Agarwal M, Wilke CA, et al. IL-17A deficiency mitigates bleomycin-induced chronic activation during lung fibrosis. *FASEB J.* (2017) 31:5543–56. doi: 10.1096/fj.201700289R
47. Martini T, McManigle WC, Kelly FL, Nelson ME, Sun J, Zhang HL, et al. IL-17A contributes to lung fibrosis in a model of chronic pulmonary graft-versus-host disease. *Transplantation.* (2019) 103:2264–74. doi: 10.1097/TP.0000000000002837

48. Slika PF, Hisch CL, Lipovska A, Plett FD, Locklear J, Namovic MT, et al. Small molecule and pooled CRISPR screens investigating IL17 signaling identify BRD2 as a novel contributor to keratinocyte inflammatory responses. *ACS Chem Biol.* (2019) 14:857–72. doi: 10.1021/acschembio.8b00260

49. Sugimoto N, Suzukawa M, Nagase H, Koizumi Y, Ro S, Kobayashi K, et al. IL-9 blockade suppresses silica-induced lung inflammation and fibrosis in mice. *Am J Respir Cell Mol Biol.* (2019) 60:232–43. doi: 10.1165/rcmb.2017-0287OC

50. Ensaat S, Bernau K, Torr EE, Bochkov YA, Jarjour NN, Sandbo ND. RNA-sequencing analysis of lung primary fibroblast response to eosinophil-degranulation products predicts downstream effects on inflammation, tissue remodeling and lipid metabolism. *Respir Res.* (2017) 18:188. doi: 10.1186/s12931-017-0669-8

51. Pereira PR, Oliveira-Junior MC, Mackenzie B, Chiovatto JE, Matos Y, Greiff FR, et al. Exercise reduces lung fibrosis involving serotonin/AntiK signal. *Med Sci Sports Exerc.* (2016) 48:1276–84. doi: 10.1249/MSS.0000000000000907

52. Andrade-Sousa AS, Rogerio PP, MacKenzie B, Oliveira-Junior MC, Assumpciao-Neto E, Brandao-Rangel MA, et al. Aerobic exercise attenuated blemycin-induced lung fibrosis in Th2-dominant mice. *PLoS ONE.* (2016) 11:e0163420. doi: 10.1371/journal.pone.0163420

53. Lee SJ, Park JH, Lee JY, Jeong YJ, Song JA, Lee K, Kim DJ. Establishment of a mouse model for pulmonary inflammation and fibrosis by intratracheal instillation of polyhexamethylenebiguanide phosphate. *J Toxicol Pathol.* (2016) 29:95–102. doi: 10.1293/tox.2015-0067

54. Dennis EA, Coats MT, Griffin SE, Hale JY, Novak L, Briles DE, Crain MJ. The role of transforming growth factor-beta1 signaling in the onset of alcoholic liver disease. *J Hepatol.* (2015) 67:454–61.e9. doi: 10.1016/j.jhep.2015.01.023

55. Stephenson ST, Brown LAS, Helms MN, Qu H, Brown SD, Brown MR, et al. Small molecule and pooled CRISPR screens investigating IL17 signaling via compensatory up-regulation of CXCR2–related chemokine activity. *J Biol Chem.* (2018) 293:14423–39. doi: 10.1074/jbc.M118.016037

56. Ma HY, Yamamoto G, Xu J, Liu X, Karin D, Kim JY, et al. IL-17 signaling in steatotic hepatocytes and macrophages promotes hepatocellular carcinoma in alcohol-related liver disease. *J Hepatol.* (2019) 72:946–59. doi: 10.1016/j.jhep.2019.12.016

57. Qiu S, Xiao Z, Piao C, Zhang I, Dong Y, Cui W, et al. AMPKalpha2 reduces renal epithelial transdifferentiation and inflammation after injury through interaction with CK2beta. *J Pathol.* (2015) 237:330–42. doi: 10.1002/path.4597

58. Strubos E, Seelen MA, van Goor H, Olinga P, Mutsaers S, et al. Circulating innate lymphoid cell in experimental nonalcoholic steatohepatitis. *Int J Mol Sci.* (2019) 20:701026

59. Ghosh M, Thangada S, Dasgupta O, Khanna KM, Yamade HT, Kashigaram M, et al. Cell-intrinsic sphingosine kinase 2 promotes macrophage polarization and renal inflammation in response to unilateral ureteral obstruction. *PLoS ONE.* (2018) 13:e0194053. doi: 10.1371/journal.pone.0194053

60. Zhao Y, Zhu L, Zhou T, Zhang Q, Shi S, Liu L, et al. Urinary CXCL1: a novel predictor of IgA nephropathy progression. *PLoS ONE.* (2015) 10:e0119303. doi: 10.1371/journal.pone.0119303

61. Ye Y, Zhang Y, Wang B, Walana W, Wei J, Gordon JR, et al. CXCR1/CXCR2 antagonist G31P inhibits nephritis in a mouse model of uric acid nephropathy. *Biomed Pharmacother.* (2018) 107:1142–50. doi: 10.1016/j.biopha.2018.07.077

62. Ravichandran K, Wang Q, Ozkok A, Jani A, Li H, He Z, et al. CD4 T cell knockout does not protect against kidney injury and worsens cancer. *J Mol Med.* (2016) 94:433–55. doi: 10.1002/jm.24866

63. Wang DT, Huang RH, Cheng X, Zhang ZH, Yang YJ, Lin X, Tanshinione IA attenuates renal fibrosis and inflammation via altering expression of TGF-beta/Smad and NF-kappaB signaling pathway in 5/6 nephrectomized rats. *Int Immunopharmacol.* (2015) 26:8–12. doi: 10.1016/j.intimp.2015.02.027

64. Wang D, Chen X, Fu M, Xu H, Li Z. Tacrolimus increases the expression level of the chemokine receptor CXCR2 to promote renal fibrosis progression. *Int J Mol Med.* (2019) 44:2181–8. doi: 10.3892/ijmm.2019.4368

65. Wong D, Yiu WH, Chan KW, Li Y, Li R, Lok S, et al. Activated renal tubular Wnt-beta-catenin signaling triggers renal inflammation during overload proteinuria. *Kidney Int.* (2018) 93:1367–83. doi: 10.1016/j.kint.2017.12.017

66. Tse GH, Johnston CJC, Kluft D, Grant D, Hughes J, et al. Intercellular adhesion molecule-1 modulates bile duct injury by targeting the suppressor of injury and fibrosis in experimental nonalcoholic steatohepatitis. *Antioxid Redox Signal.* (2015) 23:1253–69. doi: 10.1089/ars.2014.6108

67. Yang YM, Fukui M, Wang Z, Miao F, Karriker MJ, Seki E. Interventional potential of recombinant feline hepatocyte growth factor in a mouse model of non-alcoholic steatohepatitis. *Front Endocrinol.* (2018) 9:3378. doi: 10.3389/fendo.2018.00378

68. Zhou Z, Xu MJ, Cai Y, Wang W, Jiang JX, Varga ZV, et al. Neutrophil-hepatic stellate cell interactions promote fibrosis in experimental steatohepatitis. *Cell Mol Gastroenterol Hepatol.* (2018) 5:399–413. doi: 10.1016/j.cmg.2018.01.003

69. Yang L, Miura K, Zhang B, Matsuhashi H, Yang YM, Liang S, et al. TRIF differentially regulates hepatic steatosis and inflammation/fibrosis in mice. *Cell Mol Gastroenterol Hepatol.* (2017) 3:469–83. doi: 10.1016/j.cmg.2016.12.004

70. Zubieta-Franco I, Fernandez-Tussy P, Barbier-Torres L, Simon J, Fernandez-Ramos D, Lopitz-Otsoa F, et al. Deregulated neddylation in liver fibrosis. *Hepatology.* (2017) 65:694–709. doi: 10.1002/hep.28933

71. Karababa A, Groos-Sahr K, Albrecht U, Keitel V, Shafigullina A, Gorg B, Haussinger D. Ammonia attenuates LPS-induced upregulation of pro-inflammatory cytokine mRNA in co-cultured astrocytes and microglia. *Microchem J.* (2017) 127:37–49. doi: 10.1016/j.micchem.2016.02061–4
cytokine signaling 1 in biliary atresia. *Pediatr Res.* (2017) 82:1007–16. doi: 10.1038/pr.2017.87

83. Chen K, Wei Y, Alter A, Sharp GC, Braley-Mullen H. Chemokine expression during development of fibrosis versus resolution in a murine model of granulomatous experimental autoimmune thyroiditis. *J Leukocyte Biol.* (2005) 78:716–24. doi: 10.1189/jlb.0205102

84. Zhu X, Sun Y, Mu X, Guo P, Gao F, Zhang J, et al. Phospholipase Cε deficiency delays the early stage of cutaneous wound healing and attenuates scar formation in mice. *Biochem Biophys Res Commun.* (2017) 484:144–51. doi: 10.1016/j.bbrc.2017.01.054

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2021 Wu, Yin, Wang and Ying. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.