Medical Journal of Bakırköy

Med J Bakirkoy 2022;18:419-426
DOI: 10.4274/BMJ.galenos.2022.2022.2-6

Research

The Role of the Chemokine CXCL12 on the Pathogenesis of Several Diseases

Kemokin CXCL12'nin Bazı Hastalıkların Patogenezindeki Rolü

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ABSTRACT

Objective: The aim of this study was to evaluate the possible role of the chemokine CXCL12 in the pathogenesis of some diseases. It also aims to research diseases and connect with each other with bioinformatic tools.

Methods: STRING/GeneMANIA/KEGG PATHWAY/GSEA/MSigDB for gene set enrichment analysis for gene protein and pathway interaction, TargetScan/miRDB for miRNAs targeting CXCL12, Blood eQTL Browser/ to target CXCL12 BIOS/QTLdb, GRASP and GWAS CXCL12 and miRNA region SNPs were used for disease associations.

Results: Gene set enrichment analysis of the gene set co-expressed in the GSEA/MSigDB tool revealed the association of genes related to allergic disease, arthritis, autoimmune disease of the musculoskeletal system, osteomyelitis (FDR<5E-06). Five hundred and ninety-three miRNAs were identified. As a result of examining the disease associations of SNPs from each miRNA gene region in GWAS databases, it was determined that P<7E-40 for B lymphoblastic leukemia/lymphoma. SNPs in CXCL12 did not show any GWAS associations, but blood eQTL/meQTL for CXCL12 showed associations with respiratory system disease, intestinal disease, combined immunodeficiency, multiple sclerosis, hepatitis (P<8E-06) and GWAS.

Conclusion: It is thought that CXCL12 may play a strong role in autoimmunity, inflammation, cancer and other diseases.

Keywords: CXCL12, pathways, SNP, diseases

ÖZ

Amaç: Bu çalışmanın amacı kemokin CXCL12'nin bazı hastalıkların patogenezindeki olası rolünü değerlendirmektir. Ayrıca biyoinformatik araçlarla hastalıkları araştırmayı ve birbirleriyle bağlantı kurmayı amaçlamaktadır.

Gereç ve Yöntem: Gen-protein ve yolak etkileşimi için STRING/GeneMANIA/KEGG PATHWAY/GeneCards gen seti zenginleştirme analizi için GSEA/MSigDB, CXCL12'yi hedefleyen miRNA'lar için TargetScan/miRDB, CXCL12'yi hedeflemek için Blood eQTL Browser/BIOS/mQTLdb, hastalık ilişkileri için GRASP ve GWAS CXCL12 ve miRNA bölgesi SNP'leri kullanıldı.

Bulgular: GSEA/MSigDB aracında birlikte eksprese edilen gen setinin gen seti zenginleştirme analizi, alerjik hastalık, artrit, kas-iskelet sisteminin otoimmün hastalığı, osteomyelit (FDR<5E-06) ile ilgili genlerin ilişkisini ortaya koydu. Beş yüz doksan üç miRNA tanımlandı. GWAS veri tabanlarında her bir miRNA gen bölgesinden SNP'lerin hastalık ilişkilerinin incelenmesi sonucunda, B-lenfoblastik lösemi/lenfoma için P<7E-40 olduğu saptandı. CXCL12 içindeki SNP'ler herhangi bir GWAS ilişkisi göstermedi, ancak CXCL12 için kanda eQTL/meQTL olarak, solunum sistemi hastalığı, bağırsak hastalığı, kombine immün yetmezlik, multipl skleroz, hepatit (P<8E-06) ile GWAS ilişkileri gösterildi.

Sonuç: CXCL12 otoimmünite, enflamasyon, kanser ve diğer hastalıklarda güçlü bir rol oynayabileceği düşünülmektedir.

Anahtar Kelimeler: CXCL12, yolaklar, SNP, hastalıklar

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Cite as: Gürer EE, Şentürk Çiftçi H, Oğuz SR, Kıvanç D, Kalayoğlu Beşışık S. The Role of the Chemokine CXCL12 on the Pathogenesis of Several Diseases. Med J Bakirkoy 2022;18:419-426

Received: 11.02.2022
Accepted: 21.10.2022

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INTRODUCTION

Approximately 50 chemokines have been identified in humans (1). Chemokines are protein molecules with a molecular weight of 8-12 kD and multiple domains. *Chemokine* genes 17q11.2-12 and *C-X-C chemokine* genes are also located at 4q13 locus. Stromal cell-derived factor 1 is a chemokine coded by the *CXCL12* gene and this gene on chromosome 10 in human (2). It has been shown in multiple tissues and cells. CXCL12 has a ligand relationship with the CXCR4 receptor. In adulthood, endothelial progenitor cells in the bone marrow (BM) are involved in angiogenesis by the CXCL12-CXCR4 mechanism (3).

CXCL12 is expressed in multiple sites, including the thymus, kidney, heart, spleen, liver, lung, brain, and BM. The *CXCL12* gene has chemotactic properties for lymphocytes (4). In embryogenesis, it regulates the formation of large blood vessels and the migration of hematopoietic cells from the fetal liver to the BM. Additionally, CD20 expression in B cells is regulated by CXCL12 signaling (5). CXCL12, which is also chemotactic for mesenchymal stem cells (MSCs), has a suppressive effect on osteoclastogenesis. It does this by controlling the inflammatory process during bone destruction (6).

SDF-1, an intercrine alpha family member, is composed of two forms. These are "SDF-1α/CXCL12a" and "SDF-1β/CXCL12b" formed by an alternative splicing mechanism. Chemokines are defined by four conserved cysteines forming two disulfide bonds and two disulfide bonds they form. The proteins belonging to the *CXCL12* gene are in the CXC chemokine group and are separated by the insertion of an amino acid between the first cysteine pair. Also, the first eight regions of the CXCL12 N-terminal function as a kind of receptor binding site, but only "Lys-1" and "Pro-2" are even directly involved in the activation of the receptor. The RFFESH motif is located at the loop site (residues 12-17) and acts as a CXCL12 insertion site for receptor binding (7).

It plays a role in functional states such as embryogenesis, angiogenesis, development of the immune system, development of infection, tissue homeostasis, tumor growth, metastasis. All chemokine receptors are membrane-bound molecules and contain 7-transmembrane domains in their structures and form pairs with G-proteins. Chemokine receptors are "G-protein-coupled proteins" and are expressed on leukocytes. The chemokines communicate with specific G-protein-coupled cell surface receptors on target cells, thereby initiating intracellular signaling. It induces activation and cell migration. Up to 20 chemokine receptors have been identified to date (8).

Substances such as platelet-derived growth factor, vascular endothelial growth factor-A released from platelets after the stimulus that initiates the inflammatory process in the tissue outside the vessel (bacteria, surgery, ag-ab complex, etc.), chemokines such as CXCL1, CXCL5, CXCL7, CXCL4 in the CXC type, act against the invading microorganism in the first stage. These are effective in creating barriers (9). Under the inhibitory effect of IL-1 and tumor necrosis factor-, the production of CXCL12, which is synthesized from fibroblasts and keratinocytes, gradually decreases until the 6th day. Then, from the 14th day onwards, many lymphocytes accumulate in the region under the effects of CXCL9 and CXCL10. A population of non-hematopoietic cells expresses intensely high degree levels of CXCL12 and stem cell factor (SCF), forked box C1 (FOXC1) and early B-cell factor 3 (EBF3) in human adult BM (10).

The CXC chemokine ligand has BM-specific MSCs called "reticular CXCL12 abundant reticular (CAR) cells" that strongly interact with leptin. Lep receptor (r) + stomal cells are the key component of hematopoietic stem cell (HSC) niches in murine BM (11). CAR T-cells that characterized MSCs by several distinctive features, including much higher expression of the LepR and HSC niche factors. Needed for the maintenance of HSCs, CXCL12, SCF and transcription factors are expressed relative to other cell types such as FOXC1 and EBF3 (12).

Multiple myelomas (MM) is known as a plasma cell malignancy characterized by the uncontrolled growth of malignant plasma cells starting in the BM. MM is the most common type of cancer seen in plasma cells. Targeting plasma cell precursors rather than HSCs is controlled by the chemokine CXCL12 (13,14). This chemokine also binds its receptor, CXCR4, on MM malignant cells, regulating their integration into the BM, transendothelial migration, and target identification (15-17). In the BM microenvironment, CXCL12 is mainly produced by specialized reticular BMSCs known as CAR cells.

This study aimed to evaluate the role of CXCL12 in MM and other diseases using Search Tool for Retrieval of Interacting Genes/Proteins (STRING), GeneMANIA, KEGG PATHWAY, the Molecular Signatures Database (MSigDB), TargetScan, miRDB Blood eQTL Browser/BIOS/mQTLdb, genome-wide repository of associations between SNPs and phenotypes (GRASP) and genome-wide association studies (GWAS).

METHODS

GeneCard

GeneCards is a searchable, integrative database of all annotated and found human genes providing extensive and detailed user-friendly information. The knowledge base

automatically presents gene-centered data to the user using ~150 web resources, involving genomic, proteomic, genetic, transcriptomic, clinical and functional information (https://www.genecards.org/cgi-bin/carddisp.pl?gene=CXCL12).

STRING

STRING is a biological database and comprehensive web resource of known and predicted protein-protein interactions (PPIs).

PPIs are the key components toward system-level understanding of cellular functions. It is a platform used for processing functional genomic data and distinguishing functional, structural and evolutionary features of the protein (https://string-db.org/).

GeneMANIA

GeneMANIA helps understand and reveal the function of the desired gene or gene clusters. GeneMANIA finds other genes associated with the selected gene using a countless set of functional data associations. Association data included co-expression, co-localization, protein, and genetic interactions, pathways, and protein domain similarity (https://genemania.org/).

KEGG Pathway

KEGG Pathway (https://www.genome.jp/kegg/pathway.html); provides information about the molecular reaction, interrelation and relationship networks for each substance listed below:

1. Metabolism
2. Genetic information processing
3. Environmental information processing
4. Cellular processes
5. Organismal systems
6. Human diseases
7. Drug development

GSEA/MSigDB

Gene set enrichment analysis (GSEA) is a computational method that determines whether an a priori defined set of genes. This method uses a statistical approach to show significant, concordant differences between two biological states.

MSigDB is a collection of descriptive gene set databases with using GSEA software (https://www.gsea-msigdb.org/gsea/msigdb/).

Target Scan Human

Target Scan is a web server in bioinformatics that predicts its biological targets by scanning sites [microRNAs (miRNAs)] that paired the seed region of each miRNA. For many species, 3'-compensating sites have been defined as other site types (http://www.targetscan.org/vert_80/).

Blood eQTL Browser/BIOS/mQTLdb

The eQTLGen consortium has been set up to identify the downstream consequences of trait-related genetic variants. The consortium incorporates 37 datasets, with a total of 31,684 individuals. These websites show the results of the cis-eQTL, trans-eQTL, eQTS, and replication: (Blood eQTL Browser: http://www.genenetwork.nl/bloodeqtlbrowser), (BIOS eQTL Browser: http://genenetwork.nl/biosqtlbrowser), (mQTLdb: http://mqtldb.org).

GRASP

GRASP is a web-based site. All information is obtained from the content and articles, and gives results by making genetic associations. All relationships with $p<0.05$ from GWAS defined as ≥25,000 markers tested for one or more than one features. (https://grasp.nhlbi.nih.gov/Search.aspx)

GWAS

GWAS attempt to identify genotypes and related genotypes. GWAS look for markers of the entire genomes of different individuals and offer statistical analysis at the population level. Thus, it reveals genotype-phenotype relationships (https://www.ebi.ac.uk/gwas/).

Data banks were used in this study and statistical analysis not done. This study includes bioinformatic analysis that does not require ethics committee approval. The study does not require financial support and this information is included in the method section.

RESULTS

STRING identified 32 genes interaction with CXCL12, including 8 additional CXCL genes in the vicinity of CXCL12 (Figure 1).

GeneMANIA showed 77.64% of CXCL12-related physical interactions (Figure 2). Also, it showed 8.01% CXCL12-related co-expression (Figure 3).

GeneCards showed 5,052 genes associated with CXCL12. We used Target Scan to select the miRNAs targeting CXCL12 and determined their other target genes. These results nearly significant as the co-expressed gene set, suggesting that miRNA's play a major role in the regulation of CXCL12 expression (Table 1).

The most meaningful co-expression pattern was noted in the BM followed by other organs (brain, heart, lung, kidney and skin). The KEGG Pathway Database found 35 pathways related to CXCL12 (Table 2). The GSEA of the co-expressed

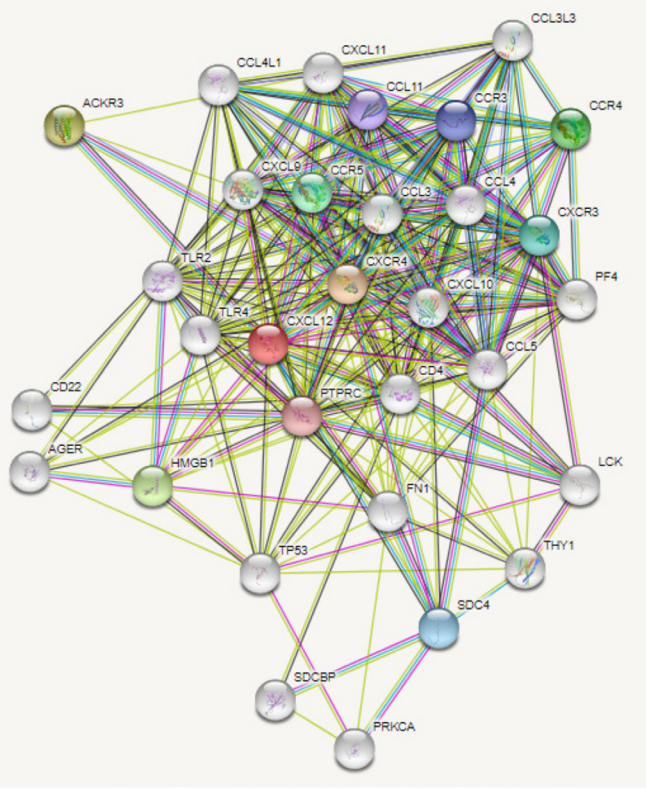


Figure 1. Gene interaction with CXCL12 (https://string-db.org/cgi/network?taskId=bjF8HZ0B6xjl&sessionId=bAKq4YR4db7U)

gene set in the GSEA/MSigDB tool suggested the enrichment of genes involved in allergic disease, arthritis, autoimmune diseases of the musculoskeletal system, bone inflammation disease (false discovery rates <5E-06). The investigation of disease associations of single nucleotide polymorphisms (SNPs) from each *miRNA* gene region in GWAS databases yielded results for B-lymphoblastic leukemia/lymphoma (p<7E-40). SNPs acting as eQTL/meQTL in blood for CXCL12 showed GWAS associations with; respiratory system disease, intestinal disease, combined immunodeficiency, multiple sclerosis, hepatic (p<8E-06).

DISCUSSION

Almost all *in vitro* studies of MM cell accumulation and MM cell migration have specifically selected the "CXCL12a isoform". Additionally, reported in vivo studies are lacking in conclusions regarding the specific functions of other isoforms of "CXCL12". This is because the mice used carry a complete excision of CXCL12 or a deletion of CXCR4, the cognate receptor for all isoforms (18-21). Additionally, the recently identified CXCL12 (CXCL12γ) gamma isoform showed much higher activity than the "canonical" CXCL12a isoform (15), inducing leukocyte recruitment and angiogenesis.

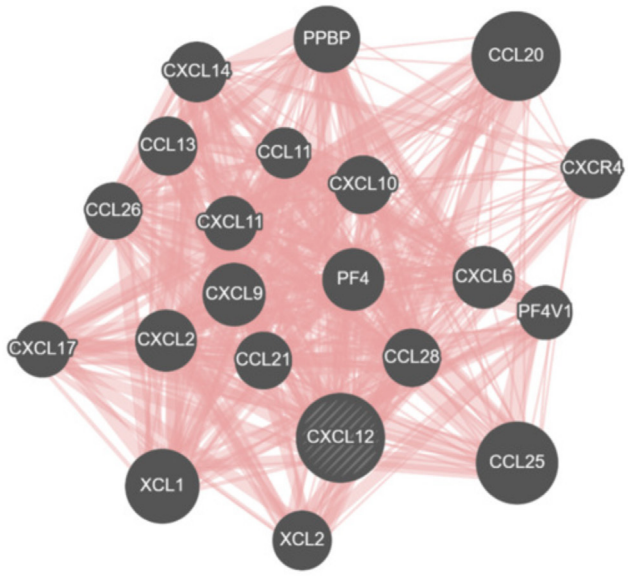


Figure 2. Physical interactions with CXCL12 (https://genemania.org/search/homo-sapiens/cxcl12)

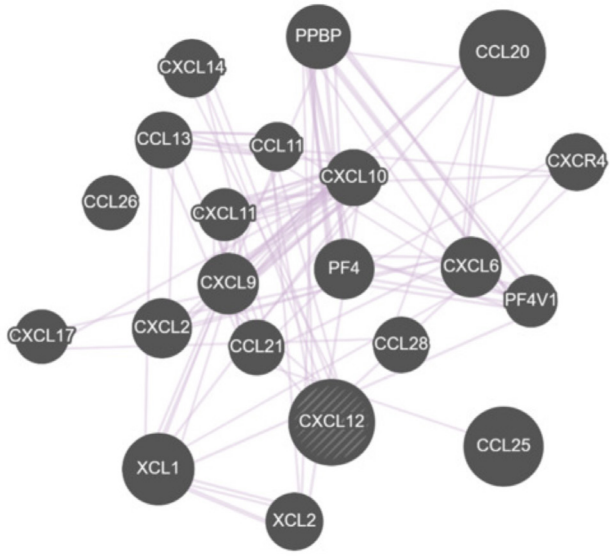


Figure 3. Co-expression with CXCL12 (https://genemania.org/search/homo-sapiens/cxcl12)

However, CXCL12γ plays similar roles during its interaction with the BM microenvironment in hematological malignancies is still open to debate and investigation (22).

Because of the induction of increased bone resorption by osteoclasts by activation of CXCL12 molecules, the release of factors such as IL-6 by osteoclasts can provide growth factors for the protection and expansion of multiple myeloma plasma cells in the bone environment (23).

Although CXCL12 signaling in osteoclast formation is highly complex, selective replacement of the hematopoietic

Table 1. miRNAs targeting CXCL12

miRNA	Position in the UTR	Seed match	Context ++ score	P_{CT}	Predicted relative K_D
Conserved sites					
hsa-miR- 135a-So	1306-1312	7mer-1A	-0.67	0.53	-2.353
hsa-miR-135b-5n	1306-1312	7mer-1A	-0.65	0.53	-2.353
bsa-miR-130a-So	1452-1458	7mer-m8	-0.59	0.18	-2.7
hsa-miR-23a-3n	1452-1458	7mer-m8	-0.55	0.18	-2 57
hsa-miR-23b-3o	1452-1458	7mer-m8	-0.53	0.18	-2.57
hsa-miR-23c	1452-1458	7mer-m8	-0.52	0.18	-2.57
hsa-miR-137	1472-1479	8mer	-0.52	0.77	-5.307

P_{CT}: Probability of preferentially conserved targeting, K_D: Relative K_D values are predicted using a convolutional neural network (CNN) that predicts binding affinity between any miRNA and any 12-nt sequence

population with CXCR4-deficient cells results in increased (rather than decreased) osteoclast number and bone resorption demonstrated in several studies (24).

As CXCR4/CXCL12 signaling during hematopoiesis is associated with the persistence of HSCs and the BM, whether CXCR4/CXCL12 antagonism can impair hematopoiesis should be further examined for more rational therapeutic strategies. Disruption of the CXCR4/CXCL12 relationship may affect the long-term activities of HSC, as this axis has been shown to be involved in the protection of HSCs against oxidative stress (25).

The relationship between CXCR4 and CXCL12 is crucial for targeting MM cells to the protective BM niche (26). However, CXCL12 is associated with human immunodeficiency virus (HIV), warts, hypogammaglobulinemia, infections and myelokathexis (WHIM) syndrome, cardiovascular disease, immunodeficiency, cancer types (27).

The CXCL12/CXCR4 communication mechanism maintains proliferation, tumor cell survival, and migration in cancer (28). Studies have identified CXCR4 expression as a prognostic marker in various human cancers, including ovarian, breast and pancreatic adenocarcinoma (29). CXCR4 plays a substantial role in the metastatic process and is a promising CXCL gene receptor for developing new therapeutic treatments against cancer (30).

In HIV disease, CXCR4 is the main co-receptor facilitating viral pathogen entry (31). This allows the viral molecules to fuse with the host cell membrane, thereby inducing the entry of the HIV into the target cell. It has been explained to block HIV-1 and HIV-2 infections early in the viral cell cycle through selective inhibition of CXCR4 (32).

CXCL12 has been widely studied in the context of atherosclerosis. It has also been observed that it is expressed at a significant level by various cell types in coronary artery disease, such as smooth muscle and endothelial cells of atherosclerotic plaques (33,34).

However, the results of experiments that use the mouse as a model are not sufficient to understand the biological effect of CXCL12 and its ligand (CXCR4) in atherosclerosis because the intercellular mechanism is very complex (35). Genetic studies have identified the CXCL12 locus as a novel site in coronary artery disease, and alleles that increase the risk have also been associated with increased CXCL12 gene expression (36).

Increasing knowledge of the mechanisms explaining the CXCL12/CXCR4-mediated aberrant responses is beginning to provide insight into the pathogenesis of the disorder (37).

Most of the 50 the syndrome of WHIM patients reported so far have one of four mutations that result in a 10-19 amino acid truncation in the C-terminal domain of the ligand-induced and receptor crucial CXCR4. McDermott and colleagues demonstrated a case of *de novo* WHIM syndrome where the deletion of the 5 base pair CXCR4 open reading frame nucleotide 986-990 resulted in a frameshift. This mutation results in impaired CXCL12-induced receptor desensitization and enhanced ligand-induced receptor signaling (38,39).

Observations obtained because of studies have shown the role of the CXCL12/CXCR4 axis in inflammatory responses. In one study, serum levels of CXCL12 were shown to be significantly elevated in patients with Parkinson's disease (PD) compared with healthy controls. Additionally, it was observed that CXCR4 expression increased in patients with PD (40). CXCL12 is involved in leukocyte migration across the blood brain barrier. For this reason, it is considered a key chemokine in neuroinflammation (41).

Table 2. Pathways related to CXCL12

Pathway	Description	False discovery rate
hsa04061	Viral protein interaction with cytokine and cytokine receptor	2.05e-27
hsa04062	Chemokine signaling pathway	2.16e-06
hsa04620	Toll-like receptor signaling pathway	3.26e-34
hsa05340	Primary immunodeficiency	3.97e-14
hsa04060	Cytokine-cytokine receptor interaction	5.01e-06
hsa05323	Rheumatoid arthritis	5.63e-29
hsa04623	Cytosolic DNA-sensing pathway	6.45e-07
hsa04064	NF-kappa B signaling pathway	9.14e-11
hsa05163	Human cytomegalovirus infection	0.00012
hsa05142	Chagas disease	0.00013
hsa05235	PD-L1 expression and PD-1 checkpoint pathway in cancer	0.00019
hsa05205	Proteoglycans in cancer	0.00041
hsa05146	Amoebiasss	0.0014
hsa05145	Toxoplasmosis	0.0021
hsa04670	Leukocyte transendothelial migration	0.0024
hsa05167	Kaposi sarcoma-associated herpesvirus infection	0.0024
hsa04657	IL-17 signaling pathway	0.0024
hsa05135	Yersinia infection	0.0024
hsa04933	AGE-RAGE signaling pathway in diabetic complications	0.0024
hsa05170	Human immunodeficiency virus 1 infection	0.0034
hsa04660	T-cell receptor signaling pathway	0.0046
hsa04514	Cell adhesion molecules	0.0076
hsa05161	Hepatitis B	0.0083
hsa05164	Influenza A	0.0114
hsa05203	Viral carcinogenesis	0.0182
hsa05162	Measles	0.0182
hsa05226	Gastric cancer	0.0182
hsa05224	Breast cancer	0.0189
hsa05132	Salmonella infection	0.0192
hsa04810	Regulation of actin cytoskeleton	0.0202
hsa05131	Shigellosis	0.0463
hsa04151	PI3K-Akt signaling pathway	0.0463
hsa04010	MAPK signaling pathway	0.0492
hsa05200	Pathways in cancer	0.0492

PD: Parkinson's disease, MAPK: Mitogen-activated protein kinase, AGE-RAGE: Advanced glycation end product-receptor, NF: Nuclear factor

In addition to all these, studies on the epigenetic regulation of CXCR4 are increasing. The most common use of epigenetic regulation is to control how a gene is expressed. This arrangement defines the function of the cell. Generally, epigenetic, non-coding RNAs such as miRNAs (42), long non-coding RNAs (43) and circular RNA gene expression can be silenced using. Epigenetic regulation of gene expression can occur through processes such as methylation (generally

associated with gene silencing) and acetylation (generally associated with gene activation). Many studies have been reported supporting the epigenetic regulation of CXCR4 via non-coding RNAs, methylation, or acetylation.

As is known, some molecules, such as acetyl-11 keto-β-boswellic acid, cause decreased CXCR4 gene expression, resulting in changes in cancer behavior, including reduced invasion and migration (44). Thus, there are many direct and indirect ways in which the expression of CXCR4 can be epigenetically controlled.

CONCLUSION

We found strong evidence for miRNA-mediated CXCL12 expression, the variants near miRNA's showed stronger genetic associations with lymphoblastic leukemia/lymphoma, respiratory system disease, intestinal disease, combined immunodeficiency, multiple sclerosis, hepatitis, and MM. We conclude that the role of CXCL12 is stronger in autoimmunity, inflammation and possibly MM. This study demonstrates the feasibility of preliminary dry laboratory projects before starting wet laboratory experiments.

Acknowledgementdge:

Süleyman Rüştü Oğuz contributed as equal author.

ETHICS

Ethics Committee Approval: This study includes bioinformatic analysis that does not require ethics committee approval.

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Authorship Contributions

Concept: E.E.G., Design: E.E.G., S.R.O., S.K.B., Data Collection or Processing: E.E.G., S.K.B., Analysis or Interpretation: E.E.G., H.Ş.Ç., Literature Search: E.E.G., D.K., Writing: E.E.G.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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